Neutrophil-to-lymphocyte ratio and platelet distribution width: A potential new peripheral biomarker in adolescent depression

Nötrofil-lenfosit oranı ve trombosit dağılım genişliği: Adolesan depresyonunda potansiyel yeni bir periferik biyobelirteç

Masum Ozturk[1], Yekta Ozkan[2], Sermin Yalin Sapmaz[3], Hasan Kandemir[4]

[1]M, D., Dicle University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Diyarbakır, Turkey, https://orcid.org/0000-0002-9989-7051

[2]M.D., Çankırı State Hospital,Department of Child and Adolescent Psychiatry, Çankırı, Turkey, https://orcid.org/0000-0003-2220-9967

[3]Assoc. Prof., [4]Prof., Manisa Celal Bayar University, Faculty of Medicine, Department of Child And Adolescent Psychiatry, Manisa, Turkey, https://orcid.org/0000-0002-1084-5053, https://orcid.org/0000-0002-1138-4973

SUMMARY

Objective: The aim of this study is to evaluate the role of inflammation in the underlying pathophysiology of adolescent depression by evaluating neutrophile-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and hemogram parameters and also to determine whether there is a relationship between depression severity and inflammatory parameters. **Method:** This retrospective study was carried out on 93 major depressive disorder (MDD) patients and 65 healthy control. Clinical features such as diagnosis date, diagnosis during admission to hospital using DSM-5 diagnostic criteria, comorbid physical and psychiatric illness, drug use, previous psychiatric diagnosis, history of suicide attempt were determined. In addition, hemogram parameters of the participant included in the study in the hospital data system were used. **Results:** NLR and platelet distribution width (PDW) were found to be statistically significantly higher in the patient group than in the control group ($p<0.05$). A weakly significant positive correlation ($p=0.039$, $r=0.165$) was found between NLR and depression severity scale; a positive correlation was found between PDW and depression scale scores and depression severity scale total scores ($p<0.001$, $r=0.317$; $p<0.001$, $r=0.320$, respectively). **Discussion:** NLR and PDW were found to be significantly higher in patients with MDD than in healthy controls, and it supports the possible role of low-grade inflammation in the pathophysiology of MDD. In the next years, prospective studies in which hemogram parameters are evaluated together with proinflammatory cytokines will more clearly illuminate the role of inflammation and platelet activation in the etiology of MDD in adolescents.

Key Words: depression, adolescent, neutrophile-lymphocyte ratio, platelet distribution width, inflammation

ÖZET

Amaç: Şizofreni, otizm spektrum bozukluğu ve dikkat eksikliği hiperaktivite bozukluğu (DEHB) gibi nörogelişimsel bozuklukların bağırsak-beyin ekseniyle ilişkili olabileceği son zamanlarda vurgulanmıştır. Zonulin, gastrointestinal mukoza hücreleri arasındaki sıkı bağlantıların bütünlüğünü değiştiren bir proteindir. DEHB'li çocuklarda serum zonulin düzeylerini ve semptom şiddeti ile ilişkisini araştırmayı amaçladık. **Yöntem:** 21 DEHB hastası ve 19 kontrol dahil edildi. Zonulin seviyeleri kan örneklerinden elde edildi. DEHB belirtilerinin klinik şiddeti, Conners' Ebeveyn Derecelendirme Ölçeği-Gözden Geçirilmiş/Uzun Form (CPRS-R/L) ve Conners' Öğretmen Derecelendirme Ölçeği-Gözden Geçirilmiş/Uzun Form (CTRS-R/L) ile değerlendirildi. **Bulgular:** Gruplar arasında yaş, cinsiyet ve vücut kitle indeksi (VKİ) açısından anlamlı fark yoktu. DEHB grubunun ortalama serum zonulin düzeyi 13.45 ± 9.08 ve kontrol grubunda 21.32 ± 19.96 idi. Gruplar arasında anlamlı fark yoktu ($t=1.99$, $p=0.51$). DEHB grubunda serum zonulin düzeyleri ile CTRS-R / L skorları arasında anlamlı korelasyon ($R=0.82$, $p<0.01$) bulundu. Bu korelasyon, VKİ ve cinsiyet değişkenleri kontrol edildiğinde de devam etti ($R=0.85$, $p<0.01$). **Sonuç:** DEHB semptom şiddeti ile serum zonulin düzeyleri arasında anlamlı bir ilişki bulunmakla birlikte, DEHB olan çocuklar ve kontroller arasında anlamlı bir fark bulunamamıştır.

Anahtar Sözcükler: Dikkat eksikliği, zonulin, çocuk, bağırsak

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INTRODUCTION

Epidemiological studies have revealed that the prevalence of depression is between 2% and 8% in youth. Although most young people with major depressive disorder (MDD) recover after their first depressive episode, 40% to 70% of them suffer a relapse within 3 to 5 years. (1). MDD is associated with an increased risk of suicide, poor school performance, deterioration in social skills, social withdrawal, and substance use in childhood and adolescence (2). Despite increasing studies in recent years, the patophysiology of major depressive disorder is still not fully elucidated. Studies have focused on various mechanisms such as alterations in serotonergic, noradrenergic, dopaminergic and glutamatergic systems, increase in inflammation, abnormalities of hypothalamo-pituitary axis, vascular changes and decreased neurogenesis. While the various biological mechanisms existed in depression indicate that MDD may actually represent several biologically different diseases, studies have shown that all these pathways are interrelated (3).

Increasing evidence highlights the role of low-grade inflammation in the underlying pathophysiology of MDD (4, 5). Smith first revealed that inflammation caused by macrophages had an important role in the pathophysiology of depression (6). Subsequent studies reported a close relationship between proinflammatory changes and depression (7). It was found that the levels of inflammatory markers such as IL-1β, IL-2, IL-6, TNF-α, CRP and PGE2 increase in patients with depression (8). High levels of inflammatory markers and proinflammatory cytokines in MDD, the relationship between MDD and many different factors (stress, medical diseases, obesity, inadequate diet, decrease in sleep duration, social isolation) resulting in an increase in inflammatory markers, the mood affected by the drugs that affect the immune system (such as interferon), the high incidence of MDD in inflammatory or autoimmune diseases, the similarity of major depression between the situation called "illness behavior" in response to the increase of proinflammatory cytokines in infection or inflammation, the effect of psychotropic drugs-especially antidepressant drugs on inflammatory processes supports the role of inflammatory mechanisms in the pathophysiology of major depressive disorder (9, 10).

Neutrophiles, lymphocytes, and platelets play a role in the control of inflammation, and systemic inflammation is associated with changes in the amount and composition of blood cells in circulation (11). Neutrophiles are the first defense cells of innate immunity that contribute to phagocytosis and apoptosis via inflammatory mediators. Lymphocytes represent the regulatory and protective part of the immune response (12). It has been stated that the neutrophile/lymphocyte ratio (NLR) is an indicator of systemic inflammation and stress in important diseases (13). In addition, it has been found that the level of CRP, which is frequently used and which is an indicator of inflammation, has a high correlation with white blood cell count and NLR ratio (14). Platelet and platelet-derived agents have a role in angiogenesis, inflammation and immunity. Platelet activation primarily performs the process of hemostasis if any damage occurs in the blood vessel. Besides, platelet activation occurs during the acute and chronic inflammatory response process (15). Mean platelet volume (MPV) is determined by the number of existing megakaryocytes during platelet production, and this factor is associated with platelet function and activation (16). MPV has been found to be an indicator of platelet activation in the evaluation of prothrombotic and pro-inflammatory processes in various diseases (17). Platelet distribution width (PDW) is defined as a measure of variation in platelet size, which may be an indicator of active platelet release (18). MPV, PDW, NLR and platelet-lymphocyte ratio (PLR) are low-cost and easily reproducible tests that can be measured in simple laboratory conditions and can be easily calculated from white blood cell count(13, 19, 20). Recently, MPV, platelet PDW, NLR and PLR have been examined as new inflammatory markers in many psychiatric diseases such as adult schizophrenia, bipolar disorder, and MDD (21-23).

As far as we know, there are few studies aiming to evaluate neutrophile-lymphocyte ratios and platelet-lymphocyte ratios in adolescent depression (24). The aim of this study is to evaluate the role of inflammation in the underlying pathophysiology of adolescent depression by evaluating neutrophile-lymphocyte ratio, platelet-lymphocyte ratio and

hemogram parameters (MPV, PDW, RBC) and also to determine whether there is a relationship between depression severity and inflammatory parameters.

METHOD

This retrospective study was carried out on 93 MDD patients and 65 healthy control who applied to Manisa Celal Bayar University Faculty of Medicine Child and Adolescent Psychiatry Clinic between January 2017 and December 2019. The current study was carried out by scanning the files of patients who applied to Manisa Celal Bayar University Medical Faculty Hospital. Also, clinical features such as diagnosis date, diagnosis during admission to hospital using DSM-5 diagnostic criteria, comorbid physical and psychiatric illness, drug use, previous psychiatric diagnosis, history of suicide attempt were determined. In addition, hemogram (hemoglobin (Hb), erythrocyte count (RBC), hematocrit (Hct), white blood cell count (WBC), neutrophil, lymphocyte, platelet, PDW, MPV) data in the hospital data system of the cases included in the study were noted down.

Patients aged between 11 and 18 years who were diagnosed with major depressive disorder according to the DSM-5 diagnostic criteria were included in the MDD group. Patients with comorbid mental retardation, psychotic disorders, bipolar disorder and autism spectrum disorder were excluded from the study. Cases with suicide attempts in the last 6 weeks were not included in the study due to recent studies showing that suicide attempts (taking medication or other methods) increase inflammation in the body. Aged between 11-18, who applied to our clinic for various reasons (academic failure, forgetfulness, adolescence age problems, relationship problems) and was not diagnosed with any psychiatric disorder. Participants who met the inclusion and exclusion criteria and had DSM-5 level-2 depression, DSM-5 depression severity scale-child form scales were included in the study. No structured interview form was applied to the participants. The healthy control group was consisted of young people who did not have a psychiatric disorder (in the past and during the study period) or did not attempt suicide. Exclusion criteria for all participants were determined as having a family history of bipolar disorder, presence of acute (infection) or chronic medical disease (diabetes mellitus, hypertension, cardiological disease), genetic or neurological disease, use of any medication (anti-inflammatory drug in the last 1 month or immunosuppressant drug use in the last 6 months), psychotropic drug use in the last 3 months, alcohol or substance addiction, smoking, body mass index above 30, WBC above 10,500 and below 4000, anemia or leukopenia detection in the laboratory tests.

Depression severity of the participants in the study was obtained by using the DSM-5 Depression Severity Scale Child Form and DSM-5 Level-2 Depression Scale Child Form scale scores. DSM-5 Level-2 Depression Scale Child Form is designed to be used in the initial evaluation and treatment of children and adolescents with or without a diagnosis of depressive disorder (or with or without clinically severe depressive disorder symptoms). Its validity and reliability were made by Sapmaz et al. (25). DSM-5 Depression Severity Scale Child Form is designed to be used in the initial evaluation and treatment of children and adolescents diagnosed with depressive disorder (or clinically severe depressive disorder symptoms). Its validity and reliability were established by Sapmaz et al. (26).

The hemogram data of the cases included in the study were used during the first application before the psychotropic medication was started. NLR was determined by comparing absolute neutrophile and absolute lymphocyte counts; the platelet-lymphocyte ratio (PLR) was obtained by comparing the absolute platelet and absolute lymphocyte ratio. All hemogram evaluations were performed by using the Sysmex XT 2000i Automated Hematology Analyzer (GMI, MN, USA). The study was performed in accordance with the provisions of the World Medical Association Declaration of Helsinki and approval was obtained from the local ethics committee with the decision numbered 20.478.486.

Statistical analysis

The data obtained from the study were evaluated by using the SPSS (The Statistical Package for

Social Sciences) 21.0 package program. Continuous variables obtained by measuring were expressed as mean±standard deviation; categorical variables were expressed as percentages and numbers. The numerical data suitability for the normal distribution was tested with the Shapiro Wilk test. The Student-t test was used in independent groups to compare the mean between two groups with normal distribution among numerical variables, and the Mann Whitney U test, which is a non-parametric test, was used for those who did not show normal distribution. Chi-square analysis and Fisher's Exact Test were used to compare categorical data. In order to determine the direction and level of the relationship between numerical variables, Pearson correlation test was used for those with normal distribution, Spearman correlation test was used for those who did not show normal distribution. A p-value<0.05 was accepted as statistically significant in all analyses.

RESULTS

Of 398 patients in the first sample group diagnosed with MDD, 120 of them had psychotropic drug use, 27 of them had medical disease, 34 of them had anti-inflammatory drug use, 16 of them had concomitant psychiatric disorder (included in the exclusion criteria), 14 of them had obesity, 8 of them was smoking, 18 of them had inappropriate (WBC above 10,500 or below 4000) hemogram parameters, 64 of them had incomplete hemogram parameters or file records, 4 of them had a family history of bipolar disorder ; therefore, they were excluded from the study and the other 93 patients were included in the study.

Sociodemographic and Clinical Features

The study includes 93 (58.9%) MDD patients and 65 (41.1%) healthy control patients. There is no statistically significant difference between the groups in terms of age, gender and body mass index. The mean age of the MDD group was detected as 14.61±1.79 years, and 14.12±1.84 years in the healthy control group (p=0.096). The number of female patients is higher than the number of male patients in both the patient group and the healthy control group. In the MDD group, it was determined that 61 (65.5%) patients had concomitant comorbid psychiatric disorders, while 32 (34.5%) patients had no concomitant comorbid disorder. The sociodemographic and clinical features of the cases included in the study are shown in Table 1.

Hemogram Parameters

As shown in Table 2, NLR and PDW were found to be statistically significantly higher in the patient group than in the control group (p<0.05). There was no statistically significant difference between the groups in terms of Hb, Htc, WBC, neutrophile, lymphocyte, platelet and MPV levels (p>0.05).

The relationship between hemogram parameters and depression scale and severity of depression was evaluated with Spearman Correlation analysis. In the analysis, no significant difference was found between the neutrophile, lymphocyte, platelet, PLR, MPV levels and the depression scale and depression severity scale total scores (p>0.05).

A weakly significant positive correlation (p=0.039, r=0.165) was found between NLR and depression severity scale; a positive correlation was found between PDW and depression scale scores and depression severity scale total scores (p<0.001, r=0.317; p<0.001, r=0.320, respectively).

The NLR and PDW values showing significant differences between the MDD and control groups

Table 1. Sociodemographic and Clinical Characteristics of the MDD Group and the Healthy Control Group

	MDD (n=93)	Healthy control (n=65)	p value
Age	14.61–1.79	14.12–1.84	0.096*
Female gender (n %)	66 (%70)	45 (%69)	0.814**
Body mass index (mean–sd)	21.49–1.21	21.32–1.16	0.618**
Presence of Psychiatric Disease in the Family (n %)	44 (%47)	12 (%18)	<0.001**
Suicide Attempt History (n %)	25 (%27)	0 (%0)	<0.001**
Depression Scale Total Score (mean–sd)	54.41–9.67	25.32–7.19	<0.001*
Depression Severity Scale Total Score (mean–sd)	18.42–4.60	4.47–3.86	<0.001*

* Mann Whitney U test, ** Ki-kare test, sd: Standart deviation

were further analyzed using AUC. NLR and PDW had favorable diagnostic value for MDD. AUC value for NLR and PDW was found to be similar (AUC:0.606, 95% CI: 0.51–0.69; p = 0.024 and AUC: 0.664, 95% CI: 0.58–0.74; p < 0.001, respectively). Using a cut-off point (>1.55) of NLR, the sensitivity, specificity, and likelihood ratio for MDD were 62.4%, 53.8% and 1.35, respectively. Using a cut-off point (>16.05%) of PDW, the sensitivity, specificity, and likelihood ratio for MDD were 61.3%, 63.1% and 1.42, respectively.

When the hemogram parameters of MDD patients with comorbid disorders and MDD patients without comorbid disorders were evaluated, no statistically significant difference was found between the groups (p>0.05).

In the patient group, hemogram parameters were compared in terms of gender. Hb, Htc and Rbc levels were found to be significantly lower in girls than boys (p<0.001). There was no significant difference between genders in the patient group in terms of WBC, neutrophil, lymphocyte, platelet, MPV, PDW, NLR and PLR levels. There was no significant difference between genders in terms of total depression scores (DSM-5 Depression Severity Scale Child Form and DSM-5 Level-2 Depression Scale Child Form) in the patient group (respectively, p= 0.774 and p= 0.084).

Hemogram parameters of patients with a history of suicide attempt and those without a history of suicide attempt were compared in the patient group. In the analysis, no significant difference was found between the groups in terms of WBC, Hb, Htc, MPV, lymphocyte, NLR, PLR, MCV, PDW, neutrophil levels (p>0.05). Platelet and RBC levels were found to be significantly higher in patients without a history of suicide attempt than in patients with a history of suicide attempt (p= 0.010, p=0.012, respectively).

Table 2. Comparison of hemogram parameters, neutrophil -lymphocyte ratios and platelet-lymphocyte ratios between major depressive disorder group and healthy control

Parameter	MDD (n=93) (mean–sd)	Healthy control (n=65) (mean–sd)	p value
Hb (g/dL)	13.18–1.28	13.42–1.09	0.225*
Htc (%)	39.36–3.44	40.26–2.86	0.090*
RBC	4.73–0.41	4.96–1.13	0.074**
WBC (10^3/uL)	7.38–1.5	7.13–1.41	0.311*
Neutrophil (10^3/uL)	4.20–1.18	3.87–1.03	0.068*
Lymphocyte (103/uL)	2.46–0.56	2.57–0.58	0.220*
Platelet (10^3/uL)	274.69–58.68	284.26–57.79	0.312*
MPV	9.32–1.03	9.58–0.92	0.109*
NLR	1.78–0.61	1.56–0.50	**0.024****
PLR	115.91–31.06	115.42–35.17	0.535**
PDW	16.18–0.52	15.94–0.33	**0.001***

Hb: Hemoglobin, Hct: Hematocrit, RBC: Erythrocyte count, WBC: White blood cell count, NLR: Neutrophil/lymphocyte ratio; PLR: Platelet -lymphocyte ratio; MPV: Mean platelet volume, PDW: Platelet distribution width, sd: Standart deviation

*: Student-t test, **Mann Whitney U test

DISCUSSION

The main finding of this study is that NLR and PDW were found to be higher in drug-naive depressive adolescents compared to healthy control patients although there was no significant difference between the groups in terms of WBC, neutrophil, lymphocyte and platelet counts. Also, a significant relationship was found between the severity of depression and NLR and PDW.

Despite the growing literature searching the relationship between depression and inflammatory markers in children and adolescents, results to date have been inconsistent. Although some studies in particular have reported that the beginning of depression leads to inflammation, the relationship between depression and inflammation is unclear (27). In a meta-analysis study conducted with children and adolescents in 2019, a positive relationship was found between TNF-alpha and depression compared to healthy control groups (28). In another recent meta-analysis study conducted with children and adolescents, a significant relationship was found between CRP and IL-6 and depressive symptoms (27).

Inflammatory ratios which reflect the proportion of cells involved in different immune or inflammatory pathways provide a simple way to search variations in leukocyte subpopulations (29). These ratios are less affected by exercise, catecholamine release, and other confounding factors and provide better information than other leukocyte parameters measured alone or other commonly used markers of inflammation (30). Inflammation rates have less cost and less limitations in terms of availability than other inflammation markers such as cytokines (29).

As these inflammatory rates reflect two immune pathways, they are probably less affected by confounding factors and are more reliable in evaluating inflammation than evaluating neutrophils, monocytes, platelets, or lymphocytes individually (31, 32). When the literature is examined, it is evident that there are limited studies with the adolescent age group although there are many studies conducted with depressed adults. In studies conducted with adolescents who did not use medication recently and had depression; no significant difference was found between the depressive group and the healthy control group in terms of PLR although NLR was found to be significantly higher in patients with depression compared to healthy control group (24,33). In the same studies, a positive correlation was found between NLR and the severity of depression. In studies conducted with depressed adults, NLR was found to be higher in patients with depression than in healthy control group (21, 34). In addition, in a meta-analysis study conducted with the adult group, NLR levels were found to be higher in patients with depression compared to healthy control group (35). In this respect, the current study is similar to previous studies and supports that NLR has an increase in patients with depression and is correlated with the severity of depression.

In this study, PDW was found to be higher in depressed adolescents compared to healthy control group, and there was a positive correlation between PDW level and depression severity. PDW measures volume variability in platelet size, platelet activation-related changes, and reflects heterogeneity in platelet morphology (36). Platelet activation is mediated by inflammatory molecules such as serotonin, dopamine, glutamate, cytokines and P-selectin (29). Additionally, platelets carry large amounts of serotonin and glutamate in their granules and contain serotonin receptors and transporters on their cell surfaces (39, 40). As it is known, serotonin, dopamine and glutamate pathways are existed in the pathophysiology of depression and antidepressant drugs generally affect these pathways. As far as we know, there has been no study examining the relationship between PDW level and depression in adolescents yet. When the literature is examined, it is seen that there are studies supporting that PDW is associated with some psychiatric disorders in the adult group. In studies conducted with adult patients with first episode schizophrenia and panic disorder, PDW levels were found to be significantly higher than healthy control group (41-43). It was also emphasized that PDW could be a good diagnostic marker or predictive marker in panic disorder (42). In the current study, the platelet level has not differed significantly between the groups, and it has been determined that there is no significant relationship between the platelet count and the severity of depression. On the other hand, the fact that the PDW level, which indicates platelet activation, has been found to be higher in depressed patients and is positively correlated with the severity of depression, suggests that the change in platelet activation rather than platelet count may be involved in the etiology of depression.

Although this study provides additional evidence that inflammatory processes and platelet activation are involved in the etiology of major depressive disorder in adolescents, it has some limitations. The limitations of the current study are that it is a retrospective study, not applying a structured interview form to the participants, the duration of illness and the number of depressive episodes in adolescents with depression were not determined, the clinical subtypes of depression were not differentiated, and the level of any proinflammatory cytokines was not measured. In addition, conditions such as lifestyle, adolescence and stress factors that might affect hemogram parameters were not excluded. Evaluation of the hemogram parameters of the cases included in the study before using psychotropic drugs, the evaluation of the relationship between the severity of depression and the hemogram parameters, and the meticulous exclusion of additional medical diseases are the strengths of the study.

CONCLUSION

According to the data obtained, it is possible to say that inflammation plays a role in the etiology of MDD. This study indicates that it is available in practice and NLR and PDW obtained from available blood tests are significantly higher in patients with MDD than in healthy control group, and it

supports the possible role of low-grade inflammation in the pathophysiology of MDD. In addition, these parameters have been found to be associated with the clinical severity of depression. In conclusion, we can speculate that neutrophil-lymphocyte and PDW are useful in determining the severity of inflammation in adolescent depression. In the next years, prospective studies in which hemogram parameters are evaluated together with proinflammatory cytokines such as CRP and interleukins will more clearly illuminate the role of inflammation and platelet activation in the etiology of major depressive disorder in adolescents.

Conflicts of interest: The authors declare that they have no conflict of interest.

Correspondence address: M.D., Masum Öztürk, Kıtıbıl Mah.Dicle Üniversitesi Tıp Fakültesi Onkoloji Hastanesi Çocuk ve Ergen Psikiyatri Polikliniği 21300 Diyarbakır - Türkiye masumozturk@hotmail.com

REFERENCES

1. Birmaher B, Brent D; AACAP Work Group on Quality Issues, Bernet W, Bukstein O, Walter H, Benson RS, Chrisman A, Farchione T, Greenhill L, Hamilton J, Keable H, Kinlan J, Schoettle U, Stock S, Ptakowski KK, Medicus J. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. J Am Acad Child Adolesc Psychiatry 2007;46:1503-1526.

2. Weller EB, Kloos A, Kang J, Weller RA. Depression in children and adolescents: does gender make a difference? Curr Psychiatry Rep 2006;8:108-114.

3. Dean J, Keshavan M. The neurobiology of depression: An integrated view. Asian J Psychiatr 2017;27:101-111.

4. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010;67:446-457.

5. Kim J-W, Szigethy EM, Melhem NM, Saghafi EM, Brent DA. Inflammatory markers and the pathogenesis of pediatric depression and suicide: a systematic review of the literature. J Clin Psychiatry 2014;75:1242-1253.

6. Smith RS. The macrophage theory of depression. Med Hypotheses. 1991;35:298-306.

7. Kim YK, Maes M. The role of the cytokine network in psychological stress. Acta Neuropsychiatr 2003;15:148-155.

8. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience 2013;246:199-229.

9. Müller N, Myint A-M, Schwarz MJ. Inflammatory biomarkers and depression. Neurotox Res 2011;19:308-318.

10. Haroon E, Raison CL, Miller AH. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. Neuropsychopharmacology. 2012;37:137-162.

11. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999;340:448-454.

12. Bhutta H, Agha R, Wong J, Tang TY, Wilson YG, Walsh SR. Neutrophil-lymphocyte ratio predicts medium-term survival following elective major vascular surgery: a cross-sectional study. Vasc Endovascular Surg 2011;45:227-231.

13. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102:5-14.

14. Gökmen F, Akbal A, Reşorlu H, Gökmen E, Güven M, Aras AB, Erbağ G, Kömürcü E, Akbal E, Coşar M. Neutrophil–lymphocyte ratio connected to treatment options and inflammation markers of ankylosing spondylitis. J Clin Lab Anal 2015;29:294-298.

15. Wagner DD, Burger PC. Platelets in inflammation and thrombosis. Arterioscler Thromb Vasc Biol 2003;23:2131-2137.

16. Jackson S, Carter J. Platelet volume: laboratory measurement and clinical application. Blood rev 1993;7:104-113.

17. Yuri Gasparyan A, Ayvazyan L, P Mikhailidis D, D Kitas G. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des 2011;17:47-58.

18. Kasperska-Zając A, Grzanka A, Jarzab J, Misiołek M, Wyszyńska-Chłap M, Kasperski J, Machura E. The association between platelet count and acute phase response in chronic spontaneous urticaria. Biomed Res Int 2014;2014.

19. Balta S, Demirkol S, Celik T, Kucuk U, Unlu M, Arslan Z, Balta I, Iyisoy A, Kocak N, Haqmal H. Association between coronary artery ectasia and neutrophil–lymphocyte ratio. Angiology. 2013;64:627-632.

20. Balta S, Demirkol S, Unlu M, Arslan Z, Celik T. Neutrophil to lymphocyte ratio may be predict of mortality in all conditions. Br J Cancer 2013;109:3125-3126.

21. Demir S, Atli A, Bulut M, İbiloğlu AO, Güneş M, Kaya MC, Demirpençe Ö, Sır A. Neutrophil–lymphocyte ratio in patients with major depressive disorder undergoing no pharmacological therapy. Neuropsychiatr Dis Treat 2015;11:2253.

22. Gundogmus İ, Algul A, Karagöz A, Kıyançiçek M. PDW and RDW are new parameters for bipolar episodes and unipolar depression. Psychiatry and Clinical Psychopharmacology 2019;29:520-526.

23. Özdin S, Böke Ö. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. Psychiatry res 2019;271:131-135.

24. Özyurt G, Binici NC. Increased neutrophil-lymphocyte ratios in depressive adolescents is correlated with the severity of depression. Psychiatry res 2018;268:426-431.

25. Yalın-Sapmaz Ş, Yalın N, Kavurma C, Uzel Tanrıverdi B, Öztekin S, Köroğlu E, Aydemir Ö. Reliability and Validity Of The DSM-5 Level 2 Depression Scale- Turkish Version (Child Form for 11-17 years and Parent Form for 6-17 Years). JCBPR 2017; 6: 15-21. Turkish.

26. Yalın Sapmaz Ş, Yalin N, Ozek Erkuran H, Oztekin S, Uzel Tanriverdi B, Koroglu E, and Aydemir Ö. "Validity and reliability of the Turkish version of DSM-5 Depression Severity Scale-Child Form/DSM-5 Depresyon Siddet Olcegi Cocuk Formu Turkce surumunun guvenilirligi ve gecerliligi." Anadolu Psikiyatri Derg 2017; 18: 237-243.

27. Colasanto M, Madigan S, Korczak DJ. Depression and inflammation among children and adolescents: A meta-analysis. J Affect Disord. 2020.

28. D'Acunto G, Nageye F, Zhang J, Masi G, Cortese S. Inflammatory cytokines in children and adolescents with depressive disorders: A systematic review and meta-analysis. J Child Adolesc Psychopharmacol 2019;29:362-369.

29. Mazza MG, Lucchi S, Rossetti A, Clerici M. Neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio in non-affective psychosis: a meta-analysis and systematic review. World J Biol Psychiatry 2020;21:326-338.

30. Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G, Jeffrey RR, Buchan KG, El-Shafei H, Hillis GS. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. Am Heart J 2007;154:995-1002.

31. Azab B, Zaher M, Weiserbs KF, Torbey E, Lacossiere K, Gaddam S, Gobunsuy R, Jadonath S, Baldari D, McCord D. Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non–ST-elevation myocardial infarction. Am J Cardiol 2010;106:470-476.

32. Venkatraghavan L, Tan TP, Mehta J, Arekapudi A, Govindarajulu A, Siu E. Neutrophil Lymphocyte Ratio as a predictor of systemic inflammation-A cross-sectional study in a preadmission setting. F1000Res 2015;4.

33. Uçar HN, Eray Ş, and Duygu M.Simple peripheral markers for inflammation in adolescents with major depressive disorder. Psychiatry Clin. Psychopharmacol 2018; 28: 254-260.

34. Demircan F, Gözel N, Kılınç F, Ulu R, Atmaca M. The impact of red blood cell distribution width and neutrophil/lymphocyte ratio on the diagnosis of major depressive disorder. Neurol Ther 2016;5:27-33.

35. Mazza MG, Lucchi S, Tringali AGM, Rossetti A, Botti ER, Clerici M. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: A meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2018;84:229-236.

36. Budak YU, Polat M, Huysal K. The use of platelet indices, plateletcrit, mean platelet volume and platelet distribution width in emergency non-traumatic abdominal surgery: a systematic review. Biochem Med (Zagreb) 2016;26:178-193.

37. De Luca G, Venegoni L, Iorio S, Secco GG, Cassetti E, Verdoia M, Schaffer A, Coppo L, Bellomo G, Marino P. Platelet distribution width and the extent of coronary artery disease: results from a large prospective study. Platelets. 2010;21:508-514.

38. Vagdatli E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F, Labrianou I. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. Hippokratia. 2010;14:28.

39. Berk M, Plein H, Belsham B. The specificity of platelet glutamate receptor supersensitivity in psychotic disorders. Life sci 2000;66:2427-2432.

40. Plein H, Berk M. The platelet as a peripheral marker in psychiatric illness. Hum Psychopharmacol 2001;16:229-236.

41. Ransing RS, Patil B, Grigo O. Mean platelet volume and platelet distribution width level in patients with panic disorder. J Neurosci Rural Pract 2017;8:174.

42. Ransing RS, Gupta N, Agrawal G, Mahapatro N. Platelet and red blood cell indices in patients with panic disorder: A receiver operating characteristic analysis. J Neurosci Rural Pract 2020;11:261.

43. Yu Q, Weng W, Zhou H, Tang Y, Ding S, Huang K, Liu Y. Elevated Platelet Parameter in First-Episode Schizophrenia Patients: A Cross-Sectional Study. J Interferon Cytokine Res 2020;40:524-529.