



Research

Increased Neutrophil to Lymphocyte and Platelet to Lymphocyte Ratios in Patients with First Episode Psychosis

İlk Epizod Psikoz Hastalarında Artmış Nötrofil/Lenfosit ve Trombosit/Lenfosit Oranı

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ABSTRACT

Objective: Inflammatory processes have a main role in the etiopathogenesis of psychosis. The aim of current study was to examine differences between the patients with the first episode psychosis's (FEPP) neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) levels with the healthy control groups. The NLR and PLR are indicators that may define the existence of systemic inflammatory response.

Methods: The participants of this study included 37 FEPP and 43 healthy individuals who had similar socio-demographic characteristics compared to the patient group. The Positive and Negative Syndrome Scale was conducted to collect data from the patient group. Additionally, participants' complete blood count parameters were analyzed for the study.

Results: The mean NLR and PLR levels of FEPP were significantly higher than the healthy control individuals ($p=0.001$ and $p=0.045$). There was no relationship between demographic variables, body mass index, smoking, severity of disease and NLR-PLR.

Conclusion: Based on the literature review and electronic database search, no previous study evaluated PLR in the context of FEP. Therefore, the current study was first examining both NLR and PLR levels in FEP as hematologic inflammatory indicators. Our results indicated that inflammatory processes may play a role in the etiopathogenesis of psychosis.

Keywords: The first episode psychosis, inflammation, lymphocyte, neutrophil, platelet

ÖZ

Amaç: Enflamatuvar süreçler psikozun etiopatogenezinde anahtar bir role sahiptir. Mevcut çalışmanın amacı, ilk epizod psikoz hastalarında (İEP) nötrofil ile lenfosit oranı (NLO) ve trombosit ile lenfosit oranı (PLO) düzeyleri arasındaki farklılıkları sağlıklı kontrol grubu ile incelemektir. NLO ve PLO sistemik enflamatuvar yanıtın varlığını tanımlayabilecek göstergelerdir.

Gereç ve Yöntem: Bu çalışmaya 37 İEP hastası ve hasta grubu ile benzer sosyodemografik özelliklere sahip 43 sağlıklı gönüllü birey dahil edilmiştir. Hasta grubundan verilerin elde edilebilmesi için Pozitif ve Negatif Sendrom Ölçeği uygulandı. Buna ek olarak, tüm katılımcıların tam kan sayımı parametreleri analiz edildi.

Bulgular: İEP hastalarının ortalama NLO ve PLO düzeyleri sağlıklı kontrol bireylerine göre istatistiksel olarak anlamlı derecede yüksekti ($p=0,001$ ve $p=0,045$). Demografik değişkenler, vücut kitle indeksi, sigara kullanımı, hastalık şiddeti ile NLO ve PLO arasında bir ilişki bulunamamıştır.

Sonuç: Literatür taraması ve elektronik veri tabanları aramasına dayanarak, daha önce yapılan hiçbir çalışmada PLO, İEP bağlamında değerlendirilmemiştir. Bu nedenle, mevcut çalışma İEP'de hemaolojik enflamatuvar göstergeler olarak hem NLO hem de PLO düzeylerini inceleyen ilk çalışmadır. Sonuçlarımız, enflamatuvar süreçlerin psikozun etiopatogenezinde bir rolü olabileceğini göstermiştir.

Anahtar Kelimeler: İlk epizod psikoz, enflamasyon, lenfosit, nötrofil, trombosit

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INTRODUCTION

The first episode psychosis (FEP) is the presence of the first psychotic symptoms in an individual. Few previous studies of FEP have examined neutrophil-lymphocyte ratio (NLR) in schizophrenia (SP) (1,2). Psychosis is a progressive, chronic and multifactorial psychiatric disorder affecting approximately 1-2% of people in the world. Studies showed that psychosis is characterized by the positive and negative psychotic symptoms, affective cognitive and psychosocial impairment (3,4). Even though researchers have not fully understood the cause and pathophysiology of psychosis, it has been reported that the immune system affects the brain and behavior through the recognized biological mechanisms (4-6). In the literature, it was known that there was a significant correlation between inflammation and psychosis (4-6). Another finding of the same studies was that the relationship between inflammation and psychosis focused to measure cytokines. As a result, the authors found that assessing cytokines showed increased levels of peripheral proinflammatory cytokines and indicators (4,6).

Leukocytes can perform different tasks in the immune system (7). For example, it has an important role in mediating inflammation. When examined more carefully, changes in the number of leukocytes may reflect the reaction of the immune system in case of inflammation (7). From here, we can derive the NLR by calculating the number of leukocytes. This is an important indicator of clinical outcomes in neuroimmune disorders (1,8,9). If addressed in terms of applicability and affordability, the NLR, as a new indicator of chronic and low-grade inflammation, is an inexpensive and repeatable test (1,8,9). Platelets are another structure included in proinflammatory secretion along with leukocytes, anti-inflammatory processes and progenitor cells accumulated in the inflammatory regions. The platelet-lymphocyte ratio (PLR) is a commonly used simple indicator that appears to be correlated with inflammation, cardiovascular and chronic diseases (1,8-10). Abnormal platelet counts and mean platelet volume parameters have been determined in some psychiatric disorders including unipolar depression, bipolar disorder and SP (1,11,12). The NLR and PLR have been used recently as an indicator in the diagnosis of various neuropsychiatric disorders. In particular, studies have shown that it has worked correctly in neuropsychiatric disorders, such as Alzheimer's disease, Parkinson's disease, bipolar disorder and SP (8,9,11,12).

A complete blood count test is cheap and can easily be performed in all laboratories that have basic tools. In other words, the NLR, PLR and other all blood counts can be

evaluated by clinicians using blood count test, which is a quick and cheap method. For instance, Varsak et al. (2) evaluated the NLR in patients with FEP (FEPP). They found that the NLR was significantly higher in FEPP compared to the control groups. However, the NLR was not significantly correlated with the severity based on Brief Psychiatric Rating Scale score. Based on our literature review, previous studies did not focus on the evaluation of the PLR in the context of FEPP. Hence, the main purpose of our study was to investigate whether there were relationships between the FEP and inflammation using the NLR-PLR or not. The second purpose was also to compare the NLR-PLR values of the FEPP with the healthy control groups

METHODS

Participants and Measures

The participants of this study included 37 patients who had the FEP and 43 healthy volunteers who were randomly selected based on the body mass index (BMI). Patients admitted to a public hospital psychiatric outpatient clinic and diagnosed with the FEP by a psychiatric specialist were included in the study. Patients with previous psychiatric diagnoses were excluded from the study. The first group consisted of participants with non-affective drug-naïve FEP. The second group included a control group (healthy participants). The FEPP who takes antipsychotics and affective psychosis patient was excluded from the study. Other criteria for exclusion were the presence of substance use disorders, psychiatric disorders other than FEP, other chronic diseases, such as hypertension, diabetes mellitus, dyslipidemia, presence of an organic condition, epilepsy or another severe neurological disorder, presence of infectious disease, pregnancy and women in the menstrual cycle. In total, eight participants with additional exclusion criteria were excluded from the study from 45 patients diagnosed with psychosis.

We collected socio-demographic information including gender, age, smoking, and BMI. All the participants underwent a physical and neurological evaluation. We conducted the study following the principles of the Declaration of Helsinki. The relevant Kilis 7 Aralık University Ethics Committee approved the study protocol (decision no: 5, date: 02.03.2020). The informed consent form was distributed and obtained from all participants. As the measure, the Positive and Negative Syndrome Scale (PANSS) was used to collect data and assess the severity of the psychosis symptoms in the patients (13). Neurological examinations were carried out by the psychiatric specialist who is the first author.

We analyzed complete blood count parameters in all participants. The blood samples were obtained from participants who were fasting between 8 and 10 am using a standard venipuncture technique from antecubital veins. The blood sample was drawn only once, just before the treatment began. The samples were studied at the biochemistry lab on the same day. The accepted reference values were white blood cell (WBC): 4.0-11.0 (/mm³), red blood cell: 4.0-6.2 (K/uL), platelet: 150-450 (K/uL), lymphocyte: 1.0-4.8 (/mm³), and neutrophile: 2.0-7.7 (/mm³).

Statistical Analysis

All the statistical analyses were conducted on Number Cruncher Statistical System (NCSS) version 2007 software (NCSS, Kaysville, UT, USA). The descriptive data included mean, standard deviation, frequency and rate. The Shapiro-Wilk test and graphical examinations were used to assess the normality of the data. The normally distributed quantitative data were compared between two groups using an independent samples t-test. The Pearson's chi-square test was conducted to compare qualitative variables. Pearson's correlation analysis was used to evaluate the relationship among the quantitative variables. Cohen's d values were calculated to measure the degree of effect size of significant differences. Power analysis was performed using the G*Power 3.1 statistical power analysis program to measure the competence of the number of participants in the study in calculating statistical analyses.

RESULTS

The FEPP group consisted of 20 males (54.0%) and 17 females (46.0%). The control group included 23 males (53.4%) and 20 females (46.6%). The results indicated that there was not a significant difference between FEPP's and control groups's age (29.73±11.23 years and 29.32±7.71 respectively, $p>0.05$). Socio-demographic information of the participants was reported in Table 1.

The NLR value of FEPP was 2.56±0.91 and the control was 1.88±0.78. The NLR value of FEPP was significantly higher than participants in the control group ($p=0.001$). PLR value of FEPP was 0.14±0.04 and the controls was 0.12±0.04. The PLR value of FEPP was significantly higher than the control group ($p=0.045$). In terms of the relationship between variables, there was no relationship between socio-demographic variables, BMI, smoking, and NLR-PLR ($p>0.05$). Biochemical characteristics of the participants were summarized in Table 1. Additionally, the results indicated that relationship between the severity of disease and NLR ($p=0.940$); and PLR ($p=0.819$) were not significant.

Cohen's d was calculated to understand the magnitude of differences in the variables of neutrophil, lymphocyte, NLR and PLR. The effect sizes for neutrophil ($d=0.59$) and lymphocyte were medium ($d=0.50$), for NLR was large ($d=0.92$) and for PLR was small ($d=0.46$). The post hoc power analyses were conducted for independent samples t-tests. The results indicated that the power was achieved for neutrophil (0.83) and NLR (0.99). However, lymphocyte (0.72) and PLR (0.65) were under 0.80.

DISCUSSION

Researchers have examined the relationship between psychosis and inflammation for a long time. Results of the previous studies (4-6) supported the hypothetical relationship of SP with proinflammatory cytokine increase, various infectious diseases, metabolic syndrome, cardiovascular diseases and autoimmune diseases (4-6).

The main purpose if this study was to examine the associations between the NLR-PLR and the FEP. The findings of this study were as follows: 1) Increased NLR and PLR were found to be significantly higher in FEPP. 2) There was no relationship between socio-demographic variables, BMI, smoking, and NLR-PLR. 3) There was no relationship between NLR-PLR and severity of disease (PANSS total scores).

Abnormal ultrastructure of blood cell formation and blood cell count in SP was reported in some studies (14). Total WBC count -even inside the normal range- is an indicator of low-grade inflammation, which can encourage vascular injury and atherosclerosis (15). When the relationship between SP and neuroinflammation is evaluated; the results showed differences in serum levels of cytokines such as interleukin-1 (IL-1), IL-2, IL-6, interferon-gamma, and tumor necrosis factor (TNF)-alpha (16,17). A positive relationship between NLR-PLR and inflammatory markers including IL-6 and TNF-alpha was found (18). In addition to inflammation, NLR reflected inflammation in the blood vessel wall, while PLR was indicative of high blood viscosity (19,20). In several studies, the results indicated that schizophrenia patients had higher NLR values than control groups (healthy patients) (1,11,21). Three studies investigated the NLR values in FEPP. Similar to the current study, two of the studies followed similar procedures. A study demonstrated that the experimental group (patients) had higher levels of NLR compared to the control group (2,22). Meanwhile, the other study did not find differences in NLR in patients compared to controls (23).

Researchers stated that the PLR was a more sensitive indicator of inflammation than the NLR (24,25). Platelets display a significant role in atherogenesis, particularly

Table 1. Characteristics of the participants

Variables	FEPP group (n=37)	Control group (n=43)	Significance	p
Age (years)	29.73±11.23	29.32±7.71	0.190*	0.850
Sex (female/male)	17/20	20/23	0.003**	0.960
BMI (kg/m ²)	24.53±4.86	24.15±3.44	0.412*	0.682
Smoking (+/-)	16/21	12/31	2.056**	0.152
PANSS total score	100.64±17.79	-	-	-
WBC count (/mm ³)	8.04±1.84	7.39±1.95	1.505*	0.136
RBC count (K/uL)	4.87±0.51	4.97±0.58	-0.780*	0.438
Platelet (K/uL)	278.10±48.47	271.37±58.76	0.545*	0.587
Lymphocyte (/mm ³)	2.10±0.57	2.40±0.64	-2.203*	0.031
Neutrophil (/mm ³)	5.27±1.62	4.33±1.53	2.652*	0.010
NLR	2.56±0.91	1.88±0.78	4.068*	0.001
PLR	0.14±0.04	0.12±0.04	2.037*	0.045

BMI: Body mass index, NLR: Neutrophil-lymphocyte ratio, PANSS: Positive and Negative Syndrome Scale, PLR: Platelet-lymphocyte ratio, WBC: White blood cell, RBC: Red blood cell, FEPP: Patients with the first episode psychosis, *Independent sample t-test, **Pearson's χ^2 test; $p < 0.05$

in the progress of inflammation (26,27). Platelets may interplay with several cell types including neutrophils, endothelial cells, T-lymphocytes and mononuclear phagocytes. As stated in the literature, platelets may initiate and exacerbate inflammation on the arterial wall due to its interactions with other cell types especially leukocytes (28,29). It was found higher PLR levels bipolar disorder patients compared to healthy controls in a study (30). Moreover, the results indicated that the NLR and PLR were significantly higher in attention deficit hyperactivity disorder patients than in the control group (31). When the previous studies were reviewed, there was a dearth of studies evaluated the PLR in the context of the FEPP. Hence, this study is the first to demonstrate increased PLR levels in the FEPP. Based on the results of literature and current study's findings, we think that increased NLR-PLR levels may reflect inflammation in SP.

In our study, no significant differences were found between NLR-PLR and severity of disease (PANSS total score). Even though, it was found that NLR at clinical remission decreased compared with the acute psychotic state in a psychotic adolescent group (32), the NLR appeared not to be related to the severity of disease in the FEP and SP (2,11). In another study conducted by Kulaksizoglu and Kulaksizoglu (21) found significant relationship between the severity of disease and NLR. In this study, there was not a significant difference between gender and NLR-PLR in all subjects. However, it was reported that circulating neutrophils, fewer lymphocytes, and higher NLR levels had been found after major surgery in female patients (33). In

our study, no significant differences were found between NLR-PLR and severity of disease, we think that it had a relatively small sample size.

Another important finding worth discussion is the differences between NLR-PLR and smoking. The results showed that there was no significant difference between NLR-PLR and smoking. Smoking seems to be associated with increased NLR in the previous studies in general population and increased neutrophil and lymphocyte counts (34-37). However, the PLR was not associated with smoking in the general population (35,37), and similarly no significant difference was found between PLR and smoking in our study. Lack of evidence was reported more frequently that there was a relationship between platelet count and smoking (38,39); even though, lower platelet counts in smokers were also determined (37,40,41).

In this study, the BMI was not significantly correlated with NLR-PLR. However, there are studies claiming the opposite of our findings stating the BMI was related to increased NLR in the general population (34,42) and obesity is often considered to be related to chronic inflammatory conditions (43,44). Hence, dietary habits are considered to influence both leukocyte and platelet counts (45).

Nonetheless, there are some limitations to this study. The first limitation is related to this study's data. This study had cross-sectional data and collected from only one psychiatric clinic. It had a relatively small sample size. Therefore, it affected the power of PLR and lymphocyte; and this prevents the generalization of the findings related to these variables.

We believe that the analysis of inflammatory cytokines, such as cortisol, IL-1, IL-6 as well as NLR, PLR would allow a better understanding of the complex relationship with a higher sample size.

CONCLUSION

Consequently, no previous studies have examined PLR in the context of FEPP. This study was the first to show the NLR-PLR levels (the hematologic inflammatory markers) in the FEPP. Both the NLR and PLR levels in the FEPP were higher than controls among our participants. The NLR and PLR are basic, easy, and inexpensive instruments that should be used for predicting the systemic inflammatory response in the FEPP.

ETHICS

Ethics Committee Approval: We conducted the study following the principles of the Declaration of Helsinki. The relevant Kilis 7 Aralık University Ethics Committee approved the study protocol (decision no: 5, date: 02.03.2020).

Informed Consent: The informed consent form was distributed and obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: M.Ş., C.S., Concept: M.Ş., M.A.K., E.Ö.Ç., D.A., C.S., Design: M.Ş., C.S., Data Collection or Processing: M.Ş., Analysis or Interpretation: M.Ş., M.A.K., E.Ö.Ç., D.A., C.S., Literature Search: M.Ş., M.A.K., E.Ö.Ç., D.A., C.S., Writing: M.Ş., M.A.K., E.Ö.Ç., D.A., C.S.

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