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Research / Araştırma

Neutrophil-to-Lymphocyte Ratio as a Potential Differential Diagnostic Marker for Alzheimer's Disease, Major Depressive Disorder, and Parkinson's Disease

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ABSTRACT

Neutrophil-to-lymphocyte ratio as a potential differential diagnostic marker for Alzheimer's disease, major depressive disorder, and Parkinson's disease

Objective: Major depressive disorder, Alzheimer's, and Parkinson's diseases are among the leading causes of dementia in the elderly. These diseases are often misdiagnosed because of overlapping symptoms. This study aimed to evaluate whether neutrophil-to-lymphocyte ratio, which has been used as an indicator of systemic inflammation, can be used for the differential diagnosis of these diseases.

Method: A total of 95 patients with major depressive disorder, Alzheimer's, or Parkinson's disease were enrolled. Neutrophil-to-lymphocyte ratios of the participants were calculated using their past complete blood count results. We compared the three groups according to mean neutrophil-to-lymphocyte ratio and mean neutrophil-to-lymphocyte ratio adjusted for age. We used the receiver operating characteristics curve analysis to predict the sensitivity and specificity of this ratio for the differential diagnosis between depression and Alzheimer's disease.

Results: The mean neutrophil-to-lymphocyte ratios for the depression, Alzheimer's, and Parkinson's disease groups were 2.2±0.7, 2.9±1.2, and 2.2±0.9, respectively (p=0.005). The age-adjusted mean neutrophil-to-lymphocyte ratios for the depression, Alzheimer's, and Parkinson's disease groups were 2.20±0.93, 2.80±0.97, and 2.20±0.96, respectively (p=0.025). Receiver operating characteristics curve analysis predicted that the sensitivity and specificity for the differential diagnosis between depression and Alzheimer's disease were 54.8% and 80.0%, respectively.

Conclusion: This study suggests that a simple arithmetic calculation could help clinicians in the differential diagnosis between depression, Alzheimer's, and Parkinson's disease. Neutrophil-to-lymphocyte ratio can be used as a secondary line of evidence, along with the initial clinical assessment.

Keywords: Alzheimer, depression, inflammation, Parkinson

ÖZ

Nötrofil-lenfosit oranının majör depresif bozukluk, Parkinson hastalığı ve Alzheimer hastalığının ayırıcı tanısındaki potansiyel yeri

Amaç: Özellikle yaşlı popülasyonda görülen demans ile ilişkili semptomların en sık sebepleri arasında Alzheimer hastalığı, majör depresif bozukluk ve Parkinson hastalığı yer almaktadır. Ancak bu hastalıklar benzer klinik özelliklere sahip olduğu için sıklıkla yanlış tanı almakta ve uygun tedavi görememektedir. Biz araştırmamızda, bu hastalıkların ayırıcı tanısında, sistemik bir enflamatuvar belirteç olan nötrofil-lenfosit oranının potansiyel yerini araştırdık.

Yöntem: Araştırmamıza Alzheimer hastalığı, majör depresif bozukluk veya Parkinson hastalığı bulunan toplam 95 hasta dahil edildi. Bu hastaların dosyalarından hemogram bilgileri alınarak nötrofil-lenfosit oranları hesaplandı. Gruplar nötrofil-lenfosit oranına ve yaşa göre düzeltilmiş nötrofil-lenfosit oranına göre karşılaştırıldı. Ayrıca alıcı işletim karakteristik eğrisi kullanılarak nötrofil-lenfosit oranının Alzheimer hastalığı ve majör depresif bozukluğun ayırıcı tanısındaki duyarlılığı ve özgüllüğü hesaplandı.

Bulgular: Alzheimer hastalığı için ortalama nötrofil-lenfosit oranı 2.9±1.2 olarak, aynı değeri majör depresif bozukluk için 2.2±0.7 ve Parkinson hastalığı için 2.2±0.9 olarak bulundu. Nötrofil-lenfosit oranı değerleri açısından karşılaştırıldığında grupların arasında istatistiksel olarak anlamlı fark bulundu. Nötrofil-lenfosit oranını yaşa göre düzelttiğimizde değerleri sırasıyla 2.80±0.93, 2.20±0.97 ve 2.20±0.96 olarak hesaplandı (p=0.025). Alıcı işletim karakteristik eğrisi analizleri ile incelendiğinde nötrofil-lenfosit oranı için majör depresif bozukluk ve Alzheimer hastalığı arasındaki ayırıcı tanıda sensitivitesi %54.8 ve spesifisitesi %80.0 bulundu.

Sonuç: Birbiri ile sıklıkla karışabilen bir kliniğe sahip olan Alzheimer Hastalığı, majör depresif bozukluk ve Parkinson hastalığı arasında ayırıcı tanıda temel olarak hikaye ve klinik muayene kullanılır. Ancak rutin kan tetkiklerinden elde edilen sonuçlarla hesaplanabilen nötrofil-lenfosit oranının, destekleyici veri olarak klinik rutine eklenmesi yanlış tanı sıklığını azaltacağını düşünüyoruz.

Anahtar kelimeler: Alzheimer, depresyon, inflamasyon, Parkinson

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INTRODUCTION

According to the WHO, major depressive disorder (MDD) is estimated to be the second most debilitating disease in the near future (1). It is commonly encountered among the elderly, and approximately 25% of the elderly population is affected by MDD. Although more than half of these older patients present mild symptoms, MDD is one of the most debilitating diseases in this age group (2).

The incidence of Alzheimer's disease (AD) is mostly age-specific. It affects approximately one-tenth of the population aged over 65 years worldwide. In addition, the prevalence of AD is known to increase drastically with age. Almost one-third of the population aged over 85 years is diagnosed with AD, which is the leading cause of dementia, especially in the elderly (3). Typically, AD presents with anterograde amnesia and deterioration of cognitive functions, the symptoms of which are common among geriatric patients with MDD.

Symptoms of dementia, such as attentional, executive, and memory dysfunctions, are also frequently encountered in patients with Parkinson's disease (PD), a state known as Parkinson's disease dementia. Although extrapyramidal symptoms usually present much earlier than cognitive impairment, PD should be considered in the differential diagnosis for dementia (4-6). Although not as frequently encountered as MDD or AD, PD is reported in 1 in 100 individuals aged over 65 years, thereby being the second most common neurodegenerative disease in this age group (7).

Because of overlapping symptoms among these three medical conditions, patients are often misdiagnosed and mistreated. As the symptoms of MDD usually subside after a simple and cost-effective treatment, an elderly patient with MDD misdiagnosed as AD is most likely to be mistreated.

Although some other forms of diagnosis have been suggested, currently the only viable tool for differential diagnosis between MDD, AD, and PD is a comprehensive examination by a psychiatrist or a neurologist, and in many cases both. For example, a definitive diagnosis of AD cannot be achieved without a brain biopsy. Thus, a definitive diagnosis of AD can only be obtained after eliminating other possible diseases through a differential diagnosis.

As a comprehensive examination of these diseases is time-consuming, they can easily be overlooked by other physicians, thereby worsening our current situation into an epidemic of misdiagnosis of elderly patients with MDD, AD, and PD. The misdiagnosis of these diseases has many consequences, such as elderly patients with MDD being treated with AD medication, which is usually more expensive and is of no benefit to patients with MDD (8). Moreover, these misdiagnosed patients who could have been easily treated with proper medication and therapy sometimes become dependent on constant daily care or, in some cases, are referred to care homes. Thus, exploring and establishing a simple, reliable, cost-effective, and accessible method to help clinicians in the differential diagnosis of MDD, AD, and PD is crucial.

In recent years, the neutrophil-to-lymphocyte ratio (NLR) has been introduced as a diagnostic tool in psychiatry (9-14) and suggested as an upcoming diagnostic method for MD (9-13) and schizophrenia (14) in the field of psychiatry, where the use of laboratory instruments for diagnosis is sparse. However, NLR has been used by other physicians for a long time, as it indicates acute and chronic systemic inflammation. For example, it is considered a viable diagnostic method for appendicitis, acute bacterial meningitis, various cancer types, and several other diseases (15-17).

While NLR is a novel experimental tool in the field of psychiatry, neurologists are far more experienced in the subject. NLR has long been a valid diagnostic method for AD (18,19). The current consensus about the mechanism underlying local and systemic inflammation in the central nervous system is that the accumulation of amyloid-ß, which is said to trigger processes such as gliosis, excitotoxicity, and oxidative stress generation in the central nervous system, induces an inflammatory response (20). In addition, cytokine imbalance, leukocyte infiltration through the brain-blood barrier into the neuronal tissue, and mitochondrial oxidative stress are also suggested as possible suspects in the pathophysiology of AD (20-22).

This study aimed to evaluate whether NLR can significantly differentiate between MDD, AD, and PD and can be complementary to clinical examination in the differential diagnosis of these diseases.

METHOD

We retrospectively collected the data of 95 patients aged >65 years diagnosed with AD (n=42), PD (n=23), or MDD (n=30) who had been admitted to Balikesir University outpatient clinic between 01/01/2015 and 12/01/2015.

Participants with MDD and Alzheimer's disease were diagnosed according to DSM-IV-TR at our outpatient clinic. Participants with Parkinson's disease were referred for consultation to the neurology department of our hospital and were given a diagnosis by a neurology specialist. Patients diagnosed with more than one of the three disorders under investigation (AD, PD, MDD) were excluded from our study. We also excluded patients diagnosed with diabetes, cancer, renal or hepatic failure, infectious diseases, or autoimmune diseases.

This research was approved by the Balikesir University School of Medicine Clinical Research Ethics Committee on 12/02/2015 with the approval number 2015/84. Written informed consent for the therapy and for the data being used for scientific research was received from all patients at the time of their admission to our outpatient clinic.

Neutrophil-to-lymphocyte ratio (NLR)

In this study, neutrophil and lymphocyte counts were performed using hematology analyzer LH 780 auto-analyzer (Beckman Coulter, ABD). Neutrophil-to-lymphocyte ratios of the participants were calculated using their complete blood count results at the time of admission.

Sociodemographic Data

We obtained patients' data regarding age and sex from their medical records in the outpatient clinics.

Statistical Analysis

We used SPSS version 15.0 for Windows (SPSS, Inc., Chicago, IL) for all statistical analyses in this study. While ANOVA test was used for comparing the mean scores among all three groups (AD, PD, and MDD), the Tukey test was used when groups were compared in pairs. In addition, NLR was adjusted for age when compared among groups with covariance analysis for eliminating the confounding effects of age. The chi-square test was used for assessing categorical variables. Furthermore, we used receiver operating characteristics (ROC) curve analysis to predict the sensitivity and specificity of NLR for the differential diagnosis between MDD and AD. We considered $p<0.05$ as statistically significant. The clinical laboratory data were expressed as the mean±standard deviation (SD) and covariance analysis data as the mean±standard error (SE).

RESULTS

In this study, the mean age of patients in the MDD, AD, and PD groups was 71.6±4.7, 75.3±5.5, and 71.5±6.0 years, respectively. We observed a

Table 1: Mean age, Neutrophil-to-Lymphocyte Ratio, and age-adjusted NLR for the Major Depressive Disorder, Alzheimer Disorder, and Parkinson Disorder groups

	Neutrophil-to-Lymphocyte Ratio		Alzheimer Disorder		Parkinson Disorder		
	Mean	SD	Mean	SD	Mean	SD	p
Age	71.60	4.70	75.30	5.50	71.50	6.00	0.005 (F=5.60)
NLR	2.20	0.70	2.90	1.20	2.20	0.90	0.005 (F=5.64)
Age-adjusted NLR	2.20	0.93	2.80	0.97	2.20	0.96	0.025 (F=3.84)

NLR: Neutrophil-to-lymphocyte ratio, SD: Standard deviation

statistically significant difference in the mean age between the three groups (p=0.005). The post hoc analysis for the mean age revealed a significant difference between the MDD and AD groups (p=0.014) and PD and AD groups (p=0.022). However, no statistically significant difference was observed between the MDD and PD groups (p=0.999; Table 1).

A statistically significant difference was also observed for sex between the MDD and AD groups (p=0.004) and MDD and PD groups (p=0.006). However, no such result was observed between the AD and PD groups (p=0.867). In addition, sex demonstrated no significant effect on NLR when examined using linear regression analysis (p=0.471).

The mean NLR for the MDD, AD, and PD groups was 2.2±0.7, 2.9±1.2, and 2.2±0.9, respectively. We observed a statistically significant difference in NLR between the three groups (p=0.005). In addition, a statistically significant difference was observed between the MDD and AD groups (p=0.020) and between the PD and AD groups (p=0.015) in the post hoc analysis. However, no such difference was noted between the MDD and PD groups (p=0.946; Table 1).

In this study, NLR was adjusted for age using covariance analysis. The adjusted mean NLR for the MDD, AD, and PD groups was 2.2±0.93, 2.8±0.97, and 2.2±0.96, respectively. The difference in the mean NLR adjusted for age was statistically significant (p=0.025), which applied to the mean NLR difference between the MDD and AD groups (p=0.018) but not to the difference between the MDD and PD groups (p=0.756; Table 1).

In addition, linear regression analysis of gender revealed no significant effect on NLR (p=0.296). When the cutoff value for NLR was determined as 2.71, sensitivity and specificity for the differential diagnosis between MDD and AD were 54.8% and 80.0%, respectively (area under the curve = 0.654; 95.0% confidence interval: 0.528-0.780; p=0.027; Figure 1).

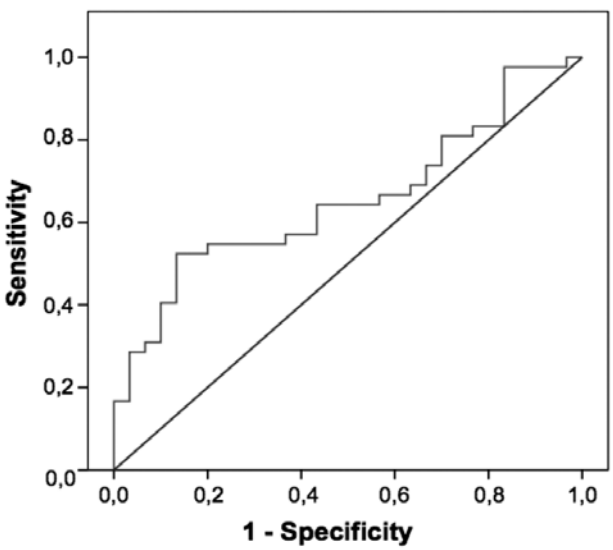

Figure 1: ROC (Receiver Operating Characteristics) curve showing the diagnostic efficiency of NLR (Neutrophil-to-Lymphocyte Ratio) in differentiating between MDD (Major Depressive Disorder) and AD (Alzheimer's Disease)

DISCUSSION

MDD has been established as a pro-inflammatory disease (22). Reportedly, NLR is higher in patients with MDD than in healthy controls (10-13). However, the results of this study indicated that NLR is significantly lower in patients with MDD than in those with AD. Moreover, we observed no significant difference in NLR between MDD and PD.

Studies have attributed the pro-inflammatory feature of MDD to a cytokine imbalance. In addition, an increase in the number of inflammatory cytokines, such as IL-6 and TNF-α, has been reported in patients with MDD (23). In fact, IL-6 is considered as one of the major cytokines in the inflammatory process and has been shown to increase NLR. However, it is not the only cytokine affecting NLR, because an increase in the number of other cytokines, such as IL-8, IL-2, colony-stimulating factors, and growth factors has also been shown to increase NLR (22,24). A meta-analysis study reported increased serum levels of IL-6 among patients with MDD than healthy controls. However, the same study established no significant difference in IL-2 and 8 levels, which are also known to increase NLR, between patients with MDD and healthy controls (23). Hence, despite the existence of a cytokine imbalance and activation of various inflammatory processes in MDD, there is not much evidence to confirm whether NLR is affected by these

mechanisms. This could be a hypothesis to be tested in future studies.

In their cohort study of 1112 participants, Rembach et al. reported that NLR for healthy controls was 2.34±1.07 and for patients with AD 2.76±1.37 at the baseline (19). The same subjects were re-examined after 18 months. At the later assessment, NLR for healthy controls was 2.28±1.06, and for patients with AD it was 3.05±1.58, which is consistent with our results.

Arguably, the statistically significant difference in NLR between the MDD group and the two other groups in our study could be attributed to age difference, which was also statistically significant. To eliminate such a possibility, we performed covariance analysis, which also revealed a statistically significant difference between the AD and MDD groups in terms of NLR adjusted for age. Hence, the difference in NLR between the MDD and AD groups in our study cannot be attributed to the age difference between these groups. This study suggested that NLR is a selective measure to distinguish between AD, MDD, and PD.

In our study, we have not confirmed systemic inflammation by other tests and markers such as C-reactive protein, sedimentation, or cytokines. In future studies, diagnostic predictivity of NLR can be corroborated with such tests and markers. Another limitation of our study was not including patients with a diagnosis of co-occurring AD, MDD, or PD. However, co-occurrence of MDD either with AD or PD is not rare. For that reason, patients with a diagnosis of such co-occurring disorders can be included as separate groups in future studies. Given the relatively small sample size and lack of a control group in our research, multi-centric studies with control groups are warranted in the future. Our study design examines the predictive power of NLR for differentiating between AD, MDD, and PD. However, we have not investigated if the value of NLR was associated with the severity of the disorders. Therefore, we would recommend including measurements such as Hamilton Depression Scale and Mini Mental State Examination in future studies.

We do not have enough information about the trends of systemic inflammation markers correlated with the progress of psychiatric and neurological disorders. The rise of systemic inflammation markers might also be temporary. The retrospective design of our study limits our data on this subject. Prospectively investigating the trends of systemic inflammation markers with the progression of psychiatric and neurological disorders can be used to overcome this limitation.

Some neurological and psychiatric disorders, such as AD being mentioned in our study, have been found to be correlated with systemic inflammation. However, recent studies have shown that these disorders are more associated with neuro-inflammation rather than systemic inflammation (25). Therefore, in future studies the differential diagnosis we discussed in this article should be investigated with neuro-inflammation markers.

The findings of this study suggest that a simple arithmetic calculation could help clinicians in the differential diagnosis between AD and MDD, given that a complete blood cell count is a routine blood panel already in use, requiring no further sample collection to calculate the NLR. Conversely, NLR is not sufficient for diagnosis without a comprehensive examination. NLR should be evaluated just like most other diagnostic tests, as a secondary line of evidence supporting or opposing the initial clinical assessment. In a field where numerous patients are misdiagnosed, NLR can be complementary to clinical assessment. Overall, this cost-effective test can help to achieve a proper diagnosis for patients and save the financial burden of mistreatment.

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