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Can the systemic immune-inflammatory index be a new indicator for the diagnosis and follow-up of alzheimer's disease?

Sistemik immun-inflamatuar indeks alzheimer hastalığının tanısı ve takibi için yeni bir gösterge olabilir mi?

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ABSTRACT

Background: Alzheimer's disease (AD) is a chronic neurodegenerative disease whose prevalence continues to increase in the elderly population. It has been shown that the neutrophil/lymphocyte ratio (NLR), is increased in AD compared to the normal population. However, there is no study in the literature regarding the role of systemic immune-inflammatory index (SII), which is calculated according to the formula of peripheral platelet count X neutrophil count/lymphocyte count, in AD. Therefore, our aim in this study was to reveal the role of SII in the diagnosis and follow-up of AD and to determine the relationship of this value with severity, duration of disease and drug use by comparing it with NLR.
Materials and Methods: Our retrospective study consisted of 94 gender and age matched healthy volunteers and 102 patients who applied to our clinic were diagnosed with AD.
Results: There was no difference between the patient and control groups in terms of age, gender, platelet and neutrophil counts, and SII values. While lymphocyte count was lower in-patient group; NLR and CRP detected higher (p=0.001, p=0.001, p=0.001, respectively). While SII increased as both disease duration and severity elevated; no statistically significant correlation was found between NLR and the severity and duration of the disease and drug use.
Conclusions: Based on the data of our study, we can suggest that inflammatory process increases in AD. However, the relationship of this inflammatory process with the severity and duration of the disease and drug use is still unknown.

Keywords: Neutrophil/Lymphocyte Ratio, Systemic Immune-Inflammatory Index, Inflammation, Alzheimer's Disease

ÖZET

Amaç: Tanısı ve takibinde kullanılan ideal bir biyobelirteç olmayan Alzheimer hastalığı (AH), prevalansı ileri yaş popülasyonunda artmaya devam eden kronik bir nörodejeneratif hastalıktır. Nötrofil /lenfosit oranın (NLR) AH'da normal popülasyona göre artmış olduğu gösterilmiştir. Ancak periferik platelet sayısı X nötrofil sayısı/ lenfosit sayısı formülüne göre hesaplanan sistemik immun-inflamatuar indeks (SII)'in AH'ndaki yeri ile ilgili literatürde henüz bir çalışma bulunmamaktadır. Bu nedenle bu çalışmadaki amacımız AH'nın teşhis ve takibinde NLR ile kıyaslayarak SII'nin yerini ortaya koymak ve bu değerin hastalığın ciddiyeti, süresi ve ilaç kullanımı ile ilişkisini tespit etmektir.
Materyal ve Metot: Retrospektif olarak dizayn edilmiş çalışmamıza kliniğimize başvurmuş, alınan anamnez ve yapılan nörolojik muayene ile AH tanısı konulmuş 102 hasta ile hasta grubumuza benzer yaş ve cinsiyete sahip 94 gönüllü dahil edildi.
Bulgular: Hasta ve kontrol grubu arasında yaş, cinsiyet, platelet ve nötrofil sayıları ve SII değerleri açısından fark yoktu. Lenfosit sayısı hasta grupta daha düşükken; NLR ve CRP düzeyi daha yüksek olarak tespit edildi (sırasıyla p=0.001, p=0.001, p=0.001). SII hem hastalık süresi hem de ciddiyeti arttıkça artmaktayken; NLR ile hastalığın ciddiyeti, süresi ve ilaç kullanımı arasında istatistiksel olarak anlamlı ilişki saptanmadı.
Sonuç: Çalışmamızın verilerine dayanarak AH'da her aşamada inflamatuar sürecin arttığı öne sürülebilir. Ancak bu durumun hastalığın ciddiyeti, süresi ve ilaç kullanımı ile ilişkisi henüz bilinmemektedir.

Anahtar Kelimeler: Nötrofil/Lenfosit Oranı, Sistemik İmmün-İnflamatuar İndeks, İnflamasyon, Alzheimer Hastalığı

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INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disease that affects millions of people and its prevalence is expected to continue to increase in the older population. AD is the most common cause of dementia over the age of 65. In patients with genetically inherited Alzheimer's, which constitutes 5-10% of AD, the age of onset is earlier, sometimes it can go down to the 30s. In late-onset patients who are sporadic, the disease often begins over 65 years of age (Mckhann, 1994).

Extracellular amyloid-β plaques and intracellular neurofibrillary tangles accumulating in the brain parenchyma and blood vessels constitute the pathology of AD, which causes an increasing social and economic burden. Activation of astrocytes and microglials around amyloid plaques causes the release of proinflammatory cytokines and chemokines, which is the main source of neuroinflammation (Lee, 2009).

An ideal biomarker for the diagnosis and follow-up of AD has not yet been determined; because the ideal indicator should be able to reveal both the underlying neuropathological changes in disease and the relationship of these changes with dementia. It should also be easily accessible and inexpensive. Neutrophil-lymphocyte ratio (NLR), which has been shown to be associated with cerebro and cardiovascular diseases and various malignancies, is a new, inexpensive and easily applicable inflammation marker. It has been shown in various studies that this ratio is increased in Alzheimer's patients compared to the normal population (Kuyumcu, 2012; Rembach, 2014). In addition, a relationship was found between the NLR value and the severity of the disease (Rembach, 2014). Systemic immune-inflammatory index (SII), calculated according to the formula of peripheral platelet count X neutrophil count/lymphocyte count, was first used to determine the prognosis of many cancer types such as hepatocellular cancer (Hu,2014). Recent studies have shown that it is superior to other traditional inflammatory indicators in predicting major cardiovascular and cerebrovascular events (Trifan, 2020; Yang, 2020). However, in AD, in which both inflammation and platelet, neutrophil and lymphocyte counts play an important role in its pathophysiology, there is no study yet in the literature related to SII.

Therefore, our aim in this study is to determine the relationship of this ratio with the disease severity, disease duration and drug use by revealing the role of SII ratio, which can be a new inflammatory indicator in the diagnosis and follow-up of Alzheimer's patients, by comparing it with healthy volunteers of similar age and gender.

MATERIALS AND METHODS

Establishment of the Patient and Control Group:

In our retrospectively designed study, the patients were included, who applied to Sivas Cumhuriyet University Faculty of Medicine Neurology Department between 01.01.2015 and 01.11.2021, were diagnosed with AD according to The Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV and National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, whose blood samples were taken and cranial magnetic resonance imaging's (MRI) were performed to rule out the secondary causes of dementia (Albert, 2011; Rabe-Jabłońska,1994). There was no gender restriction among the patients. All patients included in the study were evaluated in terms of cognitive status with standardized mini mental test (MMSE) and clock drawing test (Folstein, 1975). Accordingly, patients who scored less than 24 points in the MMSE were accepted as AD. It was classified as mild between 23-20 points, moderate between 19-10 points and severe phase between 0-9 points.

The patients with a diagnosis of radiological, neurological or systemic disease such as chronic heart, lung or kidney failure, coronary artery disease, connective tissue disease, hematological disease, malignancy, acute/chronic inflammatory or autoimmune disease, coagulopathy or thyroid disorder, a history of infection in the last 2 weeks, use of immunosuppressant, anticoagulant or anti-inflammatory drugs, and a history of acute coronary syndrome, acute cerebrovascular disease or surgery in the last 3 months were not included in our study, as they can cause secondary dementia.

Our control group also was composed of healthy volunteers who were of similar age and gender to our patient group, who did not have memory problems, whose cognitive test results did not meet the dementia criteria, who did not have any comorbidities or regular drug use, were examined in our polyclinic for other reasons and gave blood samples.

Informed consent was obtained from each patient and control, and only consenting patients were included in the study. Ethics committee approval for our study was received from the Ethics Committee of Sivas University Faculty of Medicine (2018-03/10).

Evaluation of Blood Parameters:

Data obtained from measurements from blood samples taken from the antecubital vein to dry (for biochemical analysis) and Ethylenediamine tetraacetic acid (EDTA) tubes (for hematological tests) were used. While complete blood counts were

performed on the Diagon branded mass, Mindray BC-6800 device; platelet, neutrophil and lymphocyte counts were obtained from these measurements. Biochemical analyzes (C-reactive protein (CRP) levels) were obtained from the full automatic nephelometric analysis using the same brand kits on the Beckman Coulter AU5800 device (Beckman Coulter Inc, Hialeah, Florida).

Statistical Evaluation:

The data obtained from our study were evaluated with the SPSS 22.0 program. The Kolmogorov-Smirnov test was used to determine whether the data showed normal distribution or not. Chi-square test was used to evaluate the data obtained by counting. Since the data did not meet the parametric conditions, Mann Whitney U test was used for two independent groups. Spearman rank correlation coefficient was used to determine the relationships between the data. Error level was taken as $p<0.05$.

RESULTS

When the patient and control groups were evaluated in terms of age and gender, no statistically significant difference was found between the two groups (p= 0.09, p=0.99, respectively). In the patient group, while 24 patients (23.5%) had hypertension and 3 (2.9%) had diabetes mellitus; 21 patients (20.6%) had both hypertension and diabetes mellitus. 54 patients (52.9%) did not have any other chronic disease. Furthermore, in this group, 21 patients (20.6%) were using donepezil, 18 patients (17.6%) were using rivastigmine, and 9 patients (8.8%) were using memantine. Eighteen patients (17.6%) were receiving rivastigmine + memantine combination; 12 patients (11.8%) were taking donepezil + memantine combination. 24 patients (23.5%) were not using medication for dementia. The mean disease duration was 4.62±3.03 years and mean MMSE value was 14.54 ± 4.78. While 15 patients (14.7%) in the patient group had mild dementia; 69 patients (67.6%) had moderate and 18 patients (17.6%) had severe dementia. When the monocytes and eosinophil count and CRP levels in the patient group were statistically significantly higher than the control group ($p<0.001$, $p<0.001$, $p<0.001$, respectively), the lymphocyte count was lower ($p<0.001$). There was no statistically significant difference between the neutrophil, platelet and white blood cell counts, and vitamin B12 and hemoglobin levels between the two groups. Considering the ratios of whole blood parameters, while NLR value was statistically higher in the patient group; there was no statistically significant difference between the two groups in terms of SII value ($p<0.001$, p=0.07, respectively) (Table 1).

When the relationship between NLR and SII values and the severity of the disease was evaluated; it was determined that there was a statistically insignificant negative relationship between NLR and the severity of the disease, and a statistically significant but weak positive relationship with SII (r=-0.14, p=0.162; r=0.29, p=0.003, respectively). In addition, as the duration of the disease increased, the SII value elevated statistically, but this correlation was also weak (r=0.25, p=0.01). There was no relationship between disease duration and NLR (r=-0.15, p=0.12). Similarly, there was a statistically insignificant relationship between these two values and drug use (r=-0.16, p=0.23; r=0.25, p=0.18; r=0.24, respectively).

In the ROC analysis performed to find the optimal cut-off value for diagnosing AD, the cut-off value for NLR was found to be 1.87 (sensitivity=70.6%, specificity: 61.7%, SD (standard deviation): 0.04, AUC (area under the curve): 0.74, 95% CI (confidence intervals): 0.67-0.80). Since the p value corresponding to the size of the AUC for SII was 0.70 (p=0.70), the size of AUC was found to be insignificant. The 95% CI also included 0.50. This showed that there was no cut-off value for SII (Figure 1).

DISCUSSION

Based on the results of our study, it can be claimed that NLR and CRP values increase in AD independent of the duration and severity of the disease and the drug therapy used. SII value can be positively related to the duration and severity of the disease. This may be related to the elevated inflammation seen at every stage of the disease in AD.

Recent studies have revealed that AD is a cerebral amyloid angiopathy (CAA) characterized by the formation of neurotoxic amyloid-β plaques in the brain parenchyma and cerebral blood vessels. It has been known for nearly 20 years that inflammation contributes to neurodegeneration in both the early and late stages of AD (Querfurth, 2010; Yu, 2012). Neutrophils are well-characterized members of the immune system that perform numerous different functions, including R reactive oxygen species (ROS) production, phagocytosis, and degranulation. Various mechanisms have been proposed to explain how neutrophils are involved in the pathophysiology of AD and how the disease process itself can lead to an elevation in neutrophil count. Cytokines such as tumor necrosis factor-α (TNF-α) are markedly increased in AD and correlate with the onset of neuropsychiatric symptoms (Stalder, 2005). In addition, it is also known that TNF-α promotes the survival of neutrophils (Holmes, 2011).

Table 1. The comprassion of the baseline demographic/ clinical characteristics and laboratory findings of patient and control groups.

	Patient Group(n=102)	**Control Group(n=94)**	**X^2**	**p**
Female, n (%)	52 (51.0%)	48 (51.1%)	0.01	0.99
Age (mean ± SD)	79.34 ± 9.17	77.44 ± 6.07		0.09
CHRONIC DISEASES				
HT Presence, n (%)	24 (23.5%)	-		
DM Presence, n (%)	3 (2.9%)	-		
HT and DM Presence, n (%)	21 (20.6%)	-		
None, n (%)	54 (52.9%)	-		
MEDICATION				
Donepezil, n (%)	21 (20.6%)	-		
Rivastigmine, n(%)	18 (17.6%)	-		
Memantine, n (%)	9 (8.8%)	-		
Rivastigmine and Memantine, n (%)	18 (17.6%)	-		
Donepezil and Memantine, n (%)	12 (11.8%)	-		
None, n (%)	24 (23.5%)	-		
CLINICAL PARAMETERS				
Disease Duration(years) (mean ± SD)	4.62 ± 3.03	-		
MMSE (mean±SD)	14.54 ± 4.78	-		
DISEASE SEVERITY				
Mild, n (%)	15 (14.7%)	-		
Moderate, n (%)	69 (67.6%)	-		
Severe, n (%)	18 (17.6%)	-		
BIOCHEMICAL ANALYSIS				
Glucose (mg/dL) (median)(IR)	145.7 (99-203)	143.7 (103-225)		0.28
Creatine (mg/dL) (median) (IR)	0.71 (0.5–0.9)	0.73 (0.5-1.0)		0.36
Vitamin B12(mg/dL) (median) (IR)	290.50 (156-873)	285.00 (157-875)		0.87
CRP (mg/dL) (median)(IR)	*13.40 (10.8-16.0)*	*4.36 (0.80-12.20)*		*0,001**
COMPLETE BLOOD COUNT VALUES				
Hb (g/dL) (median)(IR	13.35 (10.80-16.00)	13.40 (10.80-16.00)		0.87
WBC (10^9/L) (median)(IR)	6.83 (3.63–13.00)	6.84 (3.64–13.00)		0.67
Monocyte(10^9/L) (median)(IR)	*0.38 (0.04-0.88)*	*0.34 (0.12-0.59)*		*<0.001**
Eosinophil(10^9/L) (median)(IR)	*0.13 (0.01-0.75)*	*0.08 (0.01-0.17)*		*<0.001**
Neutrophil(10^9/L) (median)(IR)	4.43 (1.72-9.10)	3.93 (2.18-5.74)		0.06
Platelet(10^9/L) (median)(IR)	256.000 (127-411)	255.000 (152-416)		0.43
Lymphocyte(10^9/L) (median)(IR)	*1.69 (0.57-8.93)*	*2.26(1.36-3.62)*		*<0.001**
RATES				
SII (median)(IR)	1028.170 (375.760-3740.100)	1008.720 (450.450-1896.080)		0.07
NLR (median)(IR)	*2.47 (0.38 – 12.26)*	*1.50 (0.88– 3.46)*		*<0.001**

All values are presented mean±standard deviation (SD), median value (IR) or number (%).

Abbreviations: HT: hypertension; DM: diabetes mellitus; MMSE: standardized mini-mental state examination; CRP: C-reactive protein; Hb: hemoglobin; WBC: white blood cell; SII: systemic immune-inflammatory index; NLR: neutrophil to lymphocyte ratio.

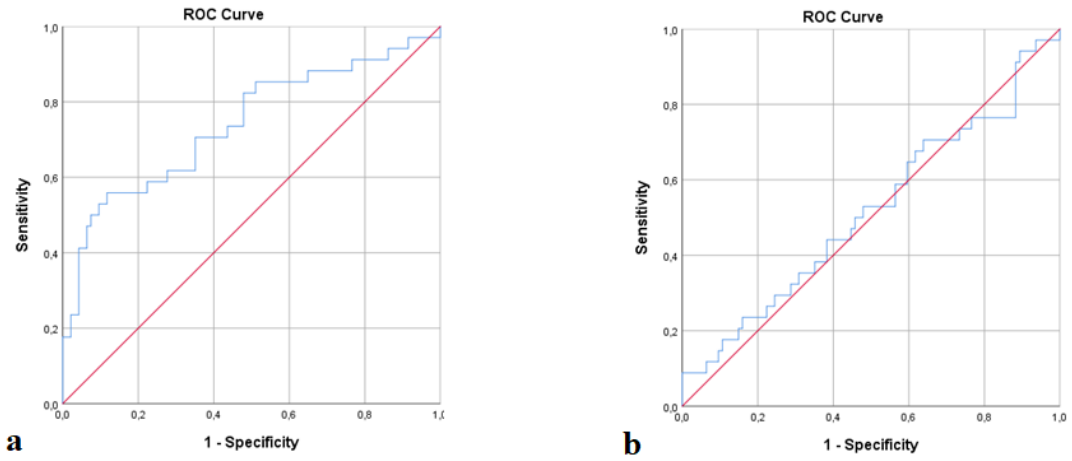

Figure 1: ROC curve analysis for NLR and SII (a, b)
a) The AUC for NLR was 0.74 and the cut-off value was 1.87 (sensitivity: 70.6%, specificity: 61.7%, SD:0.04, 95 % CI: 0.67-0.80)
b) The size of AUC was found to be insignificant (p=0.70). The 95% CI also includes 0.50. So there is no cut-off value for SII.
Abbreviations: ROC: receiver operating characteristic; AUC: area under the curve; SD: standard deviation; CI: confidence interval; NLR: neutrophil to lymphocyte ratio, SII: systemic immune-inflammatory index.

This may explain the high neutrophil counts observed in AD patients, in contrast to our study. Neutrophils themselves are essential components of AD pathogenesis. High amounts of ROS released from neutrophils contribute to increased permeability of the blood brain barrier (BBB) through disruption of tight junctions (Dong, 2018).

Several hypotheses have been proposed to explain the low lymphocyte counts observed in AD (Dong, 2019; Shad, 2013). One of the hypotheses put forward is that TNF-α takes the lymphocytes in the peripheral circulation into the central nervous system thanks to increased BBB permeability, thus reducing the number of lymphocytes in the peripheral circulation (Liu, 2010). Other mechanisms have been proposed to explain the decrease in lymphocyte count, as increased susceptibility to ROS has been demonstrated in lymphocytes from patients with AD. Another hypothesis is that high neutrophil counts may be partially responsible for the high ROS release and thus the observed decrease in peripheral lymphocytes (Ponce, 2014). In addition, certain AD-associated mutations, such as presenilin 1 mutation, can predispose circulating lymphocytes to cell death in these patients (Rezai-Zadeh, 2009). In support of these studies, in our study, the lymphocyte count in the patient group was found to be lower compared to the controls.

In addition to CAA, AD is also associated with vascular diseases such as stroke and atherosclerosis (Catricala, 2012). In patients with AD, cerebrovascular dysfunction occurs, which leads to changes in blood flow, may play an important role in the pathophysiology of neuronal loss (Thal, 2008). It is known that platelets play an important role in hemostasis and thrombosis, as well as in neuroinflammatory diseases such as AD (Mielke,2007). Platelets have been shown to exhibit enzymatic activities to produce amyloid-ß (Aß) peptides, so for many years platelets have been considered a peripheral model to study the pathophysiology of AD. Additionally, platelets are regarded a biomarker for the early diagnosis of AD. Despite all of these studies, the effect of platelets on the progression of AD has not been fully defined.

AD, which is characterized by cognitive impairment and dementia, causes heavy social and financial burden in the long term (Mckhann, 1994). Therefore, there is a requirement for a better understanding of the pathophysiology of the disease and easy screening markers that will provide an acceptable estimate of disease risk/diagnosis in the early years of the disease. For this aim, whole blood parameters and the ratios of these values to each other are evaluated intensively in AD. NLR, obtained by dividing the peripheral neutrophil count by the lymphocyte count, is a simple and noninvasive marker of systemic inflammation. The potential utility of NLR in AD was first investigated by Kuyumcu et al (Kuyumcu, 2012). This study included 241 AD patients and 175 controls, and NLR values were found to be significantly higher in AD patients compared to controls in the multivariate logistic regression analysis of the data. The second study investigating the benefits of NLR in AD, was revealed by Rembach et al (Rembach, 2014). This study had three major advantages over the study, investigated by Kuyumcu et al. Firstly, the major confounders such as the presence of ApoE4 were corrected in multivariate analyses. Secondly, the study had a prospective component (a follow-up of 54 months); this allowed a more accurate assessment of the utility of NLR as a marker in predicting transition to the cognitive dysfunction stage of AD. A third advantage was that the study classified patients

without AD as those with normal cognitive function or mild cognitive impairment, allowing a more complex analysis of the NLR value. In our study, similar to these two studies, the NLR value was found to be statistically significantly higher in the patient group than in the control group. However, in our study, unlike the study investigated by Rembach et al, no statistically significant relationship was found between this elevation and the severity of the disease. Similarly, there was no relationship between NLR and the duration of the disease and the dementia drugs used. Nevertheless, this may have resulted from the retrospective design of our study and the evaluation of a single measurement.

The systemic immune-inflammatory index (SII), which is calculated according to the peripheral platelet count X neutrophil count/lymphocyte count formula, was first used to determine the prognosis of many cancer types such as hepatocellular cancer (Hu, 2014). Recent studies have shown that it is superior to traditional indicators in predicting major cardiovascular events (Yang, 2020). Furthermore, higher SII was found to be an independent risk factor for severity of stroke in an acute ischemic stroke study (Trifan, 2020). On the other hand, recent studies have demonstrated the significance of the SII value for both long-term and short-term outcomes after intracerebral hemorrhage (Li, 2021). Whereas, there is no study in the literature on SII in AD, in which both platelet and neutrophil and lymphocyte counts play an important role in its pathophysiology. Our study is the first study in this regard. In our study, we found that the SII value was higher in AD compared to the controls, although it was not statistically significant. This situation may be related to the increase of NLR values in AD. There was no difference in platelet counts between the patient and control groups in our study, which supports the hypothesis that platelets, which play a role in the pathophysiology of AD, are more functionally active rather than numerically increased (Veitinger, 2014). The reason why the high SII values of our patient group did not reach statistical significance may be the platelet counts. Additionally, in our study, while no relationship was found between the NLR value and the duration and severity of the disease; SII value increased as both disease duration and severity elevated. This could be related to the status that platelets take a more active role in the pathophysiology as the duration and severity of the disease increase, rather than the onset of the disease. Based on our results, it can be argued that the SII is a better biomarker than NLR in the follow-up of the disease rather than diagnosing.

Unfortunately, our study had several limitations. Firstly, it was a single-center retrospective study. Therefore, the number of patients was relatively small. In addition, the data obtained from a single measurement of the patients were used and prospective follow-up of the patients could not be made. Likewise, just white blood cell count and CRP levels were evaluated among inflammatory indicators, and other inflammatory markers could not be measured. Furthermore, only MMSE was used to evaluate the severity of AD, and other general dementia assessment scales, cognitive screening scales, general and specific behavioral scales, functional scales for evaluating activities of daily living, and dementia staging scales were not taken into account.

CONCLUSION

In conclusion, based on the results of our study, it can be said that inflammatory activity increases in both mild, moderate and severe phases in AD, and NLR and CRP values elevate in accordance with this in every phase. Besides, it can be suggested that the SII is a more precious indicator in the follow-up of the disease compared to NLR, rather than diagnosing, due to its positive relationship with both disease duration and severity. However, more prospective, multicenter and large population studies are needed on SII in the future in order to make further comments.

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Ethics Committee Approval: Ethics committee approval for our study was received from the Ethics Committee of Sivas Cumhuriyet University Faculty of Medicine (2018-03/10).

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Author Contributions:

Study concept and design: Aslı BOLAYIR, **Acquisition of subjects and/or data, analysis and interpretation of data;** Tuğba RAİKA KIRAN, Aysun BAY KARABULUT; **Preparation of manuscript:** Aslı BOLAYIR

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