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RESEARCH ARTICLE

Does late and early onset depression differ in terms of inflammation?

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ABSTRACT

Objective: To compare neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and monocyte-lymphocyte ratio (MLR) values as inflammation markers in patients with early- and late-onset geriatric depression.

Method: Patients aged 60 and over who were hospitalized due to depressive disorder between 01.01.2012 and 01.01.2020 were included in this retrospective record review study. Only patients with unipolar depression were included.

Results: No difference was found in terms of NLR, PLR or MLR was found between early- and late-onset depression. However, NLR and PLR values were higher in the early- and late-onset depression groups than in the control group. Lymphocyte and monocyte counts were higher in the control group compared to the early- and late-onset depression groups.

Conclusion: NLR and PLR may be regarded as markers reflecting inflammation in geriatric depression patients rather than as markers that can differentiate geriatric depression patients in terms of disease onset time.

Keywords: Aged, inflammation, inpatients, lymphocyte, neutrophil

INTRODUCTION

Although different ages are used to define the geriatric period, each of the specified ages is a symbolic expression. In many studies, 65 years is acknowledged as the limit age for the geriatric population. Depending on the increase in average life expectancy, the population over 65 is also increasing. This is also the case for Turkey. While the geriatric population constituted 5.7% of the country's population in 2000, this corresponds to 9.0% in 2019. This rate is expected to increase further in the following years (1). With the increase in the geriatric population, diseases in the geriatric period can also be expected to increase. The prevalence of depression in the geriatric period varies between studies and the rates can reach a frequency of up to 19.7% (2). The way depressive disorder appears during this period can be in two ways. In late-onset depression (LOD), the first depressive episode occurs after the age of 60-65. Early-onset depression (EOD) occurs as the relapse of a previous depressive disorder episode in the geriatric period (3). Although there is no difference between them in terms of their symptomatic features and Magnetic Resonance Imaging findings (4), there may be various clinical differences. Some of these differences are higher relapse rates of LOD compared to EOD, more comorbid medical illness (5), the higher response rate to treatment (4), or more vascular risk factors (6).

One of the possible etiological explanations for depression in the geriatric period is the inflammation

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hypothesis. With aging, a chronic low-grade inflammatory environment, also called "inflammaging", develops in the central nervous system (7). At the same time, diseases that often accompany the geriatric period may also contribute to the inflammatory environment. It has been claimed that central nervous system functions may change with secreted cytokines and depressive symptoms may occur (8). Many markers are used to show inflammation. Because of these various explanations, findings obtained in studies investigating inflammation in geriatric depression are inconsistent (9). Geriatric depression is often accompanied by an increase in pro-inflammatory markers (10). Longitudinal studies have shown that high-onset inflammatory parameters increase the risk of depression in the future (11). It has been asserted that there may be a strong positive correlation between the CRP level and the severity of depression in depressive disorder patients in the geriatric period (12). It has also been shown that there may be a relationship between increased inflammation and a more severe course of geriatric depression (13), cognitive symptoms (14), and vulnerability (15). On the other hand, the number of studies comparing LOD and EOD with regard to inflammation is very few. In the study conducted by Rozing et al. (16) with 11 inflammatory markers, only GDF15 was shown to be higher in LOD compared to EOD. They also found that among inflammatory markers only CRP predicted depression in LOD compared to EOD.

Neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and monocyte lymphocyte ratio (MLR) are inexpensive and useful values investigated in recent years to measure inflammation level. In the case of inflammation, the number of lymphocytes decreases, and the number of neutrophils increases (17). In stress cases, the lymphocyte count may decrease by 85% in 4 hours (18). Due to the decrease in chemokines released in inflammation and the decrease of apoptosis, the number of neutrophils increases. In recent years, the role of platelet in inflammation apart from its hemostasis and thrombosis functions has been revealed. It has been found that platelets increase in inflammatory environments (19). The accumulation of monocytes in lymph tissues and inflammatory tissues during inflammation may cause a decrease in blood level (20). Accordingly, changes in NLO, PLO and MLO values may occur during inflammation. NLR value is correlated with other inflammatory markers (21). For this reason, it has been used as a prognosis and staging indicator in many different diseases in recent years. Its use in psychiatry has been increasing in recent years (22,23). Studies with geriatric depression found that the NLR value was higher than the control group and associated with symptom severity (24). It has been found that in geriatric depression, the NLR value is associated with depression, especially in women, and there is no relationship between depression and NLR value in men (25).

There are no studies in the literature evaluating PLR and MLR in geriatric depression patients and comparing these variables between LOD and EOD. In our study, NLR, PLR and MLR values of patients with geriatric EOD and LOD patients (>60 years of age) treated in hospital will be compared with the control group. This study aimed to reveal the differences in inflammation between geriatric depression and control group, and between LOD and EOD patient groups, which are two different forms of geriatric depression by age of onset. The hypothesis of our is that markers used as inflammatory markers may be higher in geriatric depression patients compared to the control group and in LOD patients compared to EOD patients.

METHOD

Patients, who were diagnosed with depressive disorder aged 60 and over, and who were hospitalized in Ondokuz Mayis University Faculty of Medicine between 01.01.2012-01.01.2020, were included in this study, which was carried out with retrospective file review. Patients with comorbid cognitive impairment, infectious disease, psychiatric illness other than a depressive disorder, or using drugs affecting the inflammation level (nonsteroidal anti-inflammatory drugs, corticosteroids or immunosuppressive drugs) were not included in the study. 55 of the 159 patients hospitalized with a diagnosis of depressive disorder during the abovementioned period were not included in the study in terms of the exclusion criteria, and 104 were included in the study. The sociodemographic data and the disease-related variables of the patients were obtained from the hospital automation system and patient files. According to the working procedure of the psychiatry clinic, the diagnoses of the patients during their hospitalization were made by at least two research assistants and a faculty member after the clinical interview. Those who had their first depressive episode over the age of 60 were included in the LOD (n=47), and those who had their first depressive episode under the age of 60 were included in the EOD group (n=57). The complete blood count results of the patients were

evaluated with blood samples taken within 24 hours of hospitalization. The control group was selected from a family health center population over 60 years of age without cognitive impairment, infectious disease or psychiatric illness, and who did not use medications that affect inflammation level (nonsteroidal anti-inflammatory drugs, corticosteroids or immunosuppressive drugs). For the evaluations, the family health center's electronic information system, www.enabiz.gov.tr and www.medeczane.sgk.gov.tr websites were used. Lack of response to two antidepressants with sufficient doses and duration was used as a treatment-resistant depression criterion (26). Neutrophil to lymphocyte ratio, PLR and MLR values were calculated from the neutrophil, platelet, monocyte and lymphocyte counts in the complete blood count. Approval for the study was obtained from the Ondokuz Mayis University Faculty of Medicine Clinical Research Ethics Committee (No: 2020/321).

Statistical Analysis

SPSS 15.0 package program was used for statistical evaluation of study data. The Chi-square test was used to evaluate the relationship between categorical variables. The compliance of the data to normal distribution was evaluated with the Kolmogorov Smirnov Test. Since age, neutrophil, lymphocyte, platelet and monocyte counts and NLR, PLR and MLR values did not comply with normal distribution, the Kruskal Wallis Test was used in the triple group comparison of these variables (LOD, EOD and control group). Mann-Whitney U test was carried out with Post hoc Bonferroni correction to determine in which groups the difference was among the variables that differed significantly. The significance level was accepted as $p<(0.05/3)=0.016$ in the Mann-Whitney U test with Bonferroni correction, and $p<0.05$ in other comparisons.

RESULTS

The sociodemographic and clinical characteristics of the groups are given in Table 1. In sociodemographic data, the Kruskal Wallis Test was used to compare the groups in terms of age, and the Chi-square test was used to compare categorical variables. According to the data, 47 (45.1%) of geriatric depression cases receiving inpatient treatment were LOD patients. 19 (40.4%) of LOD patients and 32 (56.1%) of EOD patients were men. The mean age of patients with LOD was 65.8±3.7; the mean age of EOD patients was 68.1±5.8, 10 (21.2%) of LOD patients and 20 (34.1%) of EOD patients had depression with psychotic features. 13 patients (27.6% and 22.8%) in late-onset and EOD groups had treatment-resistant depression episodes.

Table 1: Sociodemographic and clinical characteristics of the groups

	Late-onset depression (n=47) (%)	Early-onset depression (n=57) (%)	Control group (n=104) (%)	χ^2	df	p
Sex						
Male	19 (40.4)	32 (56.1)	45 (43.2)	0.696	1	0.487
Female	28 (59.6)	25 (43.9)	59 (56.8)			
Age, Mean±SD*	65.8±3.7	68.1±5.8	68.2±5.4	3.655	2	0.128
Psychotic feature						
Yes	10 (21.2)	20 (34.1)		2.394	1	0.134
No	37 (78.8)	37 (64.9)				
Treatment-resistant depression						
Yes	13 (27.6)	13 (22.8)		0.324	1	0.651
No	34 (72.4)	44 (77.2)				
Benzodiazepine recommendation at discharge						
Yes	15 (31.9)	23 (40.3)		0.791	1	0.418
No	32 (68.1)	34 (59.7)				
Antipsychotic recommendation at discharge						
Yes	25 (53.1)	35 (61.4)		0.712	1	0.431
No	22 (46.9)	22 (38.6)				

*Age comparison between groups was made using the Kruskal Wallis Test, SD: Standard deviation, df: Degrees of freedom

Benzodiazepine was added to 15 (31.9%) of the LOD patients in addition to antidepressant treatment at their discharge, and antipsychotic was added to 25 (53.1%). There were no differences between the groups in terms of age (p=0.487), gender (p=0.487), treatment resistance (p=0.324), psychotic features (p=0.134), additional benzodiazepine (p=0.418) or antipsychotics to the treatment at their discharge (p=0.431) (Table 1).

Kruskal Wallis Test was used to compare the groups in terms of NLR, PLR and MLR values and other elements in the complete blood count, and the post hoc Mann Whitney U test was used for significantly differentiated values. There was a significant difference between the groups in terms of NLR and PLR values (p-value: <0.001 for both values). Post hoc analysis revealed that this difference was due to higher in the LOD (p-value for NL: <0.001, p-value for PLR: <0.001) and EOD (p-value for NL: <0.001, p-value for PLR: <0.001) compared to the control group. There was no difference between early and LOD in terms of NLR (p=0.173), PLR (p=0.554) and MLR (p=0.737). Neutrophil count was also higher in LOD (p<0.001) and EOD (p<0.001) groups compared to the control group. Lymphocyte and monocyte counts were significantly higher in the control group than late-onset (p-value for lymphocyte count: <0.001, p-value for monocyte count: 0.015) and EOD (p-value for lymphocyte count: <0.001, p-value for monocyte count: 0.012) groups. The statistical significance in the platelet numbers was due to the higher platelet count in LOD compared to the control group (p=0.015) (Table 2).

DISCUSSION

The main finding of our study is that inflammatory markers were higher in geriatric depression patients compared to the control group, supporting the inflammation hypothesis of geriatric depression. In geriatric patients with depression, increased inflammation and changes in central nervous system functions depending on age and other accompanying diseases may lead to the development of depression (8). No significant difference was found between the study subgroups, LOD and EOD, in terms of variables, except for the number of platelets. In a small number of studies comparing LOD and EOD in terms of inflammation, it was observed that low-grade inflammation was more common in LOD (16). Arabska et al. (24) found that the NLR value was higher in EOD and LOD patients compared to the control group. At the same time, the NLR value was found higher in LOD than EOD. In our study, however, no difference was found between the two. A possible explanation for this fact may be the difference between the mean ages of the groups in the studies. In the study, the mean age of the LOD group was found to be statistically significantly higher than the EOD group. In our study, there was no difference between the EOD and LOD groups by age. Considering that inflammation increases with aging, the result in our study is consistent with that of Arabska et al. (24). It may also be assumed that the retrospective nature of our study may cause the study findings to differ from other studies. It is claimed that the NLR value can be used in the differential diagnosis of major depressive disorder, Alzheimer's disease and Parkinson's disease in the geriatric period (27). When adult depression patients were classified according to the severity of depression, higher PLR values were found in psychotic depression compared to mild, moderate and severe depression (28). In adolescent depression patients, the NLR value was found to be higher than the control group (29). In a recent meta-analysis, it was indicated that NLR and PLR values are higher in depression compared to the control group (30).

Table 2: Comparison of NLR, PLO, and MLO values of late- and early-onset geriatric depression patients with the control group

	Late-onset depression (n=47)	Early-onset depression (n=57)	Control	χ^2	df	p	Post-Hoc
Neutrophil to lymphocyte ratio	129.82	146.42	70.08	69.678	2	<0.001	LOD=EOD>C
Platelet lymphocyte ratio	130.06	133.42	77.10	43.202	2	<0.001	LOD=EOD>C
Monocyte lymphocyte ratio	109.80	112.88	97.51	2.869	2	0.238	LOD=EOD=C
Neutrophil	130.29	136.92	75.08	50.038	2	<0.001	LOD=EOD>C
Lymphocyte	83.32	78.04	128.58	33.490	2	<0.001	C>LOD=EOD
Platelet	123.65	112.03	91.72	10.339	2	0.006	LOD>EOD=C
Monocyte	91.76	90.57	117.89	10.327	2	0.006	C>LOD=EOD

Kruskal Wallis test results. Statistical significance was accepted as p<0.016 in post hoc analysis. LOD: Late-onset depression, EOD: Early-onset depression, C: Control group. NLO: Neutrophil lymphocyte ratio, PLO: Platelet lymphocyte ratio, MLO: Monocyte lymphocyte ratio. Values are given as mean ranks, df: Degrees of freedom

In our study, following the literature, in late and early onset geriatric depression; NLR and PLO values were found to be higher than the control group, supporting the inflammation hypothesis of depression. Obtaining results for the geriatric period similar to those with earlier ages may indicate that the depression factor may have an effect on these values rather than the age factor.

MLR has been less studied than the other two markers in the literature. There are no studies on MLR in depression. The lack of difference between the control group and the LOD and EOD groups in terms of MLR in the present study is a new finding that contributes the literature. This finding may indicate low MLR sensitivity in geriatric depression relevant to NLR and PLR. In the Netherlands Study of Depression in Older Persons (NESDO), 10 inflammatory markers other than GDF15 were found at similar levels between the LOD and EOD groups (16).

Since this study is the first to compare MLR and PLR between the geriatric depression and the control group and between EOD and LOD, it can be considered to contribute to the literature on this subject. It can also be expected to guide future studies, as the number of studies comparing LOD and EOD in inflammatory parameters is still low. Considering the limitations of this study, the general limitations regarding the file review method are also valid for this study. Using the analysis method in which the frequencies of the variables in the groups and the differences between the groups are compared rather than any other method, can be considered as the statistical limitation of the study. The diagnosis of previous episodes in EOD was given according to the patient's own historical narrative. Accordingly, the diagnostic validity level of past episodes may be low. Other limitations include the possibility that patients with LOD have difficulty remembering the past, forgetting previous episodes or skipping the record files during the review. Another limitation of the study is that the depression cases in the control group selected from the family health centers were evaluated only according to the previous disease and drug information. Another limitation is the uncontrolled effect of smoking habits and body mass index values on blood results. Moreover, conducting the research only among the inpatients reduces the generalizability of this study.

In conclusion, the NLR and PLR can be considered as markers reflecting inflammation rather than being markers that can distinguish them in terms of onset of the disease in geriatric depression patients. Further studies with extensive samples are needed to investigate how NLR, PLR, and MLR variables are affected by treatment, their correlation to disease severity, and whether they differ according to depression subtypes in geriatric depression patients.

Contribution Categories		Author Initials
Category 1	Concept/Design	S.O.
	Data acquisition	S.O., S.B.O.
	Data analysis/Interpretation	S.O., S.B.O.
Category 2	Drafting manuscript	S.O.
	Critical revision of manuscript	S.O., S.B.O.
Category 3	Final approval and accountability	S.O., S.B.O.
Other	Technical or material support	N/A
	Supervision	N/A

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Informed Consent: Since it is a retrospective study, patient consent was not obtained.

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Conflict of Interest: The authors do not have any conflict of interest.

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