Original Article
Eurasian Journal of Critical Care

Examination Of Neutrophil/Lymphocyte (NLR), Monocyte/Lymphocyte (MLR), And Platelet/Lymphocyte (PLR) Ratios Between Alzheimer's Disease and Vascular Dementia

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Abstract

Background: The present study aims to investigate whether proinflammatory marker ratios in whole blood differ in these two dementia diseases.

Material and Method: This study will involve Alzheimer's disease (AD) and vascular dementia (VaD) patients who were treated as outpatients in the outpatient clinic and inpatients in the ward of the Neurology Department of Adnan Menderes University Hospital. The patients' diagnoses will be scanned in the hospital information system. The admission blood results of patients who presented between January 2018 and September 2020 will be included, and the patients' hemogram results will be scanned retrospectively. Neutrophil/lymphocyte, monocyte/lymphocyte, and platelet/lymphocyte ratios in the hemogram results will be calculated and recorded.

Result: In the AD-VaD comparison of the patients participating in the study, a significant difference was identified between the variability of platelet/lymphocyte (PLR) and NLRs (NLR) ($p<0.001$). Moreover, a significant difference was found between the mean ages of patients with vascular dementia and those with Alzheimer's dementia ($p<0.0001$).

Conclusion: While proinflammatory markers obtained secondary to inflammation are significant in AD since it is a chronic and progressive process, the use of these markers is limited due to the gradual course after an acute event in vascular dementia. Furthermore, there is a need for additional studies on peripheral blood cells to identify the potential prodromal biomarkers of AD.

Keywords: Alzheimer's dementia, NLR, proinflammatory markers, vascular dementia.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that arises with irreversible loss of neurons in the hippocampus and cortex regions of the brain. Memory impairment in Alzheimer's disease often takes place as the inability to learn new information,which is characterized by short-term memory loss. Language disorders (left hemisphere posterior heteromodal) are also evident in Alzheimer's disease (1).

The pathology of AD consists of abundant senile amyloid plaques, neurofibrillary tangle structure, significant synapse and cholinergic losses, and neuron atrophy in certain regions of the brain (2).

It is known that Alzheimer's patients have synaptic loss, especially in the hippocampus, at a rate of 45-55% (3).

Alzheimer's disease, the most common cause of dementia, is reported to be found in 5 million cases over the age of 65 nowadays, according to studies conducted in the United States of America (USA) (4).

The term dementia is a persistent, frequently progressive clinical picture that leads to impairment in mental functions and inadequacy in a person's activities of daily living. The use of the Diagnostic and Statistical Manual for Mental Disorders fourth edition (DSM-IV) diagnostic criteria has been recommended to diagnose dementia (5). TheDSM-IV criteria for dementia are as follows:

Development of multiple cognitive impairments, including memory impairment and at least one of the following: (I). Aphasia, apraxia, agnosia, disruption of executive functions (II). Cognitive impairments should meet the following criteria (III). They must be severe enough to cause deterioration in professional or social functions (IV). A decrease must be observed compared to the previous high level of function (V). Dementia cannot be diagnosed if cognitive impairments develop only during delirium (VI). However, if dementia is experienced when there is no delirium, both dementia and delirium can be diagnosed. (VII). Dementia may be etiologically related to general internal conditions, substance abuse (including toxin exposure), or a combination of these factors.

Another cause of dementia is vascular dementia (VaD). VaD is characterized by loss of clinical and

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Received: 22.11.2023 • **Revision:** 24.11.2023 • **Accepted:** 14.12.2023
DOI: 10.55994/ejcc.1394602

Cite this article as: Bulut TY, Sair A . Examination Of Neutrophil/Lymphocyte (Nlr), Monocyte/Lymphocyte (MLR), And Platelet/Lymphocyte (PLR) Ratios Between Alzheimer's Disease And Vascular Dementia. Eurasian Journal of Critical Care. 2023;5(3): 102-106

cognitive functions as a result of ischemic, hemorrhagic, or hypoperfusion damage to the brain (6). Multi-infarct dementia develops as a result of large vessel disease, whereas subcortical small vessel disease is observed in Binswanger's type VaD. Tissue loss of around 100 ml in the cortical and subcortical areas leads to dementia. In addition to tissue loss, in other words, infarct volume, the localization of the lesion is also important. The thalamus, mesial temporal area, hippocampus, frontobasal areas, and angular gyrus areas are important for these areas (7).

The present study aims to investigate whether proinflammatory marker ratios in whole blood differ in these two dementia diseases.

Materials And Methods

The current research is a hospital-based cross-sectional study. It will involve AD and vascular dementia patients who were treated as outpatients in the outpatient clinic and inpatients in the ward of the Neurology Department of Adnan Menderes University Hospital. The patients' diagnoses will be scanned in the hospital information system. The admission blood results of patients who presented between January 2018 and September 2020 will be included, and the patients' hemogram results will be scanned retrospectively. Neutrophil/lymphocyte, monocyte/lymphocyte, and platelet/lymphocyte ratios (NLR, MLR and, PLR) in the hemogram results will be calculated and recorded. Patients diagnosed with dementia other than Alzheimer's disease and vascular dementia and healthy controls will not be included in the study. If the study group exhibits a normal distribution, continuous data will be evaluated with Student's t-test. If it does not, the Mann-Whitney U test will be used. Categorical data will be evaluated with the chi-square test. Besides, a multivariate regression analysis was performed to compare the results between Alzheimer's dementia and vascular dementia patients. The study covers 33 months between January 2018 and September 2020. $p<0.05$ will be considered for statistical significance.

Results

A total of 104 patients were included in the study. Of them, 60 were male and 44 were female, 66 had Alzheimer's dementia, and 38 had vascular dementia. Of male patients,34 had Alzheimer's dementia, and 26 had vascular dementia. Of female patients,32 had Alzheimer's dementia, and 12 had vascular dementia.

The mean age of the patients included in the study was 73.51 years, and the lowest age was 59 years, while the highest age was 84 years. It was determined that the mean age of male patients was 72.76 years, the lowest age was 59 years, and the highest age was 82 years. The mean age of female patients was 74.54 years, the lowest age was 66 years, and the highest age was 84 years. The mean age of patients with Alzheimer's dementia was 75.53 years, the lowest age was 68 years, and the highest age was 84 years. The mean age of patients with vascular dementia was 70.03 years, the lowest age was 59 years, and the highest age was 78 years. A significant difference was revealed between the mean age of patients with vascular dementia and patients with Alzheimer's dementia ($p<0.001$).

In the evaluation of the patients' PLRs, the mean PLR was found to be 148.14, the lowest value was 104, and the highest value was 188.24. Concerning the platelet/lymphocyte ratio of Alzheimer's dementia patients, the mean platelet/lymphocyte ratio was 155.85, the lowest platelet/lymphocyte ratio was 131, and the highest was 188. In patients with vascular dementia, the mean platelet/lymphocyte ratio was 134.75, the lowest platelet/lymphocyte ratio was 104, and the highest platelet/lymphocyte ratio was 181. A significant difference was determined between the patients' diagnoses and the variability of PLRs ($p<0.001$).

In the evaluation of the patients' NLRs the mean NLR was 9.15, the lowest value was 3.05, and the highest value was 18.20. The mean NLR of patients with Alzheimer's dementia was 10.42, the lowest NLR was 4.5, and the highest NLR was 18.2. In patients with vascular dementia, the mean NLR was 6.95, the lowest NLR was 3.5, and the highest NLR was 15.3. A significant difference was identified between the patients' diagnoses and the variability of NLRs ($p<0.0001$).

In the evaluation of the patients' MLRs, the mean MLR was 238.81, the lowest value was 217, and the highest value was 264. It was revealed that the mean MLR value was 238.6, the lowest MLR value was 217, and the highest MLR value was 264 in patients with Alzheimer's dementia. In vascular dementia patients, the mean MLR value was 239.15, the lowest MLR value was 224, and the highest MLR value was 256. No significant difference was found between the patients' diagnoses and the variability of MLRs ($p=0.81$).

The mini-mental test (mmt) mean value of patients was found as 19.78, the lowest mmt score as 17, and the highest value as 23. The mean mmt value of patients with Alzheimer's dementia was 20.03, the lowest mmt score was 7, and the highest mmt value was 23. The mean mmt score of patients with vascular dementia was 19.36, the lowest mmt score was 17, and the highest score was 23. There was a significant weak difference between the patients' diagnoses and the variability of the mmt ratios ($p=0.049$) (Table 1).

Significant regression results were obtained between Alzheimer's dementia and vascular dementia patients when the results of logistic regression analysis were compared with age ($p<0.0001$), neutrophil/lymphocyte (0.008), platelet/lymphocyte (0.006), and mini-mental test (0.002) (Table 2).

Table 1: Comparison of inflammatory markers, age and mini-mental values between Alzheimer's dementia and vascular dementia

	Alzheimer's dementia		Vascular dementia		Statistical analysis		
	Mean	SD	Mean	SD	F	df	p
Age	75.53	3.90	70.02	4.10	0.075	102	<0.0001
Monocyte/lymphocyte	12.85	1.58	6.72	1.09	22.40	102	0.807
Neutrophil/lymphocyte	10.41	3.07	6.95	2.89	0.176	102	<0.0001
Platelet/lymphocyte	155.84	16.89	134.76	20.14	1.292	102	<0.0001
	Mean	SD	Mean	SD	U	Z	p
Mini-mental test	20.03	1.66	19.36	1.49	969.500	-1.966	0.049

Table 2: Logistic regression analysis results between Alzheimer's dementia and vascular dementia patients

İndependent variables	B	S.E	Exp. (B) %95 Cl	p
Age	-0.561	0.136	0.570 (0.437-0.744)	<0.0001
Neutrophil/lymphocyte	-0.353	0.133	0.945 (0.907-0.984)	0.008
Platelet/lymphocyte	-0.057	0.021	0.703 (0.542-0.912)	0.006
Minimental test	-1.009	0.322	0.365 (0.194-0.685)	0.001
Constant	71.868	16.542	1.629	<0.0001

Discussion

Studies comparing patients with AD and healthy individuals of the same age showed that immune functions were more impaired in AD (8-10). It has been asserted that increased immune aging, in other words, chronic oxidative inflammatory stress, may be an effective factor in the development of AD (9). Since immune functions are a good indicator of the aging rate, the analysis of these functions can be used in the early diagnosis of premature and rapid aging in humans (11,12).

In the study conducted with patients with cerebral hemorrhage, patients whose condition worsened in the first week had higher total white blood cell count, higher neutrophil count, and lower lymphocyte count. This refers to a higher NLR calculation. NLR was independently associated with neurological deterioration and was determined to be the best discriminating variable for predicting negative outcomes. In a retrospective analysis of patients with acute intracerebral hemorrhage (ICH), NLR values obtained 24-48 hours and 5-7 days after the onset of symptoms were significantly higher in deceased patients, whereas they remained relatively stable in patients who survived (13). The mean age of the patients included in the study was found to be 73.51 years. In the study by Shigemizu, D et al., a total of 271 AD patients were included, the male/female ratio was 1:2.15, and the mean age of the AD patients included in the study was 79.55. It is possible to make a comment that there is a compatibility between our study and the literature in terms of mean ages, and the high age of patients is known as a risk factor in AD cases (14).

In the study, 66 patients had AD, and 38 had VaD. Of the patients with AD,34 were male, and 32 were female. Of the cases with vascular dementia, 26 were male, and 12 were female. In the study by Claire Thompson et al., female dominance was found to be 61.5% in the AD group, and male dominance was found to be 66.2% in the VaD group (15,16). In other words, the rate of women in AD dementia is 72.7%, whereas the rate of men is 57.6%. In our study, the rate of men in vascular dementia is 43.4%, while the rate of women is 27.3%. These results were found to be consistent with the literature. This difference is explained by the long life expectancy in women (17).

In the study by Carmen Vida et al., a mini-mental test was applied to assess cognitive findings in AD cases. In the study, the value of 23 was considered as the threshold value for AD. In our study, the lowest mini-mental ratio of AD patients was 7, and the highest ratio was 23. The mini-mental test mean value of AD patients in our study was found to be 20.03. In terms of the test used, compatibility was observed between our research and the literature (18). Additional studies can be conducted to check whether there is any correlation between mini-mental values and proinflammatory markers. Neutrophil, lymphocyte, and platelet ratios in the peripheral blood of the patients were evaluated in our study. Researchers performed biomarker evaluation in peripheral blood in many diseases, including AD (19-21).

Neutrophils have been identified in the brain parenchyma of patients with Alzheimer's disease (22). In the study, neutrophil homeostasis in peripheral blood was observed to shift toward proinflammatory properties in AD patients at the later stages. Cognitive decrease in AD patients was also found to be proportional to these changes. It can be assumed that the increased levels of circulating cytokines in AD patients may be associated with cytokine production

increased by previously reported activated monocytes and lymphocytes in patients with Alzheimer's disease.

In our study, the monocyte/lymphocyte ratio was found to be 10.41±1.58 in the AD group and 6.72±1.09 in the VaD group when patients in the AD group and patients in the VaD group were compared. There was no significant difference between the two groups in terms of monocyte/lymphocyte ratio (P>0.05), but the high ratio obtained in the AD group is consistent with the hypotheses in the literature. In our study, the NLR was 10.41±3.07 in AD patients and 6.95±2.89 in VaD patients, and the significant difference between the two groups in terms of NLR (P<0.001) was found to be consistent with the literature. In the study conducted by Yuan Dong et al. (2018), blood samples collected from patients with dementia and Alzheimer's disease indicated neutrophil hyperactivation associated with increased reactive oxygen production and elevated neutrophil levels. Moreover, the same study strongly suggests that it may be a prognostic blood biomarker in patients with Alzheimer's disease. In our study, the PLR was 155.84±16.89 in AD patients and 134.76±20.14 in VaD patients, and the significant difference between the two groups in terms of PLR (P<0.001) was found to be consistent with the literature (22).

In the study performed by Kuyumcu et al., NLR was significantly higher in AD patients compared to controls. Although NLR values in the normal population are around 1-3, the NLR identified in AD cases was found to be 10.41±3.07 in the study we conducted in line with the literature (23).

Conclusion

AD is a degenerative disease. It takes time for symptoms to appear and develop. Inflammation is known to emerge earlier in AD and contribute to neurodegeneration and pathogenesis at later stages. Inflammation is continuous in AD, whereas the neurodegenerative process is not prominent in vascular dementia as in AD. In our study, proinflammatory blood parameters, which are used in many areas, were found to be significantly different in AD and VaD, as predicted. The markers obtained secondary to inflammation are therefore significant in AD, while a significant difference was determined between AD and VaD since an acute inflammation was observed in 37 vascular dementia patients but the course was not progressive and chronic, as in AD. Furthermore, there is a need for additional studies on peripheral blood phagocytes, function in lymphocytes, and oxidative-inflammatory stress changes to identify potential prodromal biomarkers of AD.

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