

## Diagnostic Value of Neutrophil/Lymphocyte Ratio in Distinguishing Peripheral and Central Vertigo in Patients with Dizziness

### Baş Dönmesi Olan Hastalarda Periferik ve Santral Vertigonun Ayırt Edilmesinde Nötrofil/Lenfosit Oranının Tanısal Değeri

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#### ABSTRACT

**Objective:** Neutrophil/lymphocyte ratio (NLR) is an inexpensive parameter that gives an idea about systemic inflammatory response and cellular immune response. This study aims to investigate the value of NLR in distinguishing peripheral and central vertigo.

**Materials and Methods:** Patients presenting with acute vertigo at the emergency clinic were included between January 2017 and December 2018. Hemogram, brain computerized tomography, and diffusion magnetic resonance imaging data were reviewed to categorize patients into peripheral and central vertigo groups. Laboratory parameters were compared between these groups.

**Results:** Neutrophil, lymphocyte, and C-reactive protein levels were higher in patients with central vertigo than those with peripheral vertigo ( $p=0.003$ ,  $p=0.003$ ,  $p=0.022$ , respectively). Moreover, the NLR value was significantly elevated in central vertigo cases (median: 3.99) in contrast to peripheral vertigo cases (median: 2.32) ( $p < 0.001$ ).

**Conclusions:** The NLR is a valuable marker for distinguishing peripheral and central vertigo in emergency department patients with dizziness. Higher NLR values suggest central vertigo.

**Keywords:** Emergency department, differential diagnosis, dizziness, neutrophil/lymphocyte ratio, vertigo

#### ÖZ

**Amaç:** Nötrofil/lenfosit oranı (NLR), sistemik inflamatuvar yanıt ve hüresel bağışıklık yanıtı hakkında fikir veren düşük maliyetli bir parametredir. Bu çalışmanın amacı, NLR'nin periferik ve merkezi vertigo arasındaki farkı ayırt etmedeki değerini araştırmaktır.

**Materyal ve Metot:** Ocak 2017 ile Aralık 2018 tarihleri arasında acil klinikte akut vertigo ile başvuran hastalar çalışmaya dahil edildi. Hastaları periferik ve merkezi vertigo gruplarına ayırmak için hemogram, beyin bilgisayarlı tomografi ve difüzyon manyetik rezonans görüntüleme verileri incelendi. Laboratuvar parametreleri bu gruplar arasında karşılaştırıldı.

**Bulgular:** Nötrofil, lenfosit ve C-reaktif protein düzeyleri, periferik vertigo hastalarına kıyasla merkezi vertigo hastalarında daha yüksek bulundu (sırasıyla  $p=0,03$ ,  $p=0,003$ ,  $p=0,022$ ). Ayrıca, NLR değeri merkezi vertigo vakalarında (ortalama: 3,99), periferik vertigo vakalarına kıyasla (ortalama: 2,32) anlamlı derecede yüksekti ( $p < 0,001$ ).

**Sonuç:** NLR, vertigo semptomlarıyla acil servise başvuran hastalarda periferik ve merkezi vertigo arasındaki farkı ayırt etmede değerli bir belirleyicidir. Yüksek NLR değerleri merkezi vertigoyu düşündürmektedir.

**Anahtar Kelimeler:** Acil servis, ayırıcı tanı, baş dönmesi, nötrofil/lenfosit oranı, vertigo

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## INTRODUCTION

Peripheral vertigo (PV) occurs in the vestibular labyrinth with nerve damage.<sup>1</sup> Central vertigo (CV) mainly occurs due to mortal causes such as brain stem and cerebellum strokes, and transient ischemic attack.<sup>2</sup> For this reason, it is vital to distinguish PV or CV in patients who present to the emergency department reporting vertigo. In patients presenting with vertigo symptoms and findings, although anamnesis and physical examination are valuable to distinguish PV or CV, advanced radiologic examinations such as brain computed tomography (BCT) and diffusion magnetic resonance imaging (MRI) are often required.<sup>3</sup>

During stress and inflammatory response, there is an increase in circulating neutrophil cell ratios. The neutrophil/lymphocyte ratio (NLR) is an easy-to-obtain, inexpensive parameter that gives an idea about the systemic inflammatory response and cellular immune response and is considered an inflammatory response indicator.<sup>4,5</sup> In acute ischemic stroke or hemorrhagic stroke, the inflammatory response increases due to post-ischemic changes and brain damage, and NLR is expected to increase.<sup>6,7</sup> Additionally, there are studies indicating an elevation in NLR levels among patients with PV.<sup>8,9</sup>

There is currently no literature evaluating NLR levels in distinguishing between PV and CV. Therefore, we aimed to investigate the value and applicability of NLR in the differential diagnosis of PV and CV.

## MATERIALS AND METHODS

**Ethics Committee Approval:** Our study was approved by the Karadeniz Technical University Faculty of Medicine Ethics Committee (Date: 31.05.2019, decision no: 24237859-439). During the study, the Helsinki Declaration criteria were complied with to protect the patient's data.

**Study Design and Setting:** This was a single-center, retrospective, and cross-sectional study conducted in the emergency department of a tertiary university hospital to which 95,000 patients present annually. Patients who presented to the emergency medicine clinic reporting dizziness over two years between Jan 1st, 2017, and Dec 31st, 2018, were included in the study. Patients with trauma, those with an additional acute infectious disease, patients with malignancy, those with chronic inflammatory disease, patients aged under 18 years, and patients without complete blood counts were excluded from the study. Additionally, among the patients included in the PV group, those who presented to the emergency department with any infection/inflammatory disease that altered NLR, any otologic disease, or central

nervous system pathologies within the following 1-week period were excluded from the study. According to the International Classification of Diseases-10th version (ICD-10) coding system of the emergency department, the file and computer records of patients aged 18 years and over who had an ICD-10 code for vertigo (R.42) were examined, and the results of hemograms, BCT, and MRI were evaluated.

**Participants:** The BCTs and diffusion MRIs of patients who presented to the emergency department with dizziness were examined. In these images, patients without cerebral pathology (ischemia, infarction, hemorrhage, mass) were diagnosed as having PV. A group of patients diagnosed as having CV was established with patients with cerebral pathology in their imaging. The files and computer records of the patients included in the study were examined, and parameters such as sex, age, the presence of symptoms accompanying the vertigo attack, other diseases, platelet count, leukocyte count, neutrophil count, lymphocyte count, and NLR were recorded as indicated in the patient registration form.

**Statistical Analysis:** IBM SPSS Statistics 25 package program used for data analysis. Descriptive statistics are given as numbers and percentages for categorical variables in the statistical analysis of the data. Mean and standard deviation are given for parametric data for numerical variables, and median, minimum, maximum and interquartile ranges are given for non-parametric data. The independent sample t-test was used for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data to compare numerical variables in two independent groups. The receiver operating characteristics (ROC) analysis was used to determine the cut-off value of the NLR. Results of the ROC analysis were given with 95% confidence intervals (CI) and the area under the curve (AUC).  $P < 0.05$  was considered statistically significant.

## RESULTS

A total of 282 patients who were diagnosed as having vertigo in the study period were retrospectively screened. Twenty-two patients were excluded from the study. Twelve patients were excluded from the study due to infection/inflammatory disease, five patients were found to have malignancy, three patients had gastrointestinal bleeding, and a complete atrioventricular block was detected in two patients (Figure 1). A total of 260 patients were included in the study. These patients were divided into PV and CV according to their history, physical examinations, and brain CT and MRI results.

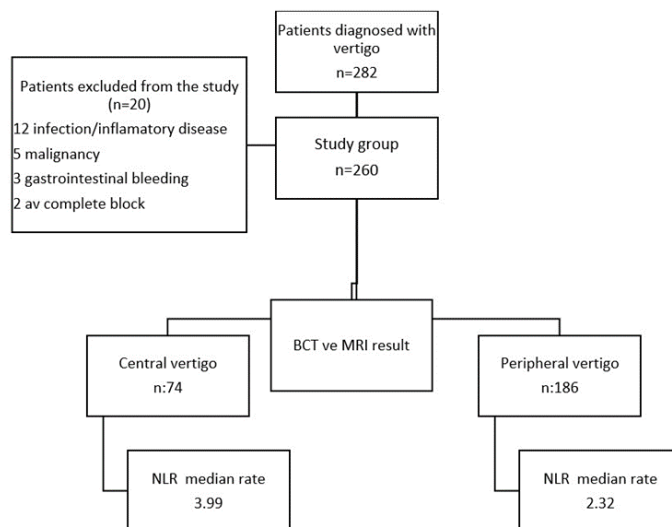


Figure 1. Study flow chart.

While 186 patients (71.5%) were diagnosed with CV, 74 (28.5%) were diagnosed with PV. Sociodemographic characteristics, comorbidities, and presenting symptoms were compared between patients with PV and CV (Table 1). More female patients were diagnosed with both PV and CV compared to male patients, although the difference was not statistically significant ( $p=0.166$ ). The median age of patients with CV was 72.5 years (range: 20-100 years), while the median age of patients diagnosed with PV was 62.0 years (range: 18-93 years), with a statistically significant difference observed ( $p < 0.001$ ). 113 (43.5%) patients had hypertension (HT), 54 (20.8%) had atrial fibrillation (AF), 49 (18.8%) had diabetes mellitus (DM), 18 (6.9%) had a history of previous stroke, and 17 (6.5%) had coronary artery disease

(CAD). The incidence of HT and CAD was significantly higher in patients with CV compared to those with PV ( $p < 0.001$  and  $p=0.027$ , respectively). Although the prevalence of AF and a history of stroke was higher in CV patients, and DM was more common in PV patients, these differences were not statistically significant. The frequency of nausea-vomiting (65.1%), and nystagmus (31.2%) were statistically significantly higher in patients with PV than in patients with CV ( $p < 0.001$ ). The frequency of hemiplegia ( $n=8$ , 10.8%), hemiparesis ( $n=20$ , 27.0%), speech impairment ( $n=17$ , 23.0%), facial asymmetry ( $n=1$ , 1.4%), and tinnitus ( $n=5$ , 6.8%) was found to be much higher in patients with CV ( $p < 0.001$ ).

Table 1. Sociodemographic characteristics, comorbidities, and presenting symptoms of the patients.

		Central vertigo	Peripheral vertigo	p-value
<b>Gender,</b>	Male	36 (48.6)	73 (39.2)	0.166
	Female	38 (51.4)	113 (60.8)	
<b>n (%)</b>	Age (years), median (IQR)	72.5 (100)	62 (93)	<b>0.001</b>
<b>Comorbidities,</b>	Hypertension	47 (63.5)	66 (35.5)	<b>0.001</b>
	Atrial fibrillation	21 (28.4)	33 (17.7)	0.082
	Diabetes mellitus	13 (17.6)	36 (19.4)	0.875
	Previous stroke	8 (10.8)	10 (5.4)	0.198
	Coronary Artery Disease	9 (12.2)	8 (4.3)	<b>0.027</b>
	<b>Symptoms, n (%)</b>	Hemiplegia	8 (10.8)	1 (0.5)
	Hemiparesis	20 (27)	2 (1.1)	<b>0.001</b>
	Speech disorder	17 (23)	-	<b>0.001</b>
	Facial asymmetry	1 (1.4)	-	<b>0.001</b>
	Nausea-vomiting	34 (45.9)	121 (65.1)	<b>0.001</b>
	Tinnitus	5 (6.8)	3 (1.6)	<b>0.001</b>
	Nystagmus	8 (10.8)	58 (31.2)	<b>0.001</b>

Table 2 shows the laboratory findings of patients with PV and CV. The median leukocyte, neutrophil, and CRP values of patients with CV were statistically significantly higher than in patients with PV ( $p < 0.05$ ). In addition, the median lymphocyte value was found to be higher in patients with PV than in those with CV ( $p < 0.05$ ). In terms of median hemoglobin values, there was no significant difference between patients with PV and CV ( $p > 0.05$ ). The median NLR (median: 3.99) of patients with CV

was significantly higher than the median NLR (median: 2.32) of patients with PV ( $p < 0.001$ ).

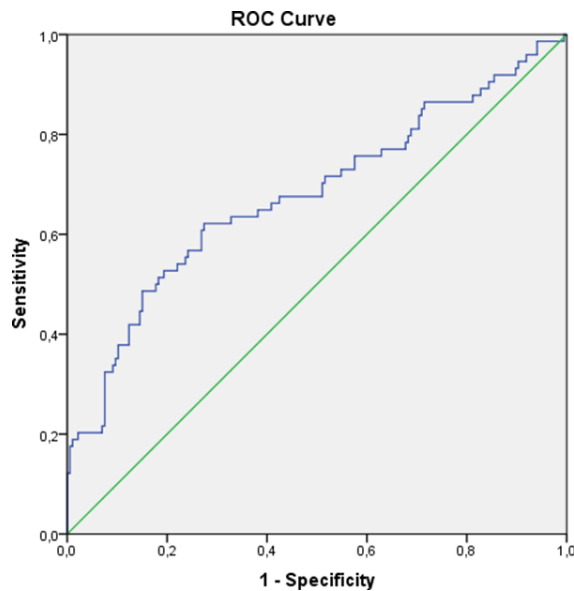
Table 3 and Figure 2 demonstrate the ROC analysis used for the threshold value calculation used to separate PV and CV. According to the results, the area under the receiver operating characteristic (ROC) curve was found as 0.679 (95% CI: 0.600-0.757), which was statistically significant in diagnosis.

**Table 2.** Laboratory findings of patients.

Laboratory findings	Central vertigo				Peripheral vertigo				p-value
	Median	Min.	Max.	IQR	Median	Min.	Max.	IQR	
Leukocyte	8680.0	3690	24150	5165	7550.0	3650	13950	2970	<b>0.003</b>
Neutrophil	5745.0	2120	22210	4398	4570.0	1250	11580	2223	<b>0.003</b>
Lymphocyte	1580.0	180	8520	1158	2035.0	500	6760	1275	<b>0.003</b>
Hb (gr/dL)	14	8.8	16.9	2.55	13.3	9.7	18.5	1.90	0.323
NLR	3.99	0.54	65.61	4.17	2.32	0.29	12.79	2.06	<b>0.001</b>
CRP	0.55	0.01	30.00	1.23	0.25	0.01	5.30	0.50	<b>0.022</b>

**Table 3.** ROC analysis of patients' neutrophil/lymphocyte ratio.

Cutoff Value	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUC p-value
NLR 3.25	62,16%	72,58%	2.27	0.52	0.679
	95% CI (50.1-73.2)	95% CI (65.6-78.9)			<b>0.001</b>



**Figure 2.** ROC curve for Neutrophil/lymphocyte ratio in the distinguishing of vertigo types.

## DISCUSSION AND CONCLUSION

The median NLR was statistically significantly higher in patients with CV than those with PV. Therefore, it can be thought that NLR can be used as a parameter in the differential diagnosis of PV and CV. In the study conducted by Lee et al. on 135 patients, the authors recommended MRI for further investigations if NLR >2.8 to find out ischemic stroke.<sup>10</sup> Çelikbilek et al. found that NLR was higher in patients with atherothrombotic acute ischemic stroke than in patients with transient ischemic attacks and controls.<sup>11</sup> The study conducted by Tokgöz et al. supported that a high NLR could be used as an independent indicator for predicting short-term deaths in patients with acute ischemic stroke.<sup>12</sup> Our results are compatible with the literature.

In the studies on vertigo, the incidence increased with age, especially in women. It has been found that benign paroxysmal positional vertigo, Meniere's disease, and migrainous vertigo are more common in women than in men.<sup>13-16</sup> The association of migraine and specific vestibular disorders may partially explain the prominent female superiority among vertigo patients because migraine is more common in women.<sup>17</sup> In the vertigo study conducted by Narita et al. with 242 patients, there was a 66% female sex dominance.<sup>18</sup> In our study, there were more female patients among the patients who presented with symptoms of vertigo; this is compatible with the literature. It has been reported that the CV rate increases with age.<sup>19</sup> In our study, no significant difference was found between the patients in terms of sex. However, the median age of the patients with CV was significantly higher than that of patients with PV.

In terms of CV, chronic diseases such as AF, HT, DM, CAD, hyperlipidemia, and cancer are seen as risk factors.<sup>20</sup> It is emphasized that CV should be excluded in patients presenting with vertigo who have risk factors. The concomitant occurrence of hypertension and diabetes mellitus has been correlated with a 4.9-fold escalation in the risk of stroke, as documented in the literature.<sup>21</sup> In our study, the frequency of HT and CAD was statistically significantly higher in patients with CV than in patients with PV.

Autonomic symptoms such as nausea and vomiting are generally more severe and evident in PV attacks than in central-induced vertigo conditions.<sup>22-24</sup> Our study showed that the frequency of nausea, vomiting, and nystagmus was statistically significantly higher in patients with PV, which is in agreement with the literature. Neurologic symptoms such as weakness, dysarthria, vision or hearing changes, paresthesia, altered consciousness, ataxia, or other sensory and motor function changes support the presence of a central cause of vertigo cerebrovascular

disease, neoplasm, or multiple sclerosis.<sup>25</sup> In our study, the frequency of hemiplegia, hemiparesis, speech disorder, facial asymmetry, and tinnitus was found to be significantly higher in patients with CV.

In addition to being suitable for use as a prognostic factor in many diseases, a high NLR has been associated with short-term mortality in intracerebral hemorrhages and 3-month mortality.<sup>26</sup> In a study of 123 patients with intracerebral hemorrhage, Wang et al. showed that NLR was independently associated with early hematoma enlargement.<sup>27</sup> In cerebral hemorrhage that may cause CV symptoms, reported NLR increase supports our study.

Several studies have reported elevated NLR levels in patients with PV. However, these studies typically compared PV patients to healthy adults. In contrast, our study individually evaluated patients with vertigo symptoms at the emergency department. In this regard, we contend that our study employs a methodology more conducive to clinical practice.

In conclusion, we think that NLR is an applicable parameter in distinguishing dizziness due to peripheral or central vertigo in patients presenting with dizziness to emergency departments. A high NLR means that dizziness is caused by central vertigo. Therefore, it supports the need for neurologic imaging as an advanced examination in these patients.

**Ethics Committee Approval:** Our study was approved by the Karadeniz Technical University Faculty of Medicine Ethics Committee (Date: 31.05.2019, decision no: 24237859-439). During the study, the Helsinki Declaration criteria were complied with to protect the patient's data.

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## REFERENCES

1. Bayındır T, Kalcioğlu MT. Peripheral vertigo. Journal of Turgut Ozal Medical Center. 2010;17:155-163.
2. Fu Y, Liu Q, Anrather J, Shi FD. Immune interventions in stroke. Nat Rev Neurol 2015;11:524-535.
3. Delémont C, Rutschmann O. Vertiges: tout tourne-t-il autour de la clinique? [Vertigo: it all revolves

- around the physical exam]. *Rev Med Suisse*. 2007;3(121):1826-1828.
4. Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. *Am J Cardiol*. 2008;102:653-657.
  5. Talley NJ. Therapeutic options in nonulcer dyspepsia. *J Clin Gastroenterol*. 2001;32:286-293.
  6. Fu Y, Liu Q, Anrather J, Shi FD. Immune interventions in stroke. *Nat Rev Neurol*. 2015;11:524-535.
  7. Wang J. Preclinical and clinical research on inflammation after intracerebral hemorrhage. *Prog Neurobiol*. 2010;92:463-477.
  8. Temirbekov D, Sakallı E. Effects of peripheral vertigo on inflammatory and immunologic laboratory markers. *Ear, Nose & Throat Journal*. 2020;99(7):470-474. doi:10.1177/0145561320920149
  9. Ozbay I, Kahraman C, Balıkcı HH, et al. Neutrophil-to-lymphocyte ratio in patients with peripheral vertigo: a prospective controlled clinical study. *Am J Otolaryngol*. 2014;35(6):699-702. doi:10.1016/j.amjoto.2014.08.004
  10. Lee SH, Yun SJ, Ryu S, et al. Utility of neutrophil-to-lymphocyte ratio (NLR) as a predictor of acute infarction in new-onset acute vertigo patients without neurologic and computed tomography abnormalities. *J Emerg Med*. 2018;54:607-614.
  11. Celikbilek A, Ismailogullari S, Zararsiz G. Neutrophil to lymphocyte ratio predicts poor prognosis in ischemic cerebrovascular disease. *J Clin Lab Anal*. 2014;28:27-31.
  12. Tokgoz S, Kayrak M, Akpınar Z, Seyithanoğlu A, Güney F, Yürüten B. Neutrophil lymphocyte ratio as a predictor of stroke. *J Stroke Cerebrovasc Dis*. 2013;22:1169-1174.
  13. Zhu RT, Van Rompaey V, Ward BK, Van de Berg R, Van de Heyning P, Sharon JD. The interrelations between different causes of dizziness: A conceptual framework for understanding vestibular disorders. *Ann Otol Rhinol Laryngol*. 2019;128(9):869-878. doi:10.1177/0003489419845014
  14. Hackenberg B, O'Brien K, Döge J, et al. Vertigo and its burden of disease—results from a population-based cohort study. *Laryngoscope Invest Otolaryngol*. 2023;8(6):1624-1630. doi:10.1002/lio2.1169
  15. Von Brevern M, Radtke A, Lezius F, et al. Epidemiology of benign paroxysmal positional vertigo: a population-based study. *J Neurol Neurosurg Psychiatry*. 2007;78:710-715.
  16. Lempert T, Neuhauser H. Epidemiology of vertigo, migraine and vestibular migraine. *J Neurol*. 2009;256(3):333-8. doi:10.1007/s00415-009-0149-2
  17. Gambacorta V, Ricci G, D'Orazio A, et al. Evaluation of cochlear symptoms in migraine patients without vestibular migraine and/or Ménière's disease. *Audiol Res*. 2023;6;13(6):967-977. doi:10.3390/audiolres13060084
  18. Narita S, Kurose M, Kobayashi K, Himi T. Study on 242 inpatients reporting vertigo and dizziness. *Nippon Jibiinkoka Gakkai Kaiho*. 2003;106:21-27.
  19. Chawla N, Olshaker JS. Diagnosis and management of dizziness and vertigo. *Med Clin North Am*. 2006;90:291-304.
  20. Goldman B. Chapter- 231: Vertigo and dizziness. In: Tintinalli JE, Stapczynski JS, Ma OJ, Cline DM, Cydulka RK, Meckler GD eds. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 6th Ed. America: The McGraw-Hill Companies; 2010.
  21. Tun NN, Arunagirinathan G, Munshi SK, Pappachan JM. Diabetes mellitus and stroke: A clinical update. *World J Diabetes*. 2017;8(6):235-248. doi:10.4239/wjd.v8.i6.235
  22. Steenerson KK. Acute vestibular syndrome. *Continuum (Minneapolis)*. 2021;1;27(2):402-419. doi:10.1212/CON.0000000000000958
  23. StatPearls. Vestibular Dysfunction. <https://www.ncbi.nlm.nih.gov/books/NBK558926/>. Accessed June, 2024.
  24. Swain K.S. *Management of vertigo made easy*. New Delhi, India: Jaypee Brothers Medical Publishers. 2016;29.
  25. Gibson WPR. Meniere's Disease. *Adv Otorhinolaryngol*. 2019;82:77-86. doi:10.1159/000490274
  26. Wang F, Hu S, Ding Y, et al. Neutrophil-to-lymphocyte ratio and 30-day mortality in patients with acute intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2016;25:182-187.
  27. Wang Z, Gong Q, Guo C, Luo Y, Chen L. Neutrophil-to-lymphocyte ratio predicts hematoma growth in intracerebral hemorrhage. *J Int Med Res*. 2019;47:2970-2975.