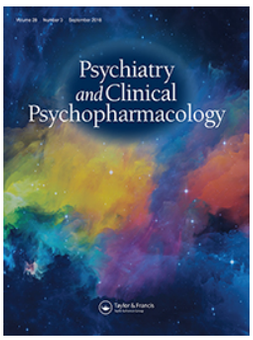

Psychiatry and Clinical Psychopharmacology

ISSN: 2475-0573 (Print) 2475-0581 (Online) Journal homepage: https://www.tandfonline.com/loi/tbcp21

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To cite this article: Halit Necmi Uçar, Şafak Eray & Duygu Murat (2018) Simple peripheral markers for inflammation in adolescents with major depressive disorder, Psychiatry and Clinical Psychopharmacology, 28:3, 254-260, DOI: 10.1080/24750573.2018.1423769

To link to this article: https://doi.org/10.1080/24750573.2018.1423769

Published online: 17 Jan 2018.

PSYCHIATRY AND CLINICAL PSYCHOPHARMACOLOGY
2018, VOL. 28, NO. 3, 254–260
https://doi.org/10.1080/24750573.2018.1423769

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Simple peripheral markers for inflammation in adolescents with major depressive disorder

Halit Necmi Uçar[a], Şafak Eray[a] and Duygu Murat[b]

[a]Department of Child and Adolescent Psychiatry, Van Training and Research Hospital, Van, Turkey; [b]Department of Child and Adolescent Psychiatry, Avcılar Hospital, İstanbul, Turkey

ABSTRACT

OBJECTIVE: Neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), mean platelet volume (MPV), and red cell distribution width (RDW) were determined to be good indicators of inflammatory status. The aim of this study was to investigate NLR, PLR, MPV, and RDW, which can provide insight into diagnosis and/or prognosis in adolescents with major depressive disorder (MDD) compared to controls.

METHOD: A total of 103 patients diagnosed with MDD, who received no antidepressant therapy within the past 1 month, were included in the study. The control group consisted of 41 healthy subjects with no organic and psychiatric disorders.

RESULTS: NLR and MPV values were significantly high in adolescents with MDD compared with healthy controls (2.00 ± 0.80 vs. 1.63 ± 0.64, $P = .011$; 10.25 ± 0.91 vs. 9.62 ± 1.23, $P = .005$). There was no difference between the groups on PLR and RDW. There was a positive correlation between NLR and Children's Depression Scale (CDI) scores in the total study group ($r = 0.229$, $P = .006$). There was also a positive correlation between MPV and CDI scores in the total study group ($r = 0.185$, $P = .028$).

CONCLUSION: The findings of the study reveal that NLR and MPV tend to be higher in adolescents with MDD, and higher NLR values are associated with higher CDI scores in adolescents. The findings of this study are consistent with the relevant literature of inflammatory status in MDD. Our study gave us an idea of the need for larger sample study on the routine use of blood parameters in adolescent depression.

ARTICLE HISTORY
Received 27 November 2017
Accepted 28 December 2017

KEYWORDS
Major depressive disorder; adolescent; neutrophil–lymphocyte ratio; platelet–lymphocyte ratio; means platelet volume; red cell distribution width

Introduction

Depression is a common disease affecting the quality of life in children and adolescents [1]. The prevalence of major depressive disorder (MDD) in adolescents is 4–8% [2]. Many factors play role in the aetiology of MDD [3]. Studies investigating the role of the immune system in the aetiology of MDD have increased in lately [4]. It has been suggested that MDD suppresses the immune system and may also increase pro-inflammatory cytokines. Acute phase reactants and pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-alpha) may play a role in the aetiology of depression [5–7]. In addition, antidepressants have been demonstrated to reduce and normalize levels of pro-inflammatory cytokines [7,8].

In clinical practice, it has been reported that haemogram parameters such as the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), mean platelet volume (MPV), and red cell distribution width (RDW) can be used as markers of systemic inflammation for different diseases [9–11]. NLR and PLR are calculated as absolute counts of neutrophils, platelets, and lymphocytes in haemogram; thus, inflammation can easily be measured in routine blood tests [12,13]. Inflammation can cause an increase in the number and activity of neutrophils and platelets, while apoptosis process characterized by the reduction of lymphocytes [14,15]. Platelet volume is defined as the number of megakaryocytes present during platelet production, which is related to platelet function and activation. The number of platelets and their size are negatively correlated [16,17]. Large platelet sizes reflect increased thrombocyte reactivity and reactive thrombocytes play an important role in inflammatory processes [18]. RDW, as part of a complete blood cell count, is measured by an automatic haematology analyser and estimates erythrocytic variability. Increased RDW reflects ineffective erythropoiesis, which may be a consequence of systemic inflammation [19]. NLR, PLR, MPV, and RDW have been determined to be potential markers for testing inflammation in many disorders. NLR has been investigated in children and adolescents with asthma [20] and allergic rhinitis [21], MPV has investigated in children with asthma [22] and obstructive apnoea syndrome [23], and RDW has been investigated in

CONTACT Duygu Murat duygucalisir44@yahoo.com

children with acute appendicitis [24], acute rheumatic carditis [25], and sepsis [26]. The association between NLR, PLR, and MPV obesity in adolescents has also been reported in the literature [27]. There are also studies on adolescents investigating the effects of diet and exercise on NLR in overweight adolescents [28], and the relationship between NLR, PLR, MPV, and RDW and ovarian neoplasm [29] and the relationship between MPV and primary dysmenorrhea [30].

Recently, increased attention has been paid to haemogram parameters in mood disorders [31,32]. Other systemic inflammation markers reported in studies are generally expensive and require special equipment [33–35]. However, haemogram parameters, such as NLR, PLR, MPV, and RDW, are less expensive and can easily be detected. NLR, RDW, and PLR have been investigated in adult MDD patients [36–40], while MPV has been investigated in patients with bipolar disorder [41]. However, only one study has examined MPVs in children with attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) [42]. These parameters have been widely studied in adult but not adolescent psychiatric patients, although they have been investigated in children with various non-psychiatric organic diseases. Thus, we hypothesized that these haemogram parameters which can provide insight into diagnosis and/or prognosis may exhibit significant differences in adolescent depression. To the best of our knowledge, there has been no study investigating NLR, PLR, MPV, and RDW in adolescent MDD patients. Therefore, we aimed to compare the routine haemogram values of treatment-naive adolescent MDD patients with those of a healthy control group to evaluate inflammation levels in both groups.

Materials and methods

Study population

This study included 103 adolescents diagnosed with MDD based on semi-structured interviews carried out by a child psychiatrist on individuals who applied to the Children and Adolescent Psychiatry Outpatient Clinic of Van Education and Training Hospital between January 1 and March 31 2017. The control group consisted of 41 adolescents who applied to the Department of Pediatrics voluntarily and were not diagnosed with any physical or mental disorder. The control group of adolescents was matched with the patient group by age, gender, and body mass index (BMI) to prevent any effects on the haemogram variables. The necessary legal permission and approval were obtained from the Van Education and Training Hospital Ethics Committee before proceeding to the data collection stage (October 10 2016, no.: 2016/10). All participants in the study and their parents gave informed consent after being informed of the methods and objectives of this study. Haemogram samples of adolescents experiencing their first depressive episode were taken prior to medical treatment. Adolescents with comorbid psychiatric diseases, chronic or inflammatory diseases, local or systemic infection in the last month, alcohol or substance users, smokers and drug users were excluded. Obesity (BMI >30 kg/m^2) is also an exclusion criterion due to chronic systemic inflammation in the metabolic syndrome etiopathogenesis [43]. Children's lengths and weights were measured by the same paediatric nurse before the examination. BMI was assessed by the researchers during their examination. The adolescents were initially requested to fill out a socio-demographic questionnaire prepared by the researchers, and then were evaluated by child and adolescent psychiatrists using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) for psychopathology (Affective Disorders and Schizophrenia Schedule for School Age Children Present and Lifetime). The severity of depression was assessed using the Children's Depression Scale (CDI). Blood was taken for biochemical analyses.

Data form descriptions

Information collection form

Information Collection Form (ICF) was created by the researchers. The ICF surveyed adolescents regarding their socio-demographic characteristics, including age and gender, and presence of chronic disease, smoking, alcohol, and/or drug use.

Kiddie schedule for affective disorders and schizophrenia–present and lifetime version (K-SADS-PL)

K-SADS-PL is a semi-structured diagnostic interview regarding the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders. It was developed by Kaufman et al. [44] and has been translated into Turkish. A validity and reliability study of the schedule for Turkish children was conducted by Gökler et al. [45].

Children's Depression Scale

Children's Depression Scale was developed by Kovacks based on the Beck Depression Scale [46]. The validity and reliability study in our country was made by Öy [47]. The self-report scale includes 27 items that can be applied to children and adolescents between the ages of 6 and 17. Each item is scored 0–2 according to depression severity. The scale maximum score is 54. High scores indicate the severe depression. The cut-off value of scale is determined as the value of 19.

Table 1. Socio-demographic characteristics of the participants.

	Patient group *n* (%)	Control group *n* (%)	*P*
Gender			
Male	32 (31.1)	19 (46.3)	.084
Female	71 (68.9)	22 (53.7)	
Age	15.64 ± 1.28	15.24 ± 1.17	.090
BMI	20.24 ± 3.19	19.77 ± 3.26	.508

Note: BMI: body mass.

Blood sampling and haemogram measurements

For blood samples, participants were invited to an outpatient clinic at 9 a.m. with 12 hours of hunger 12. The samples were taken from the participants' antecubital veins and stored in haemogram tubes. Blood tests were performed in the Van Education and Training Hospital Central Laboratory using a Sysmex XN1000. The manufacturer of Sysmex XN1000 is Sysmex Corporation from Kobe, Japan. The intra- and inter-assay CVs of WBCs were <3.0% and <4.0%, respectively. The intra- and inter-assay CVs of neutrophils and lymphocytes were <8.0% and <16.0%, respectively. The intra- and inter-assay CVs of platelets were <4.0% and <12.0%, respectively. The intra- and inter-assay CVs of MPVs were <4.0% and <8.0%, respectively. The intra- and inter-assay CVs of RDWs were <2.0% and <6.0%, respectively.

Statistical analysis

Data were evaluated using IBM SPSS Statistics 22.0 statistical software package program. The mean and the standard deviation values with minimal and maximal levels were used for the statistical expression of the groups. Whereas the comparison of the continuous variables between the groups was performed using the Student's *t*-test for normally distributed variables, comparison of abnormally distributed variables and nonparametric parameters was performed using the Mann–Whitney *U*-test. Comparison of the categorical variables of the groups was performed using chi-square tests. A Pearson correlation analysis was carried out to analyse correlations. A *P* value of <.05 was considered statistically significant.

Results

The age, sex, and BMI of all patient groups were compared with control subjects. The mean ages of patient group (15.64 ± 1.28) and the control group (15.24 ± 1.17) were similar; 68.9% ($n = 71$) of the patient group and 53.7% ($n = 22$) of the control group were girls. The distribution of sex between the groups was homogenic. The BMI of patient group (20.24 ± 3.19) and the control group (19.77 ± 3.26) were similar in terms of average. The properties of participants were shown in Table 1.

The laboratory findings for the two study groups are presented in Table 2. NLR (effect size $d = 0.51$, $r = 0.24$), MPV (effect size $d = 0.58$, $r = 0.27$), WBC (effect size d = 0.53, $r = 0.25$), neutrophil (effect size $d = 0.56$, $r = 0.27$), MCV (effect size $d = 0.62$, $r = 0.29$), and MCH values of the adolescents with MDD were significantly higher than those of the control group. RBC values of the control group were significantly higher than those of the adolescents with MDD. There were no differences between the two groups in terms of PLR, RDW, lymphocyte, haemoglobin, HCT, MCHC, platelets, and PCT values.

The patient group (26.98 ± 7.17) had significantly higher CDI scores than the control group (11.0 ± 5.98) ($P < .001$, $t = 12.590$) (effect size $d = 2.42$, $r = 0.77$). Correlations between the CDI scores and NLR, PLR, MPV, and RDW were identified for all participants taken as a whole. There were positive correlations between CDI scores and NLR and between CDI scores and MPV for all participants. The results of these analyses can be found in Table 3.

Discussion

In our study, we aimed to assess haemogram parameters to determine the inflammation status of adolescents with MDD by comparison with their healthy peers. The results of this study indicated that the NLR and MPV values in adolescents with MDD were higher than those of their healthy peers and there was no difference between the groups on PLR and RDW. In addition, a positive correlation between NLR, MPV values and depression scores in adolescents was observed.

The role of inflammation is important in the aetiology of MDD [48] and studies have reported that inflammation is increased in patients with depression [49,50]. However, the relationship between inflammatory markers and depression is still unclear. When we consider inflamatuar markers or alterations have a causative role in MDD aetiology, marker levels are a consequence of psychological distress in MDD. Cytokines associated with inflammation affect the pathophysiology of depression by altering the metabolism of relevant neurotransmitters, neuroendocrine functions, and synaptic plasticity [5,51,52]. Pro-inflammatory cytokines may affect monoamine metabolism. Serotonin transporter mRNA and proteins are upregulated by the cytokines such as IL-1, IL-6, and TNF-α cytokines, thus causes the decreases in free serotonin. The relationship between serotonin/serotonin transporters and inflammation has received attention in the aetiology of depression [51]. On the other hand, it has been stated that potential mediators of inflammation markers, including leukocytes, neutrophils, complements, and C-reactive proteins increase in response to depression [53]. Previous studies have showed that patients with depression have reduced lymphocyte answers to mitogen stimulation and disorders in

Table 2. Laboratory findings for the patient and control group participants.

	Patient group		Control group			
Variables	*M*	SD	*M*	SD	*t*	*P*
NLR	2.00	0.80	1.63	0.64	2.589	.011*
PLR	120.17	38.13	123.11	30.34	−0.441	.660
MPV (fL)	10.25	0.91	9.62	1.23	2.900	.005*
RDW (%)	13.27	1.97	13.56	0.82	−0.878	.382
WBCs (10^3/μL)	8.28	1.94	7.28	1.81	2.840	.005*
Neutrophils (10^3/μL)	4.93	1.61	4.04	1.55	3.024	.003*
Lymphocytes (10^3/μL)	2.60	0.68	2.55	0.56	0.457	.648
Haemoglobin (g/dL)	14.58	1.89	14.36	1.29	0.674	.501
RBCs (10^6/μL)	5.19	0.66	5.33	0.38	−2.167	.030**
HCT (%)	43.18	6.01	42.78	3.25	−1.100	.271
MCV (fL)	83.97	5.88	80.70	4.49	3.208	.002*
MCH (pg)	27.72	3.78	27.10	1.93	−3.250	.001**
MCHC (g/dL)	33.30	1.53	33.55	1.09	−0.971	.333
Platelets (10^3/μL)	296.04	72.58	302.63	57.01	−0.520	.604
PCT (%)	0.31	0.19	0.38	0.51	−0.279	.780

Notes: The data are expressed as the mean ± standard deviation. HC T: haematocrit; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; MCV: mean corpuscular volume; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PCT: plateletcrit; PLR: platelet-to-lymphocyte ratio; RBC: red blood cell; RDW: red cell distribution width; WBC: white blood cell.
*Student's *t*-test.
**Mann–Whitney *U*-test.

neutrophil activity [54–56]. In general, the findings of our study are consistent with those of previous studies, indicating increased neutrophil and leukocyte counts in adolescents with depression. Therefore, we conclude that adolescent depression is associated with inflammation, although the exact nature of the relationship and the mechanisms involved are not yet fully understood.

Studies have indicated that NLR values are higher in inflammatory disease of children, such as asthma, allergic rhinitis, and obese adolescents [20,21,27]. No study to date concerning this subject has been carried out in children and adolescent with psychiatric disorders. Studies regarding adult depression have reported significantly higher NLR rates in patients with depression [38,40]; however, there has also been at least one study that reported findings to the contrary [36]. In our study, NLR values were significantly higher in adolescents with depression than in healthy controls. These results also support the conclusion that evaluating NLR rather than neutrophil or lymphocyte counts, used in previous studies, would be beneficial for adolescents with depression [38]. We thought that if these results supported in large sample studies, this simple method may be taken into consideration during the assessment of patients with depression by adolescent psychiatrists.

Table 3. Pearson's correlation coefficients for each pair of variables.

	1	2	3	4	5
1. CDI scores	–				
2. NLR	0.229**	–			
3. PLR	−0.035	0.413**	–		
4. MPV	0.185*	0.119	−0.223**	–	
5. RDW	0.013	−0.002	−0.096	−0.087	–

Notes: Pearson correlation *r* scores are expressed in the table. CDI: child depression inventory; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; RDW: red cell distribution width.
*Correlation is significant at the 0.05 level (two-tailed).
**Correlation is significant at the 0.01 level (two-tailed).

In a study conducted in adult depressed patients, there was no significant difference between the patient group and the control group in terms of PLR ratios [40]. In studies investigating PLR values in adolescents, there was no significant difference in PLR values between obese adolescents and non-obese adolescents, nor was there a difference between those with and without primary dysmenorrhoea [27,30]. Our finding is in line with these studies in terms of PLR. Nevertheless, we did not find a difference with regard to PLR in MDD patients relative to controls. Some researchers have determined NLR to be a more reliable marker for subclinical inflammation when compared to PLR [57]. As our study also found no association between inflammation and PLR, we recommend the use of NLR rather than PLR as a marker of inflammation in adolescents with depression.

Studies have found elevated MPV levels in obese adolescents, children with asthma, and children with obstructive sleep apnoea syndrome when compared with those of healthy subjects [22,23,27]; thus, MPV is considered an inflammation marker. A previous study reported no relationships between MPV levels and children with ADHD and children with ASD [42], although another study reported increased MPV levels in adult MDD patients [58]. Our finding is compatible with the adult MDD study in terms of MPV. This result suggests that similar to NLR, if these results supported in large sample studies, MPV could be used as a marker of inflammation in adolescents with MDD.

RDW values were found to be significantly higher in children with acute appendicitis and acute rheumatic carditis when compared with those of healthy controls [24,25]. A study conducted by adult patients with depression has reported significantly higher RDW values in the patients with depression compared to the healthy controls [40]. In a study evaluating iron

deficiency in children and adolescents with ADHD and healthy controls, there was no significant difference in the RDW values of the ADHD group compared to the control group [59]. In another study investigating inflammation in autistic children, no significant difference was reported in the mean RDW of the patient group when compared with that of the healthy group [60]. In studies evaluating RDW in children and adolescents with organic disease and in adult patients with depression, RDW has been shown to be associated with inflammation; however, studies evaluating RDW in children and adolescents with ADHD and autism have not shown significant results. Our results also found no significant difference in RDW levels in adolescents with depression compared to their healthy peers. This result suggests that RDW in children and adolescents may be an indication of inflammation due to organic disease; however, there is insufficient data regarding inflammation in psychiatric diseases.

In a study evaluating the relationship between haemogram parameters and disease severity in children with asthma, a poor correlation was found between NLR and hospitalization [20]. In another study in which NLR was assessed in children with allergic rhinitis, those with moderate to severe symptoms had higher NLR than those with mild symptoms [21]. In a study investigating NLR in adolescents with primary dysmenorrhea, there was no significant difference in terms of PLR and NLR, although adolescents with severe primary dysmenorrhea had a significantly lower MPV levels than the control group [30]. In a study of MPV values in children with asthma, the MPV levels of the group with exacerbated asthma were found to be significantly lower than those of the stable asthma group; however, there was no significant difference between the exacerbated asthma group and the control group [22]. In a study evaluating RDW in children with paediatric acute appendicitis, there was no significant difference in the RDW values of those with perforated appendicitis cases and those with simple appendicitis cases [24]. In a study of adult patients with depression, a positive significant correlation was reported between NLR and depression severity [39]; however, another study reported no correlation between NLR and depression severity [38]. In another study on adult patients with depression, PLR values were found to be significantly higher in psychotic depressive patients than in other patients, although there was no correlation between NLR and depression severity [37]. As can be seen, when we examine the literature, there is a significant relationship between NLR and disease severity for non-psychiatric diseases. In the case of psychiatric diseases, there were contradictory findings on NLR in adult patients, and only one study shows a positive correlation between depression severity and PLR. This suggests that our results, in particular, the correlation between NLR and disease severity, may enhance our understanding of the relationship between inflammation and adolescent depression.

It is unclear that if inflammation markers were trait markers (diagnostic or diathetic), or state markers. When we examined the literature regarding the relationship between immune response and severity of depression, there were studies which were reported positive [56] and negative correlations [61] between them. There were also studies which showed no correlation between them [62,63]. While there is only one study which concerned a positive correlation between NLR and severity of depression [39], there are some studies which did not support this finding [37,38]. On the other hand, studies which were conducted with the adult depression patients have stated a significant increase in inflammation markers in MDD [38,64]. There was also a study which showed no significant increase than controls [36]. In our study, there was a significant increase than the control group in terms of NLR and MPV, and also these markers were correlated with severity of depression. Further studies with larger numbers of adolescents with MDD are needed to clarify whether inflammation markers are useful for clinicians in the diagnosis and follow-up of adolescents with MDD.

The present study has several limitations. Firstly, it would be more informative to design as a prospective study, evaluating the relationship between the treatment of depression and haemogram parameters than cross-sectional study. Since we could not define the subtype of depression for each patient, we could not evaluate the relationship between it and haemogram parameters. Another limitation is that we could not analyse the lymphocyte subtypes and cytokines in combination with haemogram parameters. Our information regarding alcohol/ substance usage, smoking, and chronic/ inflammatory diseases of subjects depends on adolescent and parent report. This may cause subjective information. One of the potential limitations of our study is that control groups were not matched with the study group in terms of number of participants, despite the patient group was large enough. Despite these limitations, our study is of critical importance as it is the first study in which NLR, PLR, MPV, and RDW were investigated in adolescents with MDD.

Conclusion

In our study, NLR and MPV tend to be higher in adolescents with MDD and higher CDI scores were associated with higher NLR and MPV levels in adolescents with MDD. A simple inexpensive blood cell count may also help clinicians evaluate the severity of depression. We suggest that this simple blood test can give the clinician an opinion about the presence

of the inflammatory process in depression. Further research is necessary to fully understand the role of inflammation in the aetiology and treatment of depression, and follow-up studies should focus on the process of inflammation in psychiatric diseases in children and adolescents.

Disclosure statement

No potential conflict of interest was reported by the authors.

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