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Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia

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ABSTRACT

The inflammation hypothesis is frequently mentioned in the pathogenesis of schizophrenia. The objective of this study was to compare inflammation markers during relapse and remission periods in patients with schizophrenia. Complete blood count (CBC) of 105 patients diagnosed with schizophrenia who were hospitalized due to psychotic relapse at Ondokuz Mayıs University Medical Faculty Psychiatry Service between 2012 and 2016 and 105 healthy control subjects were retrospectively analyzed. Relapse CBC was also compared with remission CBC of the same patients and with the control group. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR) of the patients during relapse period were found to be significantly higher when compared with the control group. MLR and PLR were found to be significantly higher in the remission period when compared with the control group. NLR, PLR and MLR values were significantly increased in the relapse period when compared with the remission period of the same patients. The findings of our study support the inflammation hypothesis of schizophrenia. As a result of our study, we believe MLR and PLR are important markers. There is a decrease in inflammatory response in schizophrenia following treatment.

1. Introduction

Schizophrenia is a severe mental illness accompanied by loss of faculty that has a prevalence of about 0.5% (McGrath et al., 2008). Many models are mentioned in its pathogenesis, including the inflammation hypothesis. Mechanisms such as increase in proinflammatory cytokines (Al-Hakeim et al., 2015; Cristiano et al., 2017), increase in autoantibodies (Samaroo et al., 2010), increase in oxidative stress products (Kulaksizoglu and Kulaksizoglu, 2016), and maternal infection in prenatal period (Krause et al., 2010) support this hypothesis. In addition, the fact that nonsteroid anti-inflammatory drugs added in antipsychotics cause a mild decrease in the positive symptoms of patients support the inflammation hypothesis (Nitta et al., 2013).

Inflammation is a response initiated by the body against endogenous or exogenous factors and is necessary but not specific to the continuation of life. Recently, many studies have been conducted on the association between inflammation and its indicative biomarkers. Since the physiological response of leukocytes to stressful conditions such as inflammation causes an increase in the number of neutrophils and a decrease in the number of lymphocytes, the ratio of these two subgroups is used as an indicator of inflammation (Zahorec, 2001). Since neutrophil/lymphocyte ratio is easily found, it has been used often as an indicator of inflammation lately. Besides neutrophil lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and monocyte/lymphocyte ratio (MLR) are also used to determine inflammation. CRP level, which is a frequently used indicator of inflammation, has been found to have a high correlation with white blood cell count and NLR ratio (Gokmen et al., 2015). NLR, MLR, and PLR have been investigated in many non-psychiatric disorders and have been used for predicting the course of diseases (Suliman et al., 2010; Que et al., 2015; Chen et al., 2016; Ji et al., 2016; Lee et al., 2016). In recent years, the use of these values has increased in psychiatric studies. While neutrophil count and NLR values were found to be higher when compared with the control, the lymphocyte count was found to be lower in patients with schizophrenia (Semiz et al., 2014; Ozdin et al., 2017). NLR values, were found to be also higher in patients with first episode psychosis (Moody and Miller, 2017). In patients with bipolar disorder, NLR and PLR values were shown to be high in both manic and euthymic periods when compared with the control group (Kalelioglu et al., 2015). Schizophrenia patients with relatively normal neutrophil and lymphocyte counts at the start of treatment showed better response to the treatment (Zorrilla et al., 1998).

Previous studies have compared NLR between schizophrenia patients and control groups. Our study is the first of its kind in the

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literature to compare the NLR, PLR, and MLR values during both relapse and remission periods of the same patients.

2. Material and methods

2.1. Participants

Our study was conducted with the retrospective analysis of complete blood count (CBC) of patients diagnosed with schizophrenia who were hospitalized at Ondokuz Mayıs University Medical Faculty Psychiatry Service between 2012 and 2016. Of the patients who were hospitalized and present for outpatient followup after discharge, those who had CBC within the first two days of hospitalization and followup remission CBC were included in the study. Those who had chronic illness (infection diseases, hypertension, diabetes mellitus, autoimmune disease) other than schizophrenia or taking drugs other than antipsychotic medicines (steroids, nonsteroid antiinflammatory drugs, antibiotics) that could interfere with CBC values were excluded from the study. Remission was determined by clinical examination by two experienced psychiatrists during outpatient followup and Positive and Negative Syndrome Scale (PANSS) assessment conducted by a psychologist. A total of 105 patients (62 male, 43 female) diagnosed with schizophrenia were included in the study.

The control group included 105 healthy donors who were age and gender matched from the blood bank of the same hospital. Individuals with chronic diseases and the drugs that could affect inflammation were screened and excluded through forms from the blood bank.

2.2. Variables and measurements

In patients who received inpatient treatment for psychotic episode; CBC taken within two days of admission were considered relapse parameters. The treatment continued with outpatient followup after discharge. Remission was confirmed at outpatient followup with clinical interview and PANSS scores. According to PANSS, remission parameters were accepted as an average score of 2 (minimum) or less from the items in all of the three scales suggested by Yen et al. (2002). Medical records of the patients were evaluated and those who received anti-inflammatory treatment (nonsteroid anti-inflammatory drugs, corticosteroids, other) that could affect blood values or those who had systemic diseases that could cause abnormal blood results (COPD, cardiac disease, hematologic disease, malignancy, etc.) were excluded from the study. Twenty seven patients were excluded from the study due to exclusion criteria. White blood count (WBC), neutrophil count, lymphocyte count, platelet count, and monocyte count were noted and NLR, PLR, and MLR were calculated.

2.3. Ethical statement

The study received ethics approval from the hospital's ethical committee.

2.4. Statistical analysis

Statistical analysis was conducted using the SPSS 15.0 package program. Kolmogorov Smirnov test was used to test normal distribution of the variables of the groups. Chi-square and Mann Whitney *U* tests were used to assess descriptive data. Mann Whitney *U* test was used to assess the non-normally distributed data of independent groups, while *T* test was used to assess normally distributed data. Wilcoxon test was used to assess the non-normally distributed data of the dependent groups. $P < 0.05$ was considered statistically significant.

3. Results

No statistically significant difference was found between patient and control groups in terms of age or gender. The average duration of disease was 9.7 years while average number of hospitalizations was 3.3; and there was no significant difference between genders in these variables. In remission, average PANSS positive symptom subscale score was 8.38, negative symptoms subscale score was 11.33, general psychopathology subscale was 19.53, and total score was found as 39.25 (Table 1).

NLR, PLR, and MLR of the patients during relapse period were found to be significantly higher when compared with the control group (Fig. 1). In addition, neutrophil count, platelet count, and monocyte count during relapse period was significantly higher than the control group, while lymphocyte count was significantly lower (Table 2).

MLR and PLR were significantly higher in the remission period when compared with the control group and lymphocyte count was significantly lower (Table 3).

NLR, PLR, and MLR values of the patients in the relapse period were significantly higher when compared with the remission period of the same patients (Fig. 1). In addition, WBC, neutrophil, platelet, and monocyte counts of the patients in the relapse periods were significantly higher when compared with the remission period. No significant difference was found between relapse and remission periods in terms of lymphocyte count (Table 4).

When blood was taken for relapse, 65 of the 105 patients had not taken medication for various reasons. There was no statistically significant differences between the patients who continued and discontinued medication. The medication used between relapse and remission periods was unchanged in 56 patients. In 25 patients, one or more drugs had been added or removed from treatment during the period until remission. In 24 patients, the medication taken during the relapse period was completely changed during the remission period. No significant difference was found between the blood levels of these three groups. Clozapine, known to have side effects on the hematopoietic system, was compared with other antipsychotics in terms of variables.

Table 1
Characteristics of patients with schizophrenia and healthy comparison subjects.

		Average age†(mean ± SD)		*T* value	*P* value
Patient(*n*:105)		32.83 ± 8.29		−0.281	0.779
Control(*n*:105)		33.19 ± 9.82			
		Gender‡		χ^2	***P* value**
		Male	**Female**		
Patient (*n*:105)		62	43	0.000	1.000
Control (*n*:105)		62	43		
		Disease duration†		***U* value**	***P* value**
Patient(*n*:105)	**Male (*n*:62)**	9 (4–13)		1290.50	0.831
	Female (*n*:43)	8 (4–14.25)			
	Total (*n*:105)	8 (4–14)			
		Number of hospitalizations‡		***U* value**	***P* value**
Patient(*n*:105)	**Male (*n*:62)**	3 (1–5)		1159	0.274
	Female (*n*:43)	2 (1–4)			
	Total (*n*:105)	2 (1–4)			
		Average of scale score ± SD			
	Total	39.25 ± 6.41			
Patient PANSS scores (*n*:105)	**PS**	8.38 ± 2.33			
	NS	11.33 ± 2.48			
	GPS	19.53 ± 4.24			

Data are expressed as the means ± standard deviation (SD) for normally distributed variables or as the median (interquartile range) for non-normally distributed variables.†: Years, ‡: Numbers.
PANSS: Positive and Negative Syndrome Scale, PS: Positive Scale, NS: Negative scale, GPS: General psychopathology scale.

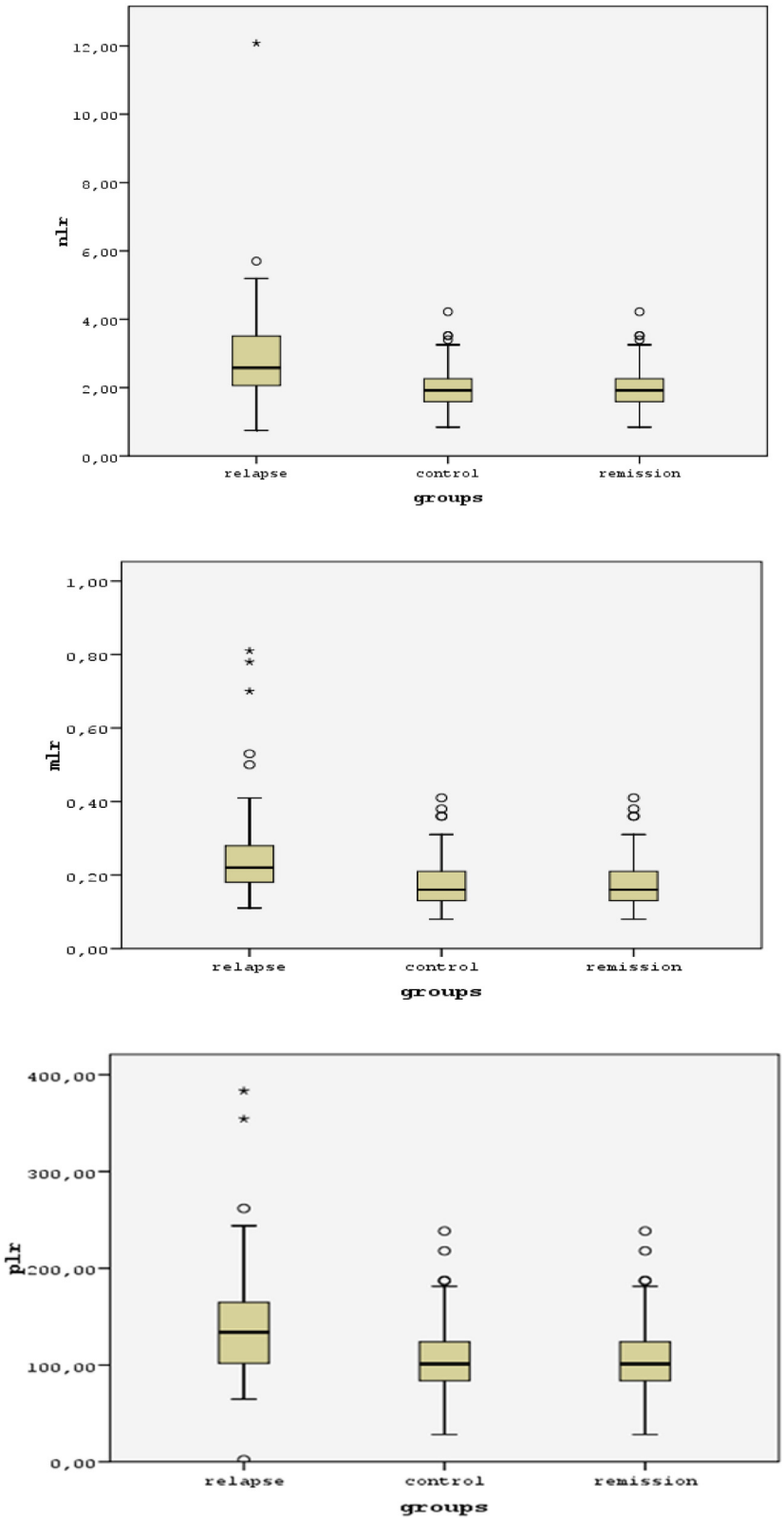

Fig. 1. NLR, MLR and PLR values in groups.

There were no significant differences between the patients who did and did not use clozapine. A total of 66 patients used only atypical antipsychotics, 8 used only typical antipsychotics, while the remaining 31 used a combination of typical and atypical antipsychotics. There were no statistically significant differences between these three groups.

4. Discussion

In our study, neutrophil, platelet, monocyte, and lymphocyte counts and NLR, PLR, and MLR measurements in relapse periods of patients were significantly different from the control group. Of these values,

Table 2
Comparison of relapse period and healthy control.

	Relapse(*n*:105)	Control(*n*:105)	*U*	*Z*	*P* value
NLR	129.53 (1.47)	81.47 (0.68)	2989.50	−5.73	0.000
PLR	126.69 (63.70)	84.31 (41.19)	3287.50	−5.05	0.000
MLR	130.62 (0.11)	80.38 (0.08)	2874.50	−5.99	0.000
WBC	112.73 (3.28)	98.27 (2.00)	4753.50	−1.72	0.085
Neutrophil	117.60 (2.62)	93.40 (1.50)	4242.50	−2.88	0.004
Platelet	114.89 (90.50)	96.11 (59.50)	4527.00	−2.23	0.025
Lymphocyte	88.18 (0.84)	122.82 (0.80)	3693.50	−4.13	0.000
Monocyte	114.21 (0.22)	96.79 (0.20)	4598.00	−2.08	0.037

Mann Whitney *U* test was used to compare the groups. Values are given as mean rank. The values in parentheses are interquartile ranges.
WBC: White Blood Cell, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, MLR: monocyte lymphocyte ratio.

Table 3
Comparison of period and healthy control.

	Remission (*n*:105)	Control (*n*:105)	*U*	*Z*	*P* value
NLR	112.58 (1.37)	98.42 (0.68)	4769.00	−1.77	0.076
PLR	119.63 (50.98)	91.37 (41.19)	4028.50	−3.37	0.001
MLR	117.24 (0.08)	93.76 (0.08)	4280.00	−2.80	0.005
WBC	100.54 (2.51)	110.46 (2.00)	4991.50	−1.18	0.237
Neutrophil	101.09 (1.72)	109.91 (1.50)	5049.00	−0.91	0.360
Platelet	111.42 (48.50)	99.58 (59.50)	4890.50	−1.52	0.158
Lymphocyte	90.98 (0.70)	120.02 (0.80)	3988.00	−3.46	0.001
Monocyte	104.56 (0.17)	106.44 (0.20)	5414.00	−0.22	0.822

Mann Whitney *U* test was used to compare the groups. Values are given as mean rank. The values in parentheses are interquartile ranges.
WBC: White Blood Cell, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, MLR: monocyte lymphocyte ratio.

Table 4
Comparison of during remission and relapse period.

	Relapse(*n*:105)	Remission(*n*:105)	*Z*	*P* value
NLR	119.80 (1.47)	91.20 (1.37)	−3.90	0.000
PLR	112.84 (63.70)	98.16 (50.98)	−2.35	0.019
MLR	121.01 (0.11)	89.99 (0.08)	−4.58	0.000
WBC	115.68 (3.28)	95.32 (2.51)	−3.21	0.001
Neutrophil	119.04 (2.62)	91.96 (1.72)	−3.81	0.000
Platelet	110.17 (90.50)	100.83 (48.50)	−2.08	0.033
Lymphocyte	101.92 (0.84)	109.08 (0.70)	−1.46	0.143
Monocyte	116.51 (0.22)	94.49 (0.17)	−3.24	0.001

Wilcoxon Rank Sum Test was used to compare the groups. Values are given as mean rank. The values in parentheses are interquartile ranges.
WBC: White Blood Cell, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, MLR: monocyte lymphocyte ratio.

only lymphocyte count was found to be lower in the patient group while all other values were higher. The association between schizophrenia and inflammation has been known for a long time (Horrobin, 1977). The inflammation hypothesis of schizophrenia has been supported with associations with proinflammatory cytokine increase (Miller et al., 2011; Al-Hakeim et al., 2015), various infectious diseases (Mortensen et al., 2007; Brown and Derkits, 2010; Krause et al., 2010), and autoimmune diseases (Eaton et al., 2006). Previous studies have shown neutrophilia and lymphopenia to be the body's response to systemic inflammation, trauma, and stress (Zahorec, 2001). Semiz et al. (2014) and Yuksel et al. (2018) found higher NLR values in patients with schizophrenia compared to the control group. High neutrophil count and low lymphocyte count was also consistent with our study (Semiz et al., 2014). Lymphocyte count was found to be lower and neutrophil count was found to be higher in schizophrenia patients with onset of initially positive symptoms. In addition, elevated neutrophil count or decreased lymphocyte count was found to be associated with decreased response of positive symptoms to treatment in a 6 month period (Zorrilla et al., 1998). Significant changes in inflammation markers of patients during the relapse period when compared with the control group support the inflammation hypothesis of schizophrenia. Elevated MLR and PLR in the relapse period of schizophrenia is an innovative information.

Lymphocyte count, PLR, and MLR values in the remission period of the disease were significantly different when compared with the control group. Lymphocyte count was found to be lower and PLR and MLR values were higher when compared to the control group. In the schizophrenia patients, cortisol levels during remission were significantly higher when compared to the control group (Girshkin et al., 2014). Increased cortisol levels were shown to cause decrease in lymphocyte count (Castelino et al., 1997). Therefore, decreased lymphocyte count can be expected during remission in patients with schizophrenia due to high cortisol levels. Meyer et al. observed a decrease in inflammatory symptoms following antipsychotic treatment (Meyer et al., 2009). The results of our study support this finding. That is, some of the findings that were indicators of inflammation during the relapse period regressed after antipsychotic treatment. While first episode schizophrenia patients had minimal changes, patients with multiple episodes had more severe changes in inflammatory parameters, when compared to the control group (Frydecka et al., 2018). Chronic peripheral inflammation of schizophrenia (Fond et al., 2015) may be related to the fact that the markers of inflammation do not return to normal in remission. However, differences in some values relative to the control group suggest that the inflammatory process persists, even during the remission period in schizophrenia patients.

When blood values of the patients in the relapse period were compared with blood values in the remission period, NLR, PLR, and MLR values and neutrophil, platelet and monocyte values were found to be significantly higher in the relapse period. No significant difference was found between lymphocyte levels. That is, neutrophil, platelet, and monocyte counts along with NLR, PLR, and MLR values of the patients decreased with treatment. The continuation of antipsychotic treatment in these patients after discharge and the fact that the disease was in remission period may have caused the change in blood values. First episode psychosis patients were found to have significantly decreased white blood cell and neutrophil count and elevated lymphocyte count following antipsychotic treatment (Stefanović et al., 2015). Changes were also found in cytokine levels, which play an important role in inflammation, following antipsychotic treatment during the relapse period (Miller et al., 2011). Changes in the blood parameters of patients following treatment are similar to previous studies. More contradictory results are found in terms of lymphocyte count (Semiz et al., 2014, Stefanović et al., 2015). Methodical difference may be the cause of this contradiction. In our study, lymphocyte count did not change after treatment. Lymphocyte counts in the relapse and remission periods were lower than in the control group, and there was no difference between them, suggesting that decreased lymphocyte count may be a trait marker of the disease. Because of its nature, schizophrenia increases serum cortisol levels, since it is a chronic psychiatric disease, and this suggests it causes decreased lymphocyte count when compared with controls in both relapse and remission periods (Girshkin et al., 2014). Inflammation has been shown to continue during the remission period (Muller et al., 2015). Other findings, excluding lymphocyte count, are similar to the results of studies which show decrease in inflammatory parameters following antipsychotic treatment (Jaehne et al., 2015; Stefanovic et al., 2015; Handley et al., 2016). Therefore, it can be said that there is a decrease in inflammatory response in remission period of schizophrenia following treatment.

It is known that lymphocyte count and function play an important role in the pathogenesis of schizophrenia. In a meta-analysis, lymphocyte counts in first episode schizophrenia patients were higher than the control group. However, lymphocyte count was lower in patients with recurrent episodes of the disease and in remission periods than in controls (Miller et al., 2013). Decreased lymphocyte count in chronic schizophrenia has been shown in many studies (Kulaksizoglu and

Kulaksizoglu, 2016, Semiz et al., 2014).

One of the limitations of our study was the absence of PANSS scores during the hospitalization period of the patients. The study's retrospective nature was another limitation. The patients were not evaluated in terms of confounding factors such as inflammatory diseases that may have occurred between relapse and remission periods. Furthermore, the WBC subtypes (Th1, Th2, NK lymphocyte etc.) were undetermined in our study, which may have caused difficulty in the evaluation of results.

The results of our study contribute to the inflammation hypothesis of schizophrenia. NLR, PLR, and MLR, which are considered indicators of inflammation, were found to be increased during the relapse period, while PLR and MLR were found to be significantly elevated in the remission period when compared to the control group. In addition, significant differences in lymphocyte count in both the relapse and remission periods when compared with the control group, but the fact that there were no differences between the two periods, suggest that lymphocyte count may be a trait marker of the disease, while significant differences between the three groups in terms of MLR and PLR brought to mind that they may be state markers of the disease. NLR value was found to be elevated only in the relapse period while it was found to be similar to the controls in the remission period.

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Conflict of interest

None to declare.

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