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ORIGINAL ARTICLE

Examining Subclinical Inflammation in Major Depressive Disorder Subtypes

Majör Depresif Bozukluk Alt Tiplerinde Subklinik İnflamasyonun İncelenmesi

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ABSTRACT

Aims: There is increasing evidence that neuroinflammation and inflammatory processes play roles in psychiatric disorders. In the present study, the purpose was to investigate the role of systemic inflammation in major depressive disorder (MDD) subtypes, to compare the inflammation rates between subtypes and healthy controls, to help elucidate the pathophysiology of the disease, and to contribute to the determination of biochemical parameters.
Material and Methods: A total of 244 participants (180 patients diagnosed with MDD; 30 from the subtypes of catatonia, melancholy, mixed, atypical, anxious distress, psychosis, and 64 healthy controls)were included in the study. Participants who had a history of comorbid medical disease and/or any medication use were excluded from the study. Hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, Monocyte/Lymphocyte Ratio (MLR), Neutrophil/Lymphocyte Ratio (NLR), and Platelet/Lymphocyte Ratio (PLR) of the groups were compared.
Results: Sex, age and Body Mass Index (BMI) values did not differ between MDD subtypes and healthy controls ($p>0.05$). No differences were detected between healthy controls and MDD subtypes in neutrophil and lymphocyte counts ($p>0.05$). NLR and MLR values differed between healthy controls and MDD subtypes ($p=0.023$, $p=0.002$, respectively). NLR and MLR were significantly higher in the MDD subtype with catatonic characteristics than in healthy controls ($p=0.002$, $p<0.001$, respectively).
Conclusion: These results may contribute to a better understanding of subclinical inflammation, pathophysiology, individualized treatment approaches, and prognostication in MDD subtypes.

Keywords: Biomarkers, catatonia, major depressive disorder, monocyte/lymphocyte ratio, subclinical inflammation, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio,

ÖZ

Amaç: Psikiyatrik bozukluklarda nöroinflamasyonun ve inflamatuar süreçlerin rol oynadığına dair kanıtlar giderek artmaktadır. Çalışmamızda Majör depresif bozukluk (MDB) alt tiplerinde sistemik inflamasyonun rolünün araştırılması, alt tipler arasındaki inflamasyon oranlarının sağlıklı kontroller ile karşılaştırılması, hastalığın patofizyolojisinin aydınlatılmasına yardımcı olunması, biyokimyasal parametrelerin tespit edilmesine katkı sağlanması amaçlandı.
Gereç ve Yöntem: Çalışmaya MDB tanısı alan 180 hasta (katatoni ile giden, melankoli, karma, atipik, bunaltılı sıkıntı, psikoz özellikleri gösteren alt tiplerin her birinden 30 hasta) ve 64 sağlıklı kontrol olmak üzere 244 katılımcı dahil edildi. Komorbid tıbbi hastalık öyküsü ve/veya herhangi bir ilaç kullanımı olan katılımcılar çalışmaya dahil edilmedi. Grupların hemoglobin, hematokrit, platelet, nötrofil, lenfosit, monosit, monosit/lenfosit oranı (MLO), nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranı (PLO) karşılaştırıldı.
Bulgular: Cinsiyet, yaş ve vücut kitle indeksi (VKİ) değerleri; MDB alt tipleri ile sağlıklı kontroller arasında farklılık göstermedi ($p>0.05$). Nötrofil ve lenfosit sayıları açısından sağlıklı kontroller ve MDB alt tipleri arasında fark saptanmadı ($p>0.05$). NLO ve MLO değerleri sağlıklı kontroller ile MDB alt tipleri arasında farklılık gösterdi (sırasıyla $p=0.023$, $p=0.002$). Katatonik özellikli MDB alt tipinde NLO ve MLO sağlıklı kontrollere göre anlamlı düzeyde yüksek saptandı (sırasıyla $p=0.002$, $p<0.001$).
Sonuç: Araştırmamızın bulguları MDB alt tiplerinde subklinik inflamasyonun, patofizyolojinin, bireyselleştirilmiş tedavi yaklaşımlarının ve prognostik değerlendirmenin daha iyi anlaşılmasına katkıda bulunabilir.

Anahtar kelimeler: Biyobelirteçler, katatoni, majör depresif bozukluk, monosit/lenfosit oranı, nötrofil/lenfosit oranı, platelet/lenfosit oranı, subklinik inflamasyon.

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INTRODUCTION

MDD is a common mental healthcare concern that severely limits individuals' functionality and quality of life, contributing significantly to the global burden of disability (1-3). Clinical presentation, course of disease, response to treatment, genetic factors, and neurobiological mechanisms are dimensions that vary significantly among MDD patients (4). The division of MDD into subtypes provides a better understanding of the biology of depression, contributing significantly to individualizing treatment approaches and improving prognostic estimates (5). DSM-5 classified the subtypes of mood disorders in 2013 as anxious distress, mixed, melancholy, atypical, with psychotic characteristics, with catatonia, peripartum onset and seasonal pattern (6).

There is increasing evidence that neuroinflammation and inflammatory processes play roles in psychiatric disorders (7, 8). There is a growing scientific consensus that inflammation plays important roles in the pathophysiology of emotional disorders such as MDD and Bipolar Disorder (BD) (9). The measurement of blood biomarkers used to elucidate the role of inflammation in the pathophysiology of psychiatric disorders is a field that still faces some methodological challenges. Inflammation indices such as Platelet/Lymphocyte Ratio (PLR), Neutrophil/Lymphocyte Ratio (NLR), and Monocyte/Lymphocyte Ratio (MLR) are low-cost and widely used biological markers that can be calculated from routine complete blood count results. In this way, it is possible to evaluate the inflammation status without the need for complex and expensive tests (10, 11).

The study aimed to evaluate the roles of subclinical inflammation in MDD subtypes, compare inflammation rates between subtypes and healthy controls, help elucidate the pathophysiology of the disease, and contribute to determining biochemical parameters associated with MDD. The data obtained in the study were obtained by a relatively less invasive and inexpensive method, such as measuring serum levels of biochemical markers.

MATERIALS AND METHODS

Sample

The study was conducted retrospectively and in line with the 2013 version of the Declaration of Helsinki. The study was approved by the Gaziantep University Ethics Committee (2022/265). All individuals who applied to the Psychiatry Clinic were evaluated based on the DSM-5 Diagnostic Criteria. The study sample consisted of 180 patients diagnosed with MDD (30 from each subtype of catatonia, melancholia, mixed, atypical, anxious distress, and psychotic features) and 64 healthy controls who applied to the Gaziantep University Mental Health and Diseases Polyclinic between June 2020 and August 2022.

Inclusion Criteria: Being between the ages of 18-65, those who were included in one of the subtypes of MDD (catatonia, melancholy, mixed, atypical, anxious distress, and psychotic characteristics) based on DSM-5 Diagnostic Criteria, not having suicidal thoughts and/or attempts, not using alcohol, cigarettes or substances, and not being pregnant.

The healthy control group sample was selected from participants who had similar characteristics to the study group (age, sex, and BMI). These individuals had not

been diagnosed with any psychiatric disorder in the mental status examination conducted by a psychiatrist during the health board evaluation, had no history of psychiatric illness, pregnancy, comorbid medical conditions, or alcohol, smoking, or substance use.

The C-Reactive Protein (CRP) and sedimentation rates of all participants were normal, no signs of active infection and/or thyroid dysfunction were detected. Participants were not using any medication.

Exclusion criteria (patients and healthy controls): Using any medication, being pregnant, alcohol-cigarette, and/or substance use, and being < 18 years of age, being > 65 years old.

Data Collection Tools

Sociodemographic Data Form

Includes demographic data such as gender, age, and BMI.

Laboratory Examinations

Hemoglobin, hematocrit, platelet, neutrophil, lymphocyte, monocyte, Monocyte/Lymphocyte (MLR), Neutrophil/Lymphocyte Ratio (NLR), Platelet/Lymphocyte Ratio (PLR) were examined in the blood samples taken from the patients before the treatment. Values were calculated manually from complete blood count results.

Statistical Evaluation

The normality of the data was analyzed with the Shapiro-Wilk Test, differences in independent groups were evaluated with the Kruskal-Wallis and Dunn Multiple Comparison Tests, and relationships between categorical data were evaluated with the Chi-Square and Fisher's exact tests. Median (25%-75%) was used for numerical data, and frequency distributions and percentage values were used for categorical data. The SPSS for Windows version 24.0 package program was employed for statistical analysis. $p < 0.05$ was accepted as statistically significant for all the analyses.

RESULTS

It was found that the MDD group, MDD subtypes, and healthy controls did not have a normal distribution in terms of age and BMI. The median value was used for comparison. No significant differences were detected between the MDD group and MDD subtypes and healthy controls in terms of sex, age, and BMI ($p>0.05$) (Tables 1 and 2).

A statistically significant difference was detected between the control and MDD groups in terms of neutrophil and lymphocyte counts ($p=0.020$, $p=0.045$, respectively), there was no difference between healthy controls and MDD subtypes ($p>0.05$). The neutrophil count was high in the MDD group, while the lymphocyte count was low. No significant differences were detected between the MDD group and MDD subtypes and healthy controls in terms of platelet counts ($p>0.05$). Table 3 presents the blood parameters of healthy controls and the MDD group, and Table 4 presents the blood parameters of healthy controls and MDD subtypes.

In the MDD group, NLR, PLR, and MLR were statistically and significantly higher compared to healthy controls ($p=0.002$, $p=0.013$, $p=0.003$, respectively). NLR and MLR were statistically different between healthy controls and MDD subtypes ($p=0.023$, $p=0.002$, respectively). Median, 25th-75th percentile values of MDD subtypes and

Table 1. Comparison of MDD and healthy controls in terms of sex, age, BMI

	Group				
	Patient		Control		
	n	%	n	%	p
Sex					0,245 *
Female	116	64,44	36	56,25	
Male	64	35,56	28	43,75	
	Median [25%-75%]		**Median [25%-75%]**		**p**
Age	29 [26-36]		29 [26-34,5]		0,758 **
BMI	23,60 [21,1-27,75]		23,75 [22,24 -28,20]		0,171 **

*Chi-Square Test, ** Mann-Whitney U-Test
Data were expressed as median (25-75th percentile), p<0.05 was considered statistically significant. BMI: Body Mass Index

healthy controls are presented in Table 4. Also, NLR and MLR were significantly higher in the MDD subtype with catatonic features than in healthy controls (p=0.002, p<0.001, respectively). Comparison of the groups in terms of NLR and MLR is presented in Table 5. The evaluation of the groups in terms of NLR and MLR is shown in Figure 1.

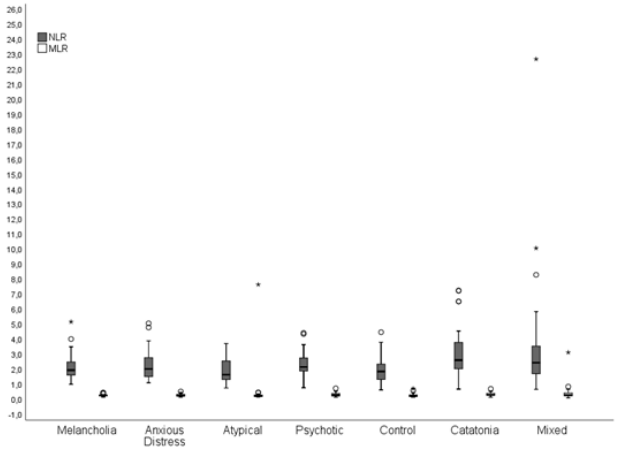

Figure 1. Box plot for comparison of NLR and MLR values of control group and MDD subgroups

DISCUSSION

In the present study, the researchers compared the neutrophil, lymphocyte, monocyte, platelet, Hb, Hct, NLR, MLR, PLR values of 180 patients who were diagnosed with MDD based on DSM-5 (showing characteristics of catatonia, melancholy, mixed, atypical, anxious distress and psychosis, 30 patients from each subtype)

Table 2. Comparison of MDD subtypes and healthy controls in terms of sex, age, and BMI.

		Melancholia	Anxious Distress	Atypical	Psychotic	Control	Catatonia	Mixed	p-value
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Sex	**Female**	23 (76,7)	21 (70,0)	25 (83,3)	16 (53,3)	36 (56,3)	16 (53,3)	19 (63,3)	0.061*
	Male	7 (23,3)	9 (30,0)	5 (16,7)	14(46,7)	28 (43,8)	14(46,7)	11 (36,7)	
		Median (25%-75%)	**Median (25%-75%)**	**Median (25%-75%)**	**Median (25%-75%)**	**Median (25%-75%)**	**Median (25%-75%)**	**Median (25%-75%)**	
Age		27 [24-32]	29 [27-33]	28 [25-35]	32 [27-39]	29 [26-34,5]	29,5 [26-37]	30 [26-45]	0,227 **
BMI		22,75 [21-26,10]	24,25 [22,6-26,8]	27,4 [22,4-27,9]	23,65 [22,7-28,3]	23,75 [22,24-28,20]	22,6 [19, 20-25,4]	23,30 [21-25,90]	0,067 **

*Chi-Square Test, ** Mann-Whitney U-Test
Data were expressed as median (25-75th percentile), p<0.05 was considered statistically significant. BMI: Body Mass Index

Table 3. Comparison of blood parameters of MDD and healthy controls

	Patient		Control		p
	Mean ±SD	Median(%25-%75)	Mean ±SD	Median(%25-%75)	
Neutrophil (10^3/µL)	5,09±2,08	4,77 (3,57-6,22)	4,34±1,52	4,04 (3,25-5,39)	**0,020**
Lymphocyte (10^3/µL)	2,23±0,74	2,15 (1,71-2,64)	2,39±0,64	2,37 (1,95-2,77)	**0,045**
Monocyte (10^3/µL)	0,67±0,91	0,56 (0,46-0,72)	0,56±0,18	0,55 (0,42-0,67)	0,233
Hb (g/dL)	13,89±1,83	13,7 (12,7-15,05)	14,31±1,23	14,20 (13,25-15,20)	0,064
Htc (%)	41,24±4,18	40,75 (38,65-44,4)	42,22±3,48	41,9 (39,75-44,25)	0,130*
Platelet (10^3/µL) NLR	291,60±71,42	285,50 (248-320,50)	274,72±55,39	270,00 (235,00-311,50)	0,120
PLR	2,6±2,05	2,17 (1,59-2,9)	1,91±0,77	1,85 (1,32-2,34)	**0,002**
	144,39±61,62	134,28 (111,08-163,53)	124,38±45,8	113,03 (89,96-149,82)	**0,013**
MLR	0,34±0,6	0,26(0,21-0,34)	0,25±0,1	0,22 (0,18-0,29)	**0,003**

Hb: Hemoglobin, Hct: Hematocrit, NLR: Neutrophil/Lymphocyte Ratio; PLR: Platelet/Lymphocyte Ratio; MLR, Monocyte/Lymphocyte Ratio

*Represents p-value from Student's t-test and all others from Mann-Whitney U-Test

Mean ± Standard deviation (SD) and Median(25%-75% Percentiles)

Table 4. Comparison of blood parameters between MDD subtypes and healthy controls

	Melancholia	Anxious Distress	Atypical	Psychotic	Control	Catatonia	Mixed	p
Neutrophil (10^3/µL)	4,25 (3,27-5,32)	4,66 (3,59-5,56)	4,22 (3,02-5,68)	4,62 (3,67-5,39)	4,04 (3,25-5,39)	5,69 (4,29-7,37)	5,87 (3,87-7,12)	0,387
Lymphocyte (10^3/µL)	2,02 (1,75-2,42)	2,25 (1,99-2,78)	2,34 (1,87-2,85)	2,10 (1,46-2,50)	2,37 (1,95-2,77)	1,98 (1,62-2,3)	2,10 (1,68-2,66)	0,230
Monocyte (10^3/µL)	0,50 (0,43-0,64)	0,56 (0,45-0,67)	0,54 (0,43-0,68)	0,51 (0,45-0,68)	0,55 (0,42-0,67)	0,56 (0,51-0,80)	0,72 (0,51-0,84)	0,112
Hemoglobin (g/dL)	13,7 (12,7-14,1)	13,4 (13,1-15,2)	13,4 (12,9-14,7)	13,8 (12,4-14,8)	14,2 (13,3-15,2)	14,7 (12,6-16)	14 (12,4-15)	0,097
Htc (%)	40,25 (39,1-42,6)	40,4 (38,6-43,8)	40,2 (38,6-43,1)	40,9 (37,8-44,5)	41,9 (39,75-44,25)	42,4 (38,7-45,9)	41,05 (38,4-45,0)	0,444
Platelet (10^3/µL)	293 (236-323)	286 (247-326)	279 (260-336)	293 (267-322)	270 (235-311,5)	258 (243-310)	272,5 (234-316)	0,236
NLR	1,94 (1,61-2,48)	2,02 (1,51-2,77)	1,64 (1,31-2,55)	2,15 (1,88-2,75)	1,85 (1,32-2,34)	2,61 (2,03-3,79)	2,44 (1,7-3,54)	0,023
PLR	135,87 (113,39-161,5)	127,2 (100,98-174,07)	124,72 (114,09-148,66)	142,94 (123,6-186,34)	113,03 (89,96-149,82)	134,46 (112,18-145,76)	133,96 (92,86-169,86)	0,523
MLR	0,26 (0,21-0,28)	0,24 (0,21-0,32)	0,23 (0,18-0,28)	0,27 (0,21-0,38)	0,22 (0,18-0,29)	0,3 (0,25-0,39)	0,29 (0,22-0,42)	0,002

Hb: Hemoglobin, Hct: Hematocrit, NLR: Neutrophil/Lymphocyte Ratio; PLR: Platelet/Lymphocyte Ratio; MLR, Monocyte/Lymphocyte Ratio. Data were expressed as median (25-75th percentile), $p<0.05$ was considered statistically significant.

Table 5. Comparison of all groups in terms of NLR and MLR

Group 1 - Group 2	p value for NLR	p value for MLR
Atypical - control	0,184	0,658
Atypical-melancholia	0,121	0,121
Atypical - anxious distress	0,121	0,606
Atypical - psychotic	0,121	0,121
Atypical - mixed	0,121	**0,039**
Atypical-catatonia	**0,010**	**0,002**
Melancholia - control	0,658	**0,027**
Anxious distress - control	0,658	0,658
Psychotic-control	**0,027**	0,184
Mixed-control	0,184	0,077
Catatonia-control	**0,002**	**0,000**
Melancholia -anxious distress	0,606	0,302
Melancholia - psychotic	0,302	0,606
Melancholia - mixed	0,121	0,121
Melancholia-catatonia	**0,010**	0,002
Anxious distress - psychotic	0,302	0,302
Anxious distress - mixed	0,121	0,302
Anxious distress - catatonia	0,071	0,121
Psychotic - mixed	0,606	0,302
Psychotic-catatonic	0,071	0,121
Mixed-catatonia	1,000	1,000

p<0.05 was considered statistically significant.

with 64 healthy controls. To our knowledge, the current study is the first to compare subclinical inflammation in MDD subtypes with healthy controls. Based on our results, MDD patients showed higher NLR, PLR, and MLR compared to healthy controls.

The role of biological markers such as NLR, PLR, and MLR in psychiatric disorders has been the focus of recent studies (12). In a study comparing 147 patients diagnosed with generalized anxiety disorder with a healthy control group, NLR and MLR were found to be statistically significantly higher (13). In a study conducted by Garip et al., patients diagnosed with first-episode psychosis, schizophrenia, and bipolar disorder were compared with a healthy control group. NLR was observed to be statistically significantly higher in patients with first-episode psychosis compared to the control group. No difference was found between the groups in terms of MLR and PLR (14). In their study, Kulu and colleagues compared peripheral inflammation markers in patients diagnosed with substance use disorder, alcohol use disorder, and healthy controls. NLR and MLR values were found to be lower in the substance use disorder group compared to the other two groups, while PLR was found to be lower in both the substance use disorder and alcohol use disorder groups compared to the control group (15).

Inflammatory markers (e.g., NLR, PLR, and MLR) are evaluated frequently in studies on the relationship between depression and inflammatory processes. However, the results of studies examining the relationship between these markers and depression are not consistent (16). Cai et al. compared NLR and PLR values of MDD patients who had not used psychotropic drugs in the last month with healthy controls and found them to be significantly higher (17). In two different studies conducted in our country, the NLR values of patients diagnosed with MDD were compared with those of healthy controls and were found to be high (18,19). NLR and PLR values were found to be higher in patients with early and late-onset depression compared with healthy controls (20). Martínez-Botía et al. reported no significant difference in NLR and PLR values between individuals with and without depression (21). Gündüz and her colleagues also found that there was no difference in the NLR and PLR values of MDD patients compared with healthy controls

in their study (22). In the study conducted by Ayhan and her colleagues, they found that while an increase in NLR was observed in individuals who attempted suicide, the presence of major depression did not affect NLR (23). In a study conducted on adolescent patients with depression, NLR levels were found to be significantly higher in the patient group compared to the control group. No statistically significant difference was observed between the groups in terms of PLR values (24). In the study conducted by Özyurt and Binici, a significant difference was found in NLR in adolescents with depression compared to the control group, but no such difference was found in terms of PLR (25). In a comprehensive study that was conducted on MDD patients, Meng et al. reported that NLR, PLR, and MLR had a nonlinear relationship with depression (26). A meta-analysis argued that depressed subjects had higher NLR levels compared to healthy controls and that antidepressant treatment could be an important factor affecting the relationship between depression and PLR (16). The meta-analysis of Cheng et al. also speculated that sex may have an effect on NLR, and they reported that PLR, NLR, and MLR were higher in the Chinese subgroup and in age- and sex-matched patients with depression compared to controls (27). In another study that examined suicidal behavior, researchers identified NLR as a potential novel peripheral biomarker of suicidal behavior in MDD (28). In this study, we compared MLR, NLR, and PLR values of patients with depression with healthy controls who did not use medication and found them to be significantly higher. The absence of significant differences between the groups in terms of sex, age, BMI, and medication use, and the absence of alcohol, cigarette, and substance use are important in terms of minimizing confounding factors that may affect MLR, NLR, and PLR levels.

Although there are studies in the literature evaluating inflammation in MDD with NLR, MLR, and PLR levels, there are a limited number of studies that evaluated the subtypes with healthy controls. In a previous study, we compared the peripheral SESN2 and HIF-1α levels of patients with MDD who presented with anxious distress, atypical, melancholic, and psychotic features with healthy controls. In the previous study, significant differences were detected between the SESN2, HIF-1α of the MDD subtypes, and the control group. Only HIF-1α and SESN2 showed no difference between the control group and the subtype showing psychotic characteristics. The findings obtained from MDD patients with the psychotic subtype suggested a distinct pathophysiological process from other MDD subtypes (melancholia, anxious distress, and atypical). The fact that the psychotic subtype had different results from other subtypes suggested that there might be differences in the pathophysiology of depression with psychotic characteristics and that clinicians should approach the psychotic subtype differently in terms of diagnosis and treatment (29). In a study comparing mild, moderate, and severe depressive patients with severe depressive patients with psychotic features, higher PLR was found in depressive patients with severe and psychotic features compared to other depressive patients. However, no significant difference was observed between different depression types in terms of NLR (30). No comparison was made with healthy controls in the study. The current study,

patients with psychotic depression were compared to healthy controls, revealing significantly higher NLR levels.

The incidence of catatonia is higher in individuals with psychiatric diseases (i.e., bipolar disorder, autism spectrum disorder, schizophrenia, major depressive disorder, and mixed diagnosis) compared to the general population (31). In the study comparing 34 patients (5 schizophrenia, 17 bipolar, 12 MDD) hospitalized in the psychiatric ward with a diagnosis of catatonia with healthy controls, NLR values were reported to be significantly higher, and this was considered to support the presence of subclinical inflammation in catatonia (32). In our results, MLR and NLR values were significantly elevated in the subtype with catatonia compared to healthy controls. These findings may guide us in distinguishing depression with catatonic characteristics from other psychiatric diseases accompanied by catatonia.

Our study has several limitations. Due to its retrospective design, data on important clinical characteristics such as depression severity, illness duration, and previous treatment history were not available. Therefore, the relationship between inflammatory markers and depression severity could not be analyzed. Furthermore, the lack of structured clinical interview tools prevented the assessment of psychiatric comorbidities such as comorbid personality disorders.

The lack of a difference in BMI between the groups in our study and the fact that the participants were not smoking are important for reducing confounding factors that have been shown to have significant effects on hematological parameters (33,34). However, individual differences in dietary and lifestyle habits can be a confounding variable in the interpretation of our results. All of these factors, along with sample size, are important factors that limit the generalizability of the study.

In future studies, evaluating inflammation levels in relation to clinical variables such as depression severity, illness duration, and previous treatment history could more clearly demonstrate the clinical utility of biomarkers.

CONCLUSION

This study is the first to compare MLR, NLR, and PLR in MDD subtypes not taking medication with healthy controls. NLR and MLR values in the subtype with catatonia were significantly higher compared to healthy controls. These findings may contribute to the differential diagnosis of MDD subtypes and personalized treatment approaches. The study will guide future studies in the evaluation of inflammation in MDD subtypes.

HIGHLIGHTS

•MDD patients showed higher NLR, PLR, and MLR compared to healthy controls.

•MLR and NLR values were significantly elevated in the subtype with catatonia compared to healthy controls.

•These findings may guide us in distinguishing depression with catatonic characteristics from other psychiatric diseases accompanied by catatonia.

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