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Alzheimer Hastalığının Periferik Kan Sayımındaki Değişkenlerle İlişkisi

Association of Alzheimer's Disease with Variables in Peripheral Blood Count

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ÖZ

Giriş: Alzheimer hastalığında nöropatolojik değişikliklerin klinik bulgulardan 10-20 yıl önce başladığı gösterilmiştir. Preklinik dönemde gösterebilecek biyobelirteçlerin belirlenmesi erken tanı ve tedavi için faydalı olacaktır. Çalışmamızda periferik kan sayımı parametrelerini Alzheimer hastalığının farklı evreleri için potansiyel biyobelirteç olarak değerlendirmeyi amaçladık.

Yöntem: Çalışmamıza ardışık olarak 48 hafif bilişsel bozukluk, 76 Alzheimer hastası ve 117 sağlıklı kontrol dahil edildi. Olguların kognitif fonksiyonları Mini Mental durum muayenesi (MMSE) ve Saat Çizim Testi ile değerlendirildi. Düşük MMSE puanı alanlara ayrıca Klinik Demans Evrelendirme (CDR) ölçeği uygulandı. Alzheimer hastalığı tanısı için DSM-IV ve NINCDS-ADRDA kriterleri kullanıldı ve Alzheimer hastaları hafif ve orta/ağır evre olmak üzere ikiye ayrıldı. Tüm hastaların rutin biyokimya ve tam kan sayımı incelmeleri yapıldı. Nötrofil/lenfosit oranı (NLO), mutlak nötrofil sayısının lenfosit sayısına bölünmesi, trombosit/lenfosit oranı (TLO) ise mutlak trombosit sayısı lenfosit sayısına bölünmesi ile elde edildi.

Bulgular: Hafif bilişsel bozukluk grubunun trombosit dağılım genişliği (PDW) düzeyleri, orta-ağır evre Alzheimer hastaları ve kontrol grubundan yüksek bulundu (p= 0,001). Hafif ve orta-ağır evre tüm Alzheimer hastalarının NLO ve TLO düzeyleri, kontrol grubundan yüksek idi (p= 0,005 ve p< 0,001).

Sonuç: Çalışmamız, kognitif yıkımda inflamasyonun oynadığı rolü desteklemektedir. Nötrofil/lenfosit ve trombosit/lenfosit oranları Alzheimer hastalığında sağlıklı bireylerden, PDW değerleri ise hafif bilişsel bozukluğunda Alzheimer hastalarından anlamlı farklılık göstermektedir. Nötrofil/lenfosit ve trombosit/lenfosit oranların Alzheimer hastalığının, yüksek PDW değerlerin de hafif bilişsel bozukluğunun biyobelirteçleri olarak potansiyel değer taşımakta olduğunu düşünmekteyiz.

Anahtar Kelimeler: alzheimer hastalığı, hafif bilişsel bozukluk, nötrofiller, kan trombositleri, lenfositler, inflamasyon

ABSTRACT

Objective: The neuropathological changes in Alzheimer's disease may begin 10- 20 years before clinical findings. Identifying biomarkers in the preclinical period will be useful for early diagnosis and treatment. In our study, we aimed to evaluate the peripheral blood count parameters as potential biomarkers in different stages of Alzheimer's disease.

Method: Fourty-eight patients with MCI, 76 AD patients and 117 healthy controls were included consecutively. Cognitive functions of the cases were evaluated with Mini Mental State Examination (MMSE) and Clock Drawing Test. Those with low MMSE scores were also administered the Clinical Dementia Rating (CDR) scale. DSM-IV and NINCDS-ADRDA criteria were used for the diagnosis of Alzheimer's disease, and Alzheimer's disease was divided into mild and moderate-to-severe stages. The neutrophil/lymphocyte ratio (NLR) was obtained by dividing the absolute neutrophil count by the lymphocyte count, and the platelet/lymphocyte ratio (PLR) was obtained by dividing the absolute platelet count by the lymphocyte count.

Results: The platelet distribution width (PDW) levels of the mild cognitive impairment group were higher than those of moderate-to-severe Alzheimer's patients and the control group (p= 0.001). NLR and PLR levels of all mild and moderate-to-severe Alzheimer's patients were higher than the control group (p= 0.005 and p< 0.001).

Conclusion: Our study supports the role of inflammation in cognitive decline. We suggest that neutrophil/lymphocyte and platelet/lymphocyte ratios and PDW value may be potential biomarkers for Alzheimer's disease and mild cognitive impairment respectively.

Keywords: alzheimer's disease, mild cognitive impairment, neutrophils, blood platelets, lymphocytes, inflammation

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INTRODUCTION

The neuropathological changes in Alzheimer's disease (AD) may begin 10-20 years before clinical findings (1). The identification of biomarkers that may indicate the onset and progression of the disease process will be useful for early diagnosis and treatment. In particular, biomarkers are needed to indicate the likelihood that patients with mild cognitive impairment (MCI) will progress to AD. Amiloid-beta (Aβ) and tau protein are the most commonly investigated markers in cerebrospinal fluid and peripheral blood. High blood levels of Aβ-42 and a low ratio of Aβ-42/Aβ-40 have been shown to be associated with an increased five-year risk of dementia, and high levels of tau protein with an increased rate of cognitive decline (2). However, since more sensitive techniques are required for the detection of low Aβ and tau protein levels in the preclinical period, their application as routine markers in the screening and diagnosis of AD is limited. Since cerebrospinal fluid examinations are invasive, a marker that can be obtained from peripheral blood tests will be important. There is a view that neuroinflammation in AD is not limited to the microglial level and that the peripheral innate immune system is also involved in the pathological process. Microglial activation and the release of proinflammatory cytokines and chemokines lead to functional and structural changes that result in cerebral neurodegeneration (3).

Lymphocyte and neutrophil counts, neutrophil/ lymphocyte ratio (NLR), platelet/ lymphocyte ratio (PLR), mean platelet volume (MPV) and platelet distribution width (PDW) have been reported to be associated with poor prognosis or short survival in many central nervous system disorders, including multiple sclerosis (4), Parkinson's disease (5), amyotrophic lateral sclerosis (6), cerebrovascular disease (7) and brain gliomas (8). High NLR has been associated with poor prognosis in coronary artery disease (9), various malignancies such as ovarian and hepatocellular carcinoma (10,11), and inflammatory diseases such as Behçet's disease (12). In our study, we investigated whether peripheral blood count variables could be a potential biomarker for mild cognitive impairment and Alzheimer's disease. In our study, we aimed to evaluate the peripheral blood count parameters as potential biomarkers in different stages of Alzheimer's disease.

MATERIALS AND METHODS

Between January 2020 and January 2022, 48 patients with MCI, 76 patients with AD and 117 subjects with normal cognitive function (≥ 65 years of age) who were consecutively admitted to the neurology outpatient clinic were enrolled. The patients' cognitive functions were assessed using the MMSE (13) and the Clock Drawing Test. Those with low MMSE scores were also evaluated with the Clinical Dementia Rating (CDR) scale (14). The MMSE scores of the control subjects was between 24- 30 points and the CDR score was 0. Controls were fully independent according to the Katz Daily Activities Scale (15). MMSE scores were between 24-30 points and CDR score was 0.5 in patients with MCI. These were non-demented patients who were able to perform activities of daily living. Patients with Alzheimer's disease met DSM-IV and NINCDS/ADRDA criteria (16,17). According to the results of the CDR assessment, patients with Alzheimer's disease were grouped into mild (CDR 1, n= 44), moderate (CDR 2, n= 27) and severe (CDR 3, n= 5) stages AD. Since the number of patients in the moderate and severe AD groups was small, these patients were combined in the same group (n= 32).

Medical history (hypertension, diabetes mellitus, coronary artery disease, medications, smoking and alcohol consumption) was obtained from all patients. Laboratory tests and brain imaging (computerized tomography or magnetic resonance imaging) were recorded. Exclusion criteria were other neurological diseases (Parkinson's disease, cerebrovascular disease), depression (as indicated by a score of ≥11 on the Geriatric Depression Scale (18)), chronic alcoholism, tumours, obvious infectious or inflammatory conditions that could affect routine blood counts, autoimmune and haematological diseases (leukemia, malnutrition anemia, aplastic anemia, hemolytic anemia, hemorrhagic anemia, platelet disorders), end-stage renal disease and chronic liver disease, abnormal vitamin B12 levels or thyroid function tests, medical treatments (anti-inflammatory analgesics, corticosteroids, antibiotics, gastrointestinal agents, anticholinergics, antidepressants and other central nervous system active agents).

Fasting venous blood samples were taken from all subjects in the morning after a 12-hour fast and analyzed within 60 minutes. The first 3 ml of blood was used for complete blood count analysis and was drawn into a vacuum tube containing ethylenediaminetetraacetic acid and studied on a Sysmex XN-1000 device. The remaining 5 ml of blood was drawn into an anticoagulant-free vacuum tube and analyzed on a Roche Cobas c702 device. Fasting blood glucose, lipid levels, leukocyte, platelet, lymphocyte and neutrophil counts, PDW, MCV and MPV were analyzed automatically. NLRs and PLRs were calculated as the ratio of neutrophil count to lymphocyte count and platelet count to lymphocyte count, respectively.

Our study was approved by the local scientific research ethics committee with the decision dated 6 January 2020 and numbered 01/08, and written informed consent was obtained from all participants for inclusion in the study. The declarition of Helsinki was followed in the study.

Statistical Analysis

The Shapiro-Wilk test was used to test the conformity of quantitative data to the normal distribution. Results were expressed as mean ± standard deviation for normally distributed quantitative variables, median (min – max) for non-normally distributed quantitative variables or number (percentage) for categorical variables. One–way ANOVA test was used to compare the normally distributed quantitative variables between the groups, and the Kruskal–Wallis test was used to compare the non-normally distributed quantitative variables. Comparisons of categorical variables were made using the chi-squared test. Area under the curve (AUC) values were calculated for the PDW, NLR, and PLR variables by the ROC curve analysis to discriminate MCI, mild or moderate-to-severe groups. Cut-off values for PDW, NLR, and PLR variables were determined. The values for sensitivity and specificity were calculated based in accordance with these cut-off points. Data were analyzed using SPSS 20.0 (IBM SPSS Inc., Chicago, IL, USA) and MedCalc 11.1.1.0 (MedCalc Software bvba, Ostend, Belgium) statistical softwares.

RESULTS

The study included 48 MCI and 76 Alzheimer's patients (44 mild AD, 32 moderate-to-severe AD). They were compared with 117 healthy

controls. The groups were similar in terms of age and gender (p> 0.05). There were no differences between the groups for hypertension, diabetes, coronary artery disease, smoking and alcohol consumption (p> 0.05). The MMSE scores of patients with MCI were higher than those of patients with mild and moderate-to-severe AD, and the MMSE scores of patients with mild AD were higher than those of patients with moderate-to-severe AD (p< 0.001). The Clock Drawing Test scores of the MCI group was higher than that of the mild and moderate-to-severe AD groups (p< 0.001). Demographic and clinical data of all patients are shown in Table 1.

PDW levels of the MCI group were higher than those of the moderate-to-severe AD and control groups (p= 0.001). The levels of NLR and PLR were higher in all patients with mild and moderate-to-severe Alzheimer's disease than in the control group (p= 0.005 and p< 0.001). There were no differences in fasting blood glucose, total cholesterol, HDL- cholesterol, LDL- cholesterol, leukocytes, neutrophils, lymphocytes, platelets and MPV between groups (p> 0.05). (Table 2)

The results of the ROC curve analysis to discriminate between MCI, mild AD or moderate-to-severe AD groups based on PDW, NLR and PLR variables are shown in Table 3.

A PDW value greater than 16.6 was found to be a significant threshold for differentiating the mild cognitive impairment group (AUC= 0.661; p= 0.001). The sensitivity and specificity of a PDW value greater than 16.6 for MCI were 70.8% and 58.6% respectively. The NLR and PLR values did not have a significant effect on the differentiation of MCI (p= 0.537 and p= 1.000). (Figure 1)

PDW (AUC= 0.615; p= 0.020), NLR (AUC= 0.618; p= 0.018) and PLR (AUC= 0.600; p= 0.045) values above 16.5 were found to be significant thresholds in differentiating the mild stage AD group from controls and moderate-to-severe stage AD patients. For the mild AD group, the sensitivity and specificity of PDW above 16.5 were 63.6% and 59.9%, respectively. For NLR values, the cut-off point at which mild AD differed from healthy control and MCI was determined to be >1.66, and the sensitivity and specificity at this point were 86.4% and 41.9%, respectively. For PLR, the cut-off point was determined to be > 98.4, with a sensitivity of 84.1% and a specificity of 38.5%. (Figure 2)

The NLR (AUC= 0.656; p =0.008) and PLR (AUC=0.728; p< 0.001) cut-off values at which the moderate-to-severe AD group differed from healthy controls and MCI were >1.65 (sensitivity 87.1% and specificity 47%) and >116 (sensitivity 80.6% and specificity 61.5%), respectively. PDW had no significant effect in differentiating the moderate-to-severe AD group (p= 0.655). (Figure 3)

Table 1. Demographic and Clinical Features of the Study

	Mild cognitive impairment (n= 48)	**Mild Alzheimer's Disease (n= 44)**	**Moderate-to-severe Alzheimer's Disease (n= 32)**	**Controls (n= 117)**	***p***
Genger (female)	22 (45.8)	22 (50.0)	20 (62.5)	64 (54.7)	0.486
Age (year)	71.6 ± 8.2	73.2 ± 8	71.7 ± 8.1	70.2 ± 7.6	0.162
Hypertension (yes)	33 (68.8)	27 (61.4)	15 (46.9)	82 (70.1)	0.089
Diabetes mellitus (yes)	17 (35.4)	17 (38.6)	4 (12.5)	37 (31.6)	0.080
Coronary artery disease (yes)	8 (16.7)	8 (18.2)	5 (15.6)	27 (23.1)	0.682
Smoking (yes)	9 (18.8)	7 (15.9)	6 (18.8)	19 (16.2)	0.968
Alcohol (yes)	6 (12.5)	4 (9.1)	4 (12.5)	14 (12.0)	0.951
CDR score	1 (1 - 1) [bc]	1 (1 - 3) [b]	3 (1 - 4)	-	**<0.001**
MMSE score	27 (25 - 29) [bc]	22.5 (10 - 23) [b]	13.5 (5 - 19)	-	**<0.001**
Clock Drawing test score	6.5 (0 - 7) [bc]	2 (0 - 7)	0 (0 - 7)	-	**<0.001**

a p<0.05 compared with controls,
b p<0.05 compared with moderate-to-severe Alzheimer's Disease
c p<0.05 compared with mild Alzheimer's Disease ,
CDR: Clinical Dementia Rating; MMSE: Mini Mental State Examination

Table 2. Laboratory Results of Study Groups

	Mild cognitive impairment (n= 46)	Mild Alzheimer's Disease (n= 43)	Moderate-to-severe Alzheimer's Disease (n= 32)	Controls (n= 117)	*p*
Leokocyte (/mm^3)	7 (3.2 – 13.7)	6.9 (3.2 – 15.2)	7 (4.4 – 9.7)	7.3 (3.5 - 47)	0.447
Neutrophil (/mm^3)	4 (0.6 – 12.4)	4.2 (1.8 – 13.1)	3.9 (2.2 – 7.4)	4.1 (1.1 – 56.8)	0.944
Lymphocyte (/mm^3)	2.0 ± 0.7	1.9 ± 0.7	1.8 ± 0.6	3.5 ± 6.6	0.085
Platelets (/mm^3)	224.8 ± 58.5	241.9 ± 76.3	253.5 ± 56.1	246.5 ± 81.5	0.283
MPV	9.2 (6.2 – 13.1)	9.1 (1.5 – 12.2)	9.1 (6.9 - 12)	9.3 (6.8 – 13.3)	0.341
PDW	16.9 (14.6- 21)[ab]	16.8 (13.2 – 18.2)	16.4 (9 – 18.3)	16.4 (10.5 – 18.3)	**0.001**
NLR	2 (0.2 – 13.8)	2.4 (1.1 – 14.6)[a]	2.2 (1 – 5.2)[a]	1.8 (0.2 - 27)	**0.005**
PLR	111.9 (37.9 – 278.5)	121.4 (51 – 299.2)[a]	143 (77.5 – 328.6)[a]	101.8 (4.8 – 461.1)	**<0.001**
Fasting Blood Glucose (mg/dL)	107.5 (72 - 274)	103 (75 - 221)	99 (4.2 - 150)	104 (73 - 266)	0.258
Total cholesterol (mg/dL)	208.3 ± 53.4	202.2 ± 41.2	194.3 ± 35.7	202.5 ± 41.8	0.595
Triglyceride (mg/dL)	146 (0 - 491)[b]	110 (46 - 410)	101 (45 - 489)	135.5 (41 - 496)[b]	**0.008**
HDL-cholesterol (mg/dL)	49.5 (0 - 112)	49 (33 - 112)	55.5 (30 - 115)	48 (24 - 80)	0.247
LDL- cholesterol (mg/dL)	133 ± 40.7	129.1 ± 30.2	124.4 ± 34	134.7 ± 33.5	0.492

a p<0.05 compared with controls
b p<0.05 compared with moderate-to-severe Alzheimer's Disease
c p<0.05 compared with mild Alzheimer's Disease
MPV: mean platelet volume; PDW: platelet distribution width; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio

Table 3. Results of the ROC Curve Analysis to Discriminate Mild Cognitive Impairment, Moderate-to-Severe Alzheirmer's Disease or Mild Alzheimer's Disease Groups Based on the PDW, NLR and PLR Variables

		AUC	SE	*p*	Cut-off	Sensitivity (%)	Specificity (%)
Mild cognitive impairment	PDW	0.661	0.043	**0.001**	**>16.6**	70.8	58.6
	NLR	0.529	0.045	0.537	>1.3	93.7	18.8
	PLR	0.500	0.045	1.000	>114.6	51.3	59.2
Mild Alzheimer's Disease	PDW	0.615	0.049	**0.020**	**>16.5**	63.6	59.9
	NLR	0.618	0.045	**0.018**	**>1.66**	86.4	41.9
	PLR	0.600	0.048	**0.045**	**>98.4**	84.1	38.5
Moderate-to-severe Alzheimer's Disease	PDW	0.474	0.061	0.655	>16	80.2	29.0
	NLR	0.656	0.051	**0.008**	**>1.65**	87.1	47.0
	PLR	0.728	0.046	**<0.001**	**>116.0**	80.6	61.5

PDW: platelet distribution width; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio

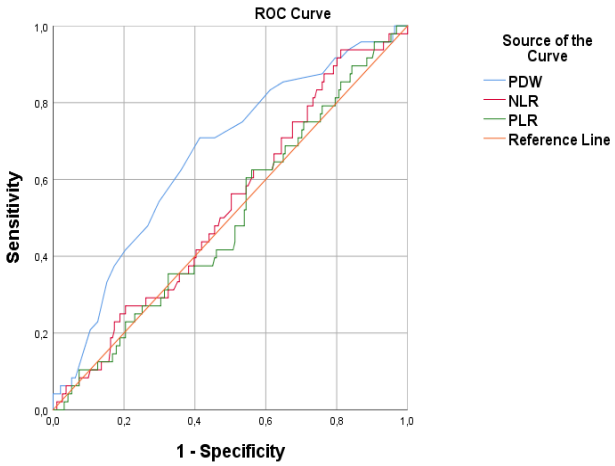

Figure 1. ROC curve of mild cognitive impairment

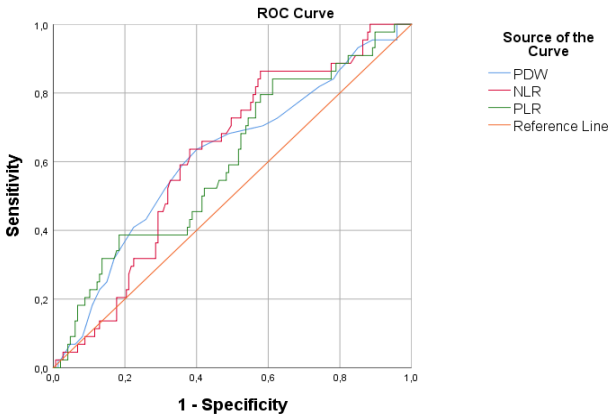

Figure 2. ROC curve of mild Alzherimer's Disease

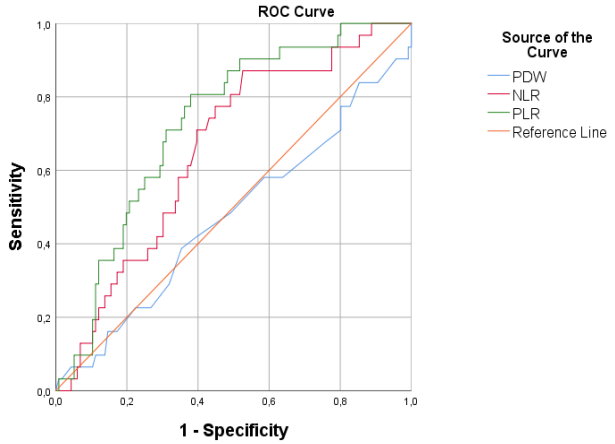

Figure 3. ROC curve of moderate-to-severe Alzheimer's Disease

DISCUSSION

In our study, we found that NLR was higher in mild Alzheimer's disease and PLR was higher in moderate-to-severe stage Alzheimer's disease than in healthy control subjects. In our study, we found that NLR and PLR were higher in mild and moderate-to-severe stage Alzheimer's disease compared to healthy controls, and PDW was higher in MCI compared to moderate-to-severe stage Alzheimer's disease and healthy controls. There is increasing evidence that neuroinflammation plays a role in the pathogenesis of AD. It has been reported that the inflammatory environment of the brain is determined by cross-reactions between microglial cells, systemic immune cells and cytokines. Genetics, environmental factors and systemic diseases (e.g. diabetes) are the main known causes of inflammation. However, it has been shown that almost all aspects of the immune system are also affected by the normal ageing process, known as 'immunosenescence'. While innate immune activity (neutrophils) increases with age, acquired immune activity (lymphocytes) decreases, and this is even more pronounced in individuals with Alzheimer's disease (19). It has been shown that the risk of dementia is increased in individuals with a markedly disturbed balance between innate and acquired immunity (20).

In the preclinical period of Alzheimer's disease, NLRs and PLRs, which integrate information from two blood cells, are reported to have a higher diagnostic value than independent inflammatory biomarkers (4-6, 9-12). Kuyumcu et al. (21) were among the first to demonstrate the predictive value of NLR. They found a higher NLR in Alzheimer's disease patients compared to healthy controls. Rembach et al. (22) examined the NLR values of patients with MCI and AD at different periods of the disease (at disease onset, 18th, 36th and 54th month) and found no difference from healthy controls except for the 18th month. The same researchers argued that the relationship between neocortical Aβ deposition and NLR is weak and that the high NLR in AD is an expected consequence of the aging process and reflects peripheral inflammatory processes rather than cognitive impairment. In their recent study, Dong et al. (23) showed that there was no significant difference between MCI and AD in terms of NLR values, but the NLRs of both groups were significantly higher compared to healthy controls. PLR has been used as an inflammatory marker in several systemic diseases (12,24), but there are not many studies showing the predictive value of elevated PLR in MCI and AD, except for the study by Kalelioglu et al. (25). In our study, we found higher NLR and PLR values in AD patients compared to healthy controls, consistent with results reported in the literature. We found that NLR and PLR values did not have a significant effect in differentiating MCI (p= 0.537 ve p= 1.000), but 1.66 for NLR and above 98.4 for PLR in mild stage AD, and 1.65 for NLR and above 116 for PLR in moderate-to-severe stage AD were the threshold values.

The MPV is an indicator of the mean size of the circulating platelets and the PDW is an indicator of the variability of the platelet volume. Both are variables used to assess platelet activity, but PDW is considered more specific than MPV (26). High MPV and PDW values have been shown to be associated with the degree of cognitive impairment as well as increased vascular risk in Alzheimer's disease (26-28). In the acute phase of inflammation, large fresh platelets released from the bone marrow are more reactive than small ones, and their granule content is more dense,

producing more cytokines and thromboxane A2, which are increasingly needed. As the inflammatory response becomes chronic, released cytokines reduce platelet size, resulting in lower MPV and PDW values. It has been shown that higher PDW values in patients with MCI compared to patients with AD may be a potential marker predicting progression from MCI to Alzheimer's disease (23,29). We found no significant difference in MPV between MCI, AD, and control groups. PDW levels were found to be statistically significantly higher in MCI patients than in moderate-to-severe AD and control groups, and we thought that this elevation might be a result of the more recent and more active inflammatory process in MCI. We found that values above 16.6 for PDW were the threshold for patients with MCI.

Limitations of our study include the small sample size, the use of a single peripheral blood sample, and the lack of evaluation of other biomarkers of the inflammatory process (C-reactive protein, erythrocyte sedimentation rate, interleukin-6). In addition, the presence of chronic co-morbidities such as hypertension, coronary artery disease, diabetes, and the use of anti-statin, anti-hypertensive (ACE inhibitors), and anti-aggregant medications are important factors that may affect patients' blood cell profiles. Compared to the evaluation of different time periods within the same disease group and studies that analyzed inflammatory markers individually, the advantage of our study is that we collected information on PDW, NLR, and PLR together and interpreted them at the same time, thus obtaining more accurate data.

CONCLUSION

Our study supports the role of inflammation in cognitive impairment. The diagnostic efficacy of NLR and PLR as potential biomarkers of Alzheimer's disease and high PDW levels as potential biomarkers of mild cognitive impairment should be confirmed in future studies with larger, longer-term patient populations from different geographic regions. The development of such diagnostic tests will also enable early diagnosis and treatment of patients with progressive neurodegenerative diseases such as Alzheimer's.

Ethics Committee Approval: Our study was approved by the local Scientific Research Ethics Committee on 06 January 2020 with decision number 11/08 and written informed consent about their inclusion in the study was obtained from all the participants. The study followed the principles outlined in the Helsinki Declaration.

Author Contributions: All authors contributed to the manuscript.

1-Concept: HO, BG, 2- Design: HO, BYB, BG, 3- Supervision: HO, BG, NS, 4- Resources: HO, BYB, BG, 5- Materials: HO, BYB, BG, 6-Data collection and/or processing: HO, BYB, BG, NS, 7- Analysis and/or interpretation: HO, BYB, BG, NS, 8- Literature search: HO, 9- Writing masnuscript: HO, 10- Critical Review: HO, BG

Conflict of Interest: There is no conflict of interest.

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Informed Consent: We confirm that each participant provided informed consent before participating in the study.

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