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EFFECTS OF MAJOR DEPRESSIVE DISORDER ON MONOCYTES, HIGH-DENSITY LIPOPROTEIN (HDL) AND MONOCYTE TO HDL RATIO: A CASE-CONTROL STUDY

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SUMMARY

Objective: *In this study, we investigated the effects of Major Depressive Disorder (MDD) on monocyte counts, High-Density Lipoprotein (HDL) levels, and Monocyte to HDL ratios (MHR) among inflammatory markers.*

Method: *This is a retrospective case-control study. The case group of our study included 120 major depressive patients. The control group included 124 healthy individuals. The data were collected using a Personal Information Form, the Clinical Global Impression Scale, and the Hamilton Depression Rating Scale. The lipid profiles and complete blood count parameters of the case and control groups were tested and compared. The collected data were analyzed using the Kruskal-Wallis test, Mann-Whitney U test and independent-samples t-test.*

Results: *A significant increase in the monocyte and MHR values and a decrease in the HDL values of the case group were observed with older ages ($p<0.01$). In the case group, the MHR and monocyte count values were higher, and the HDL levels were lower in the MDD patients who had never received treatment in comparison to those who had received treatment. As the severity of depression increased, MHR levels also increased.*

Conclusion: *Our study is the first study to show that MHR is significantly higher in MDD patients than healthy controls. It was also shown that depression severity and MHR are positively correlated. Consequently, MHR might be a simple, practical, and low-cost parameter which shows inflammation in MDD patients.*

Key words: *Major Depressive Disorder – depression - high-density lipoprotein – HDL – monocyte - monocyte to HDL ratio*

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INTRODUCTION

Major depressive disorder (MDD) is a chronic mental illness characterized by recurrent episodes of depression (Gold et al. 2015). It is classified under the heading of depressive disorders in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Depressive mood, anhedonia, sleep, appetite and concentration problems, decreased energy, thoughts of guilt, worthlessness, and suicide are the symptoms of MDD (Widiger & Costa 2013). Depression is the most common psychiatric disorder worldwide. The 12-month prevalence of depression was reported as 6.6%, and its lifetime prevalence was 16.6% (Akiskal 2009). It is two times more common in women than men. The lifetime risk of getting developing depression was found to be 20-26% in women and 8-12% in men. It is most common in women between the ages of 35 and 45 and in men after the age of 55 (Horwath et al. 2002).

Main factors such as environmental and genetic factors, neural circuits, neurotransmitter disorders, and neuroendocrine dysregulation are implicated for the etiology of MDD (Marneros 2006). There are also studies on the roles of oxidative metabolism and inflammation in MDD (Gadad et al. 2018, Haroon et al. 2018, Marneros 2006, Michel et al. 2010). It has been suggested that inflammation affects processes such as monoamine and glutamate neurotransmission, glucocorticoid receptor resistance, and hippocampal neurogenesis. These processes are thought to be important in the etiopathogenesis of MDD, and inflammation markers can be used as markers in the diagnosis of depression and response to treatment (Gadad et al. 2018, Haroon et al. 2018). Oxidants cause damage to the genetic structure by affecting the cell structure, the structure of the extracellular matrix, cilia function, and by causing Deoxyribonucleic acid (DNA) damage (Valko et al. 2006). It is known that oxidative metabolism is impaired in various medical diseases such as atherosclerosis, cancer, allergy, and diabetes (Valko et al. 2007). Oxidative stress is thought to mediate the neuropathological processes of several neuropsychiatric disorders. Scientific evidence is accumulating on oxidetive metabolism imbalances in psychiatric disorders (Amirani et al. 2020).

Monocytes and lipid-laden macrophages formed by their activation play an essential role in synthesizing and releasing proinflammatory and prooxidant cytokines. Monocytes, which constitute approximately 3-8% of leukocytes in peripheral blood, have an essential effect in controlling inflammatory processes (Ransohoff 2011). Rosenblat et al. showed that MDD patients had slightly higher proinflammatory factors than healthy controls (Rosenblat et al. 2014). It was suggested that MDD patients have slightly increased levels of chronic inflammation due to the activation of monocytes (Maes 2011). It was demonstrated that high-density lipoprotein (HDL)

cholesterol protects the endothelium from the harmful effects of low-density lipoprotein (LDL) cholesterol, and at the same time, it inhibits the oxidation of LDL cholesterol (Hui et al. 2019).

Recent studies have shown that the monocyte to HDL ratio (MHR) may be a new marker of inflammation and oxidative stress. With this aspect, it is thought that it can be used as a simple calculable criterion showing the presence and prognosis of inflammatory and inflammation-related diseases (Çetin et al. 2016, Gembillo et al. 2022). MHR was found to be significantly higher in schizophrenia patients compared to healthy individuals (Şahpolat et al. 2021). In a comparison of healthy controls to bipolar disorder patients with manic episodes, MHR was found significantly higher in manic patients (Çalışkan & Çokünlü 2021). However, there is no study in the literature examining the MHR values of MDD patients. Knowing the monocyte, HDL and MHR values of MDD patients may provide various contributions to the treatment method, the monitoring of the prognosis of the disease, and the prediction of the potential effects of these markers. Based on this information, we hypothesized that MHR may be elevated in MDD patients. We conducted this case-control study to investigate the effects of MDD on lipid and inflammatory markers including Monocyte Counts, High-Density Lipoprotein (HDL) levels, and the Monocyte to HDL Ratio (MHR).

MATERIAL AND METHOD

Design and Participants

This is a retrospective case-control study. We used the G Power 3.1.9.7 program for sample calculation. Accordingly, at least for both groups total of 134 patients were required to participate with an effect size of 0.4, a margin of error of 0.05, and a confidence interval of 0.95. The case group consisted of 120 patients diagnosed with MDD who were attending follow-ups periodically at a research and training hospital as outpatients, and the control group included 124 individuals who presented to the hospital for health follow-ups or to receive documents showing that they were healthy, constituting a total of 244 participants. In the selection of the sample, we used the purposive sampling method. The inclusion criteria for the case group were having been diagnosed with MDD at least 1 year ago, not having any comorbid or chronic disease other than MDD, being over the age of 18, and voluntarily agreeing to participate in the study. The control group consisted of healthy individuals who had similar ages and sociodemographic characteristics to the case group and did not have any chronic or comorbid diseases. Before their assignment to the groups, the individuals considered for the case and control groups were screened for infections, and those carrying infection risk, those using antibiotics, those with hematological diseases, those with suspected pregnancy, and those who were pregnant were excluded. In addition to these exclusion criteria, individuals who were smokers, those who had substance abuse problems, and those who were alcohol consumers were also excluded. The data of this study were collected by the researchers from the participants' electronic data records between 01.06.2019 and 30.05.2021.

Data Collection

After forming the case and control groups, the researchers met each participant individually and asked for permission to use their electronic data records. All participants provided verbal and written informed consent. The laboratory data records of all participants in the two groups and information on the psychometric examination results of the MDD patients were obtained from the electronic database. The researchers also collected and recorded the participants' monocyte count, HDL and MHR ratio data based on their tests studied at the laboratories of the hospital. Information about the instruments that were used for data collection is given below.

Data Collection Instruments

To collect data for our study, we used a Personal Information Form, the Clinical Global Impression Scale, and the Hamilton Depression Rating Scale, which are described below.

Personal Information Form

This form was prepared by the researchers, and it included questions on the age, sex, body mass index (BMI), marital status, education level, family history of depression, MDD- and treatment-related characteristics of the participants.

Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HAM-D) is a 17-item psychometric instrument that is used to determine the severity of depression in adults (Hamilton 1960). It was tested for validity and reliability in Turkish, and the number of items in the scale was reduced to 13. The maximum score that can be obtained in HAM-D is 53, and higher scores indicate a higher severity of depression. In HAM-D, scores of 0-7 suggest the absence of depression, 8-15 indicate mild depression, 16-28 indicate moderate depression, and scores of 29 or higher indicate severe depression (Akdemir et al. 1996, Williams 1988).

Clinical Global Impression Scale

Clinical Global Impression Scale (CGI-S) was developed by Guy to evaluate the clinical course of all psychiatric disorders (Guy 1976). It consists of 3 parts: severity of illness (CGI-S), Global Improvement (CGI-I), and the Efficacy Index. The clinician evaluates the severity of illness by CGI-S, clinical change in the patient at the point of assessment compared to baseline by CGI-I, and the therapeutic effect of the intervention by the Efficacy Index.

Table 1. Descriptive Characteristics, Monocyte Counts, HDL Levels and MHR Values of the Case and Control Groups, and Homogeneity Test Results (N=244)

Characteristics	Case Group (n=120) - MDD Patients					Control Group (n=124) - Individuals with no Depression					Homogeneity
	n	%	Monocytes[##]	HDL (mg/dl)	MHR	n	%	Monocytes[##]	HDL (mg/dl)	MHR	Test Results
Age - years											χ^2=1.131
18-28 (1)	34	28.3	0.502±0.111	53.05±13.47	0.010±0.040	33	26.6	0.493±0.081	49.84±8.97	0.010±0.003	p=0.975
29-38 (2)	44	36.7	0.611±0.239	48.97±11.12	0.013±0.060	37	29.8	0.487±0.101	49.13±9.04	0.010±0.003	
39-48 (3)	16	13.3	0.637±0.172	42.12±7.06	0.015±0.040	15	12.1	0.624±0.055	47.93±9.75	0.013±0.002	
49-58 (4)	24	20.0	0.724±0.993	33.5±11.22	0.018±0.090	37	29.8	0.566±0.145	45.05±11.14	0.012±0.004	
59 or older (5)	2	1.7	0.700±0.000	30±0.000	0.023±0.000	2	1.6	0.520±0.100	44.03±9.87	0.011±0.003	
Test			KW=23.057	KW=19.295	KW=25.123			KW=30.311	KW=11.695	KW=6.818	
p-Value			*p=0.000***	*p=0.001***	*p=0.000***			p=0.114	*p=0.009***	p=0.078	
Post Hoc			1,2,3<4,5	1>2>3>4,5	1,2,3>4,5				4,5<1,2,3		
Sex											χ^2=1.739
Female	70	58.3	0.569±0.171	51.05±12.9	0.012±0.006	83	66.9	0.507±0.87	50.55±10.12	0.010±0.002	p=0.741
Male	50	41.7	0.663±0.232	43.25±9.34	0.016±0.006	41	33.1	0.577±0.154	42.51±6.85	0.013±0.004	
Test			MWU=4.862	MWU=9.355	MWU=12.496			MWU=4.194	MWU=15.441	MWU=7.253	
p-Value			*p=0.027**	*p=0.002***	*p=0.000***			*p=0.041**	*p=0.000***	*p=0.007***	
Marital Status											χ^2=1.987
Single	44	36.7	0.587±0.246	49.86±11.59	0.016±0.006	31	25.0	0.519±0.111	48.74±9.69	0.011±0.003	p=0.140
Married	76	63.3	0.620±0.174	46.61±12.37	0.017±0.006	93	75.0	0.534±0.120	47.61±10	0.011±0.003	
Test			MWU=4.198	MWU=3.596	MWU=4.375			MWU=1.011	MWU=0.747	MWU=0.206	
p-Value			p=0.065	p=0.058	p=0.321			p=0.315	p=0.387	p=0.65	
Education Level											χ^2=3.865
Literate with no formal education	12	10.0	0.681±0.238	52.16±13.8	0.017±0.001	40	32.3	0.534±0.080	48.12±9.46	0.011±0.002	p=0.424
Primary-secondary school	58	48.3	0.584±0.159	47.79±12.81	0.013±0.006	22	17.7	0.576±0.17	52.72±14.02	0.011±0.006	
High school	36	30.0	0.637±0.121	45.96±9.44	0.012±0.004	49	39.5	0.515±0.105	47.20±8	0.011±0.003	
Higher education	14	11.7	0.741±0.339	48.85±14.17	0.016±0.07	13	10.5	0.495±0.144	41.61±5.12	0.012±0.003	
Test			KW=2.129	KW=1.232	KW=1.054			KW=4.546	KW=6.327	KW=1.476	
p-Value			p=0.098	p=0.134	p=0.564			p=0.208	p=197	p=0.688	
Socioeconomic Level											χ^2=4.317
Sufficient	74	61.7	0.601±0.233	46.33±11.90	0.014±0.007	54	43.5	0.534±0.099	48.25±10.39	0.011±0.003	p=0.105
Insufficient	46	38.3	0.612±0.183	50.17±12.28	0.012±0.006	70	56.5	0.525±0.139	47.61±9.57	0.010±0.004	
Test			MWU=0.654	MWU=0.786	MWU=4.876			MWU=0.821	MWU=0.015	MWU=2.727	
p-Value			p=0.564	p=0.412	p=0.897			p=0.365	p=0.904	p=0.099	
Working Status											χ^2=0.186
Working	30	25.0	0.670±0.252	43.66±6.48	0.015±0.005	37	29.8	0.514±0.129	47.32±8.2	0.011±0.003	p=0.198
Not working	80	66.7	0.601±0.185	47.83±12.75	0.014±0.070	79	63.7	0.545±0.119	48.17±10.49	0.013±0.003	
Student	10	8.3	0.478±0.92	56±12.80	0.008±0.025	8	6.4	0.463±0.054	53±8.62	0.009±0.003	
Test			KW=1.829	KW=1.601	KW=0.654			KW=0.673	KW=1.032	KW=3.287	
p-Value			p=0.074	*p=0.008**	p=0.178			p=0.920	p=0.879	p=078	
Post Hoc											

**p<0.01; *p<0.05; [##] - $10^3/\mu l$; χ^2 = Chi-squared test; KW = Kruskal-Wallis test; MWU = Mann-Whitney U test; Post Hoc = Scheffe test; X = Mean; SD = Standard deviation

Table 1. Continues

Characteristics	Case Group (n=120) - MDD Patients					Control Group (n=124) - Individuals with no Depression					Homogeneity Test Results
	n	%	Monocytes[##]	HDL (mg/dl)	MHR	n	%	Monocytes[##]	HDL (mg/dl)	MHR	
Family History of Depression											
Yes	40	33.3	0.641±0.198	48.82±14.15	0.015±0.008	-	-	-	-	-	
No	80	66.7	0.591±0.205	47.30±11.06	0.013±0.005	-	-	-	-	-	
Test			MWU=2.682	MWU=0.036	MWU=0.446						
p-Value			p=0.850	p=0.101	p=0.504						
Body Mass Index											χ^2=0.1015
Underweight	2	1.7	0.47±0.000	47±0.000	0.007±0.000	3	2.4	0.553±0.028	41±1.73	0.013±0.000	p=0.331
Normal weight	58	48.3	0.605±0.2	48.53±10.57	0.013±0.005	45	36.3	0.520±0.097	46.4±9.27	0.011±0.003	
Overweight	41	34.2	0.624±0.205	47.17±13.41	0.015±0.008	60	48.4	0.529±0.137	49.13±10.58	0.011±0.004	
Obese	15	12.5	0.583±0.231	41.86±11.93	0.014±0.006	13	10.5	0.558±0.103	48.75±9.4	0.011±0.003	
Morbidly Obese	4	3.3	0.650±0.207	56.50±10.96	0.014±0.006	3	2.4	-			
Test			KW=1.224	KW=13.577	KW=2.765			KW=3.420	KW=3.214	KW=1.757	
p-Value			p=0.563	p=0.209	p=0.598			0.331	0.360	0.624	
Duration of Depression Diagnosis											
1-5 years (1)	64	53.4	0.582±0.227	49.31±11.93	0.013±0.007	-	-	-	-	-	
6-11 years (2)	30	25.0	0.613±0.150	47.22±14.32	0.014±0.005	-	-	-	-	-	
12-17 years (3)	10	8.3	0.558±0.148	51.2±11.41	0.011±0.004	-	-	-	-	-	
18 years or longer (4)	16	13.3	0.732±0.183	40.75±5.07	0.018±0.004	-	-	-	-	-	
Test			KW=15.753	KW=10.043	KW=15.753						
p-Value			p=0.001**	p=0.018**	p=0.001**						
Post Hoc			1,2,3<4	1,2,3>4	1,2,3<4						
Has Attempted Suicide											
Yes	34	28.3	0.541±0.170	51.24±14	0.011±0.005	-	-	-	-	-	
No	86	71.7	0.634±0.210	46.45±11.12	0.014±0.007	-	-	-	-	-	
Test			MWU=5.933	MWU=2.589	MWU=5.703						
p-Value			*p=0.015**	p=0.108	*p=0.017**						
Type of Treatment											
Antidepressant (1)	44	36.7	0.529±0.262	46.72±12.42	0.012±0.008	-	-	-	-	-	
Antidepressant + Antipsychotic (2)	38	31.7	0.562±0.163	44.91±11.03	0.011±0.006	-	-	-	-	-	
Antidepressant + Antipsychotic + Benzodiazepine (3)	6	5.0	0.480±0.008	43.33±4.22	0.011±0.035	-	-	-	-	-	
Antidepressant + Electroconv. Ther. (4)	2	1.7	0.420±0.000	44±0.000	0.012±0.000	-	-	-	-	-	
Never had treatment (5)	30	25.0	0.746±0.134	32.46±11.06	0.016±0.003						
Test			KW=15.430	KW=20.611	KW=11.040						
p-Value			*p=0.004***	*p=0.000***	*p=0.026**						
Post Hoc			5>1,2>3,4	1,2,3,4>5	1,2,3>4,5						
Mean Scale Scores											
Hamilton Depression Rating Scale			X±SD	20.02±7.42 (Min 7, Max 40)		-	-	-	-	-	
Clinical Global Impression Scale-Severity			X±SD	4.47±0.869 (Min 3, Max 6)		-	-	-	-	-	

**p<0.01; *p<0.05; [##] - 10^3/µl; χ^2 = Chi-squared test; KW = Kruskal-Wallis test; MWU = Mann-Whitney U test; Post Hoc = Scheffe test; X = Mean; SD = Standard deviation

Statistical Analysis

After the data were coded by the researchers, they were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) 25.0. The results were interpreted in a 95% confidence interval and on a significance level of $p<0.05$. Descriptive statistics were included in the analyses. Chi-squared test was used as the homogeneity test between the case and control groups. Before the analyses, using Kolmogorov-Smirnov test, the normality of the distribution of the data was determined. Kruskal-Wallis test, Mann-Whitney U test and independent-samples t-test were used to identify the relationships between the participants' descriptive characteristics and their scale scores. Post hoc analyses were conducted to identify the sources of significant differences.

Ethical Aspect of the Study

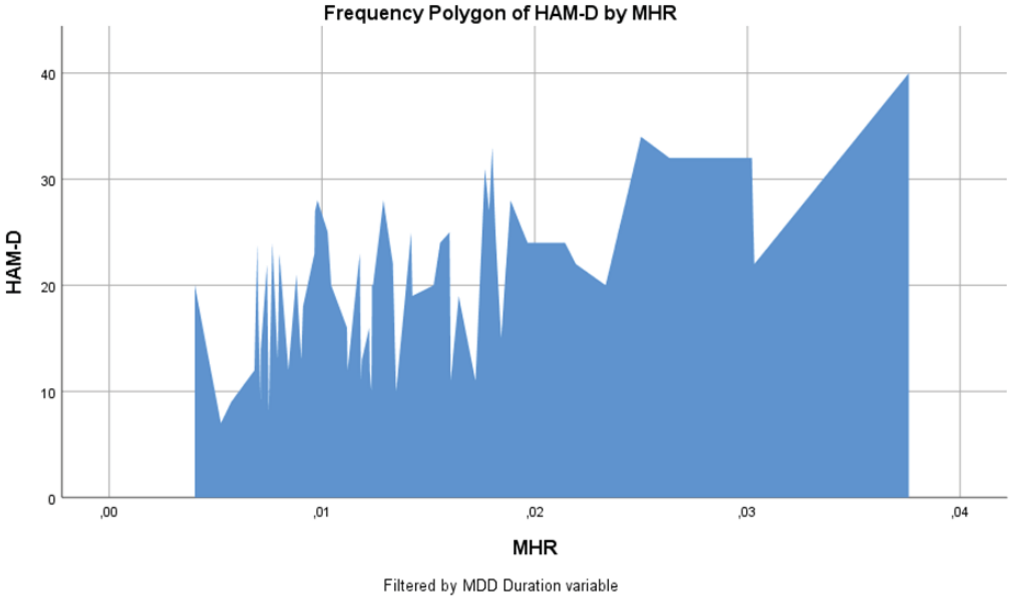
Before starting the study, the necessary permissions were obtained from the Non-Invasive Clinical Research Ethics Committee of the Faculty of Medicine at Dicle University (Date: 01/09/2021, Number: 470). In compliance with the principles of the Declaration of Helsinki, the participants were informed about the study, and the researcher read them the Informed Consent Form. The participants who voluntarily agreed to participate were included in the study after they provided verbal and written informed consent.

RESULTS

Table 1 presents the characteristics of the case and control groups, their monocyte count, HDL and MHR values, and the results of their homogeneity tests. There was no statistically significant difference between the case and control groups based on their characteristics including age, sex, or body mass index (BMI) ($p>0.05$). These results showed that the two groups were similar and homogeneously distributed based on their descriptive characteristics. 36.7% of the case group were between the ages of 29 and 38, 58.3% were women, and 53.4% were diagnosed with depression between 1 and 5 years. 29.8% of the control group were between the ages of 29 and 38, and 66.9% were women. It was determined that the monocyte, HDL and MHR values of the case group were affected by depression. Accordingly, as the ages of the participants in the case group increased, there was a significant increase in their monocyte counts and MHR values, and there was a decrease in their HDL values ($p<0.01$). In the control group, the decrease in HDL values was found statistically significant ($p<0.01$). The variable of sex was associated with similar changes in the two groups ($p<0.05$). Other individual characteristics were not significantly related to changes in the results of two groups. In the case group, the MHR and monocyte count values were higher, and the HDL levels were lower in the MDD patients who had never received treatment in comparison to those who had received treatment ($p<0.01$).

Table 2 presents the comparison of the monocyte counts, HDL levels and MHR values of the case and control groups. Monocyte and MHR were higher and HDL was lower in the case group compared to the experimental group ($p<0.05$).

There was a significant positive correlation between the MHR values and scale scores (CGI-S, HAM-D) of the case group ($p<0.05$). The frequency polygon for the MHR values and HAM-D scores is shown in Figure 1. According to Figure 1, as the severity of depression increased, the value of MHR also increased. Accordingly, as the severity of MDD increases, the MHR level also increases (Table 3, Figure 1).



HAM-D, Hamilton Depression Rating Scale; MDD, Major Depressive Disorder; MHR, Monocyte to HDL Ratio

Figure 1. Relationship between MDD and MHR in the Case Group (n=120)

Table 2. Comparison of the Monocyte Counts, HDL Levels and MHR Values of the Case and Control Groups (N=244)

Inflammation Markers	Case Group (n=120) (MDD Patients) X±SD (Min, Max)	Control Group (n=124) (Individuals with no Depression) X±SD (Min, Max)	Intergroup Comparison Test and Significance
Monocytes (10^3/µl)	0.608±0.203 (0.3, 1.45)	0.530±0.118 (0.28, 0.91)	t=1.107; *p=0.014**
HDL (mg/dl)	47.80±12.14 (28, 79)	48.89±9.9	t=0.347; *p=0.000***
MHR	0.013±0.006 (0.00, 0.04)	0.011±0.003 (0.01, 0.03)	t=0.218; *p=0.000***

X = Mean; SD = Standard deviation; t = independent-samples t-test; **p<0.01; *p<0.05

Table 3. Correlation between MHR Values and Scale Scores in the Case Group (with MDD) (n=120)

Case Group (n=120)	CGI-S	HAM-D
MHR	-	-
Pearson's correlation coefficient	0.505	0.590
p-value	*0.001***	*0.001***

MDD = Major Depressive Disorder; CGI-S = Clinical Global Impression Scale-Severity; HAM-D = Hamilton Depression Rating Scale; **p<0.01; *p<0.05

DISCUSSION

This study, where we investigated the changing monocyte counts, HDL levels and monocyte to HDL ratio (MHR) values of major depressive disorder (MDD) patients, is an important source of information. HDL dysfunction occurs during acute and chronic inflammatory disorders. This way, HDL becomes pro-inflammatory, resulting in the failure of preventing the accumulation of oxidized LDL (oxLDL) and LDL-induced monocytes with chemotactic activity (Ansell et al. 2003). oxLDL accumulation mediates leukocyte activation, proinflammatory cytokines are secreted, leukocyte adhesion molecules are expressed, cellular degranulation occurs, reactive oxygen species (ROS) are released, and endothelial dysfunction is developed (Al-Banna & Lehmann 2013). Therefore, dysfunctional HDL is a predictor of severe organ failure in the clinical picture of sepsis (Guirgis et al. 2018). In this context, HDL not only reduces the endothelial expression of adhesion molecules but also is effective in preventing monocyte recruitment to the arterial wall (Libby 2012). Recent studies have demonstrated that MHR may be a new marker for inflammation and oxidative stress. It has been suggested that HDL levels may be a predictor of inflammation (Kanbay et al. 2014, Yılmaz & Kayançiçek 2018). Oxidative stress can also mediate MDD. The MDD patients who were included in our study had been diagnosed for at least 1 year. In this sense, while the information that changes in the lipid profile and complete blood count parameters trigger MDD is available in the literature, the finding in our study that MHR values increased along with the increased severity of depression was an important finding drawing attention to the two-way relationship between these parameters. We think that there is a bilateral relationship between MHR and MDD, and they trigger the increases in each other.

Although many factors are proposed for the etiology of MDD, studies have shown that MDD is associated with inflammation and oxidative metabolism (Gadad et al. 2018, Haroon et al. 2018, Michel et al. 2010). White blood cells and their subgroups are known biological markers of inflammation, and inflammatory cytokines are released by their activation. The neutrophil to lymphocyte ratio (NLR) has been studied as a novel marker for inflammation (Imtiaz et al. 2012, Liu et al. 2020), and it has been shown to be elevated in many psychiatric disorders compared to healthy controls. In patients with bipolar disorder in euthymic, depressive, and manic periods, NLR was found significantly higher than healthy controls (Ayhan et al. 2019). Similarly, another study indicated that bipolar patients in euthymic and manic periods had higher NLR values than healthy controls, but there was no significant difference in depressive episodes compared to controls (Imtiaz et al. 2012). MDD patients have elevated NLR values compared to healthy controls (Cai et al. 2017, Demir et al. 2015, Demircan et al. 2016).

Recent studies have shown that MHR may be a novel marker for inflammation and oxidative stress. With this aspect, it is thought that it can be used as a simple calculable criterion showing the presence and prognosis of inflammatory and inflammation-related diseases (Çetin et al. 2016, Gembillo et al. 2022). In the case group of our study, it was determined that monocyte counts, HDL levels and MHR values were affected by depression severity. Accordingly, as age progressed in the case group, there were significant increases in the monocyte counts and MHR values in the group, as well as a reduction in the HDL values (p<0.01). In the case group, the MHR and monocyte count values were higher, and the HDL levels were lower in the MDD patients who had never received treatment in comparison to those who had received treatment. These results highlighted the issue that the medications that are used in the treatment of MDD also lead to changes in inflammation markers. Studies have also supported the view that MHR may be associated with smoking and obesity (Köylü & Kurtoğlu 2021, Ünal & Haspolat 2020). Thus, in this study, we created similar groups in terms of BMI. Additionally, we did not include people with smoking habits, alcohol consumption, and substance abuse in our study because of the possibility of confounding factors. It was previously observed that antidepressants changed immune functions, and antidepressant treatment had the capacity to reduce proinflammatory

factors measured in peripheral blood (Baune 2018). The results of our study were in agreement with studies that have determined reduced levels of inflammation markers with antidepressant treatment.

In our study, the mean MHR value of the case group was significantly higher than that in the control group. There was a significant and positive correlation between the MHR values and scale scores (CGI-S, HAM-D) in the case group. The results of our study were in line with studies in which MHR, an inflammation marker, was found to be significantly higher compared to healthy controls. A previous study found a significant positive correlation between the NLR values and depression severity (Sunbul et al. 2016). In our results, similar to the aforementioned study, depression severity measured by CGI-S and HAM-D showed a positive correlation with MHR. In the literature, there are studies about the evaluation of MHR in schizophrenia patients and bipolar patients in manic episodes. In the study conducted by Şahpolat et al., MHR was found to be significantly higher in schizophrenia patients in comparison to healthy individuals (Şahpolat et al. 2021). In a study comparing bipolar patients in manic episodes to healthy controls, MHR was found significantly higher in the manic patients (Çalışkan & Çokünlü 2021). The fact that our study was a single-center study, taking the verbal statements about the patients regarding their treatment compliance as a reference and the fact that the healthy controls were not subjected to full-fledged examinations were accepted as limitations of this study. Additionally, because this study was carried out in the COVID-19 pandemic period, it was not possible to reach a larger sample.

CONCLUSION

The hypothesis of this study was that MHR level could be increased in MDD patients. The findings of our study justified our hypothesis. Our study is valuable as it is the first study to show that MHR is significantly higher in MDD patients than healthy controls. It was also shown that depression severity and MHR are positively correlated. Consequently, MHR might be a simple, practical, and low-cost parameter which shows inflammation in MDD patients. We recommend the management of these markers and preventing them from increasing the severity of depression.

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Contribution of individual authors:

Betul Uyar: study conception, design data analysis and interpretation data collection.

Elif Ates Budak: drafting of the manuscript critical revision of the manuscript.

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