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Original Article

The value of laboratory markers in the differential diagnosis of acute vestibular syndrome

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Abstract

Aim: Stroke is one of the leading and most challenging problems in distinguishing between central and peripheral causes of acute vestibular syndrome. This study aims to evaluate the potential utility of neutrophil to lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and gamma-glutamyl transferase (GGT) levels in the differential diagnosis of acute vestibular syndrome.

Materials and Methods: This retrospective study included 152 patients diagnosed with vestibular neuritis (VN) and posterior circulation ischemic stroke (PCIS) within the scope of the isolated acute vestibular syndrome (AVS: vertigo, nystagmus, nausea-vomiting, postural instability, and intolerance of head movements). Of all these patients, we listed the ones having normal MRI findings and diagnosed with VN in the department of otorhinolaryngology. The diagnosis of stroke was made through neuroimaging methods (CT and MRI). NLR and GGT levels were compared among the patients diagnosed with VN and PCIS.

Results: GGT, NLR, PLR levels were significantly higher in the patients with the PCIS group ($p<0.05$). The AUC (area under the curve) and optimal cutoff values for NLR, PLR, and GGT were analyzed by ROC analysis. According to these results, the diagnostic value of NLR was higher in predicting stroke (AUC: 0.741; 95%CI: 0.652-0.829, $p<0.001$)

Conclusion: As a result, NLR, GGT, and PLR can be useful biomarkers for deciding in favor of stroke in the differential diagnosis of VN.

Keywords: Acute vestibular syndrome; vestibular neuritis; posterior circulation ischemic stroke; vertigo; gamma-glutamyl transferase; neutrophil to lymphocyte ratio; platelet-lymphocyte ratio

INTRODUCTION

Acute vestibular syndrome (AVS) is characterized by prolonged episodes of vertigo that begin abruptly, usually lasting longer than 24 hours, accompanied by nausea, vomiting, and intolerance of head movements (1). Vestibular neuritis (VN) ranks first among the most common etiological causes of AVS, while cerebellar and brainstem-induced strokes from posterior circulation rank second (2). Emergency physicians may have difficulties in clinically distinguishing the peripheral and central causes of these cases when a patient attends with acute isolated sustained vertigo. As a result, the clinician may need to differentiate between a generally self-limiting disease such as VN and a potentially life-threatening stroke. Although apart from the imaging methods, many tests were evaluated in terms of differentiating the central and peripheral causes of AVS, none of them have adequate sensitivity and specificity (3). Evidence-based recommendations about the use of diagnostic imaging methods in vertigo patients have not been established. In general, the use of tomography is prominent if there is an intracranial mass or suspected bleeding presenting with vertigo. On the other hand, magnetic resonance imaging (MRI) is still the most important imaging modality for suspected ischemic stroke. However, MRI is not a routine diagnostic tool in vertigo patients and may not be available in many emergency departments. There are also concerns about cost-effectiveness (4).

The discovery of new biomarkers that may help to determine the risk of stroke diagnosis in AVS patients can be helpful in reducing mortality and morbidity by enabling the distinction of central and peripheral vestibulopathies. As these biomarkers are inexpensive, easily available, and non-invasive, they can be easily applied in clinical

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practice. In this context, gamma-glutamyl transferase (GGT), neutrophil to lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR), which were thought to have a prognostic role in the diagnosis of stroke in previous studies, might be promising biomarkers for the differential diagnosis of central and peripheral causes of AVS (5-7). Therefore, in this study, we aimed to investigate the changes in NLR, PLR, and GGT values of patients to distinguish between VN and PCIS syndromes that are among the most common causes of acute vestibular syndromes.

MATERIALS and METHODS

Study design

This study was a retrospective cross-sectional study and was approved by the institutional review board and carried out in accordance with the "Helsinki Declaration". (Approval no: 2019 / 21-71). Our single-center study was carried out in an education and research hospital with 500,000 patients admitted to the emergency department annually.

Study population and setting

This study has aimed to elaborate on the main question of whether the measurements of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and gamma-glutamyl transferase (GGT) levels can give clinical clues to the physicians in distinguishing between VN and PCIS. Our primary objective was to analyze the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and gamma-glutamyl transferase (GGT) levels of VN and PCIS patients. In line with this objective, we scanned the patients examined neurologically in the emergency department for five years between January 2014 and January 2019 within the scope of the isolated acute vestibular syndrome and undergoing computed tomography (CT) and Magnetic Resonance Imaging (MRI) for the differential diagnosis. In this study, AVS was defined as sudden onset and continuous lengthened vertigo attack lasting at least one hour with spontaneous or gaze-evoked nystagmus on neurologic examination accompanied by at least one of the following symptoms a) nausea-vomiting, b) imbalance when walking (postural instability), and c) intolerance of head movements (8). Of all these patients, we listed the ones having normal MRI findings and diagnosed with VN in the department of otorhinolaryngology after the necessary clinical follow-ups. The diagnosis of stroke was made through neuroimaging methods (CT and MRI). The neurological consultation was held for the patients suffering from stroke, and the patients diagnosed with PCIS were identified.

No sampling method was used in the study. All patients meeting the inclusion criteria within the specified date range were invited to the study. 46 out of 198 patients diagnosed with VN and PCIS were excluded from the research due to the exclusion criteria. The remaining 152 patients meeting the inclusion criteria constituted the study group of the present research.

Inclusion criteria

The inclusion criteria of this study are: 1) being above the age of 18, 2) having prolonged vertigo with sudden onset and accompanied by nystagmus, intolerance of head movements, nausea-vomiting, postural instability, 3) having neuroimaging (Cranial CT and MRI). Patients included in the study had MRI screening in the subacute period 48 hours after the onset of symptoms.

Exclusion criteria

This study excluded patients with pathological tomography findings, previous vestibular and oculomotor disorder, those with medication intoxication, TIA, infectious disease, trauma, malignancy, coronary artery disease, pulmonary disease, chronic inflammatory disease, heart failure, under the age of 18 applying presenting to the ED, chronic liver or kidney diseases, surgery or major trauma in the previous month, history of autoimmune disease, thyroid dysfunctions, alcohol consumption, abnormal results for prothrombin time, activated partial thromboplastin time and international normalized ratio according to reference values, and pregnancy.

Outcome measures

Our primary outcome was to measure GGT, NLR, and PLR levels in VN and PCIS patients. Our second outcome was set to be the calculation of the cut-off value of GGT, NLR, and PLR levels in the differential diagnosis of VN and PCIS.

Laboratory analysis

Complete blood cell count and biochemical profile were determined from the peripheral venous blood sampling taken at the first emergency department visits Hematological parameters were measured with SYSMEX XN-1000 and biochemical parameters were measured with BECKMAN COULTER AU5800. Among these, NLR was obtained as the ratio of absolute neutrophil count to absolute lymphocyte count and platelet lymphocyte ratio (PLR) was absolute platelet count to absolute lymphocyte count.

Data Analysis

Data analyses were performed using the SPSS v22 (IBM corp, Chicago, IL, USA) Statistical software. The study variables were investigated using Kolmogorov-Smirnov test to determine whether or not they were normally distributed. As descriptive statistics, means±standard deviation was used to describe variables with normal distribution while median (interquartile range [IQR]). was used for variables that did not show normal distribution. The independent two sample t-test was used for parameters with normal distribution, while the Mann–Whitney U test was used for the comparison of nonparametrically distributed variables. Categorical data were evaluated by using the Chi-Square test. Using the ROC (Receiver Operating Characteristics) curve, we determined the accuracy of the diagnostic value of significant variables for differentiation between posterior circulation ischemic stroke and vestibular neuritis. The

sensitivity and specificity were determined according to the cutoff value with the Receiver Operating Characteristic (ROC) curve analysis. A value of p <0.05 was accepted as statistically significant.

RESULTS

Of the 152 patients, 101 were diagnosed with VN and the remaining 51 with PCIS. Cerebellar infarction was detected in 45 of the patients diagnosed with a stroke, and brainstem infarction was detected in 6 of the patients. Of the subjects who participated in the study, 96 were male and 56 were female, and the median age was 47 (42-57) years, and their ages ranged from 35 to 65. Compared with the VN group, diabetes mellitus, hypertension, dyslipidemia, albumin, AST, ALT, BUN, MPV, creatinine, platelet, and glucose levels were similar to those diagnosed with PCIS, and the data were not statistically significant (p>0.05). The demographic characteristics and blood results of the patients are summarized in Table 1.

Table 1. The comparison of patients' demographic characteristics, complete blood count and biochemical parameters between two groups

	CENTRAL AVS (PCIS)	PERIPHERAL AVS (VN)	TOTAL	p-value
Age	53 (17)	45 (16)	47 (15)	0.057
Sex (male/female)	38/13	58/43	96/56	0.039*
Diabetes mellitus, (n,%)	11 (21.6)	20 (19.8)	31 (20.4)	0.799
Hypertension, (n,%)	24 (47.1)	40 (39.6)	64 (42.1)	0.379
Dyslipidemia, (n,%)	7 (13.7)	12 (11.9)	19 (12.5)	0.745
Albumin	4.12 ± 0.37	4.26 (0.38)	4.19 ± 0.37	0.092
AST, (U/L)	25 (15)	24 (10.5)	24 (12.75)	0.941
ALT,(U/L)	23 (10)	21 (15)	21.25 (14.38)	0.357
GGT,(U/L)	33.45±14.55	20 (11)	24 (17.75)	<0.001*
Creatinin, mg/dl	0.83±0.25	0.76±0.21	0.78±0.22	0.074
BUN,mg/dl	31 (15)	30 (13)	30.9 (15.14)	0.117
Glucose, mg/dl	135 (43)	122 (47.35)	125 (51)	0.068
CRP, mg/dl	0.44 (0.72)	0.25 (0.58)	0.3(0.56)	0.043*
NLR	3.33 (3.19)	1.90 (1.37)	2.19 (1.84)	<0.001*
Leukocyte, (10^9/L)	11.15 (3.71)	9.04±2.12	9.49±2.34	0.002*
Lymphosite, (10^9/L)	1.96(1.56)	2.63(1.17)	2.49(1.34)	0.001*
Neutrophil, (10^9/L)	7.15±2.34	5.38±1.67	5.97±2.09	<0.001*
Platelet, (10^9/L)	262.12± 74.76	254.49±69.5	248 (93.75)	0.648
PDW, (%)	14.5 (4.9)	11.7 (3.6)	12.15 (4.9)	0.064
Plateletcrit , (%)	0.24 (0.1)	0.25 (0.09)	0.24 (0.1)	0.952
MPV, (fL)	9.6±(1.08)	9.9 (1.3)	9.8 (1.3)	0.072
PLR	120.41 (81.72)	91.32 (55.09)	98.43 (66.88)	0.005*

PDW: platelet distribution width; MPV: Mean platelet volume; WBC: White blood cell; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; ALT :Alanine aminotransferase; AST: Aspartate aminotransferase; GGT :Gammaglutamyl transferase;
Data were expressed as Mean ± SD and median (interquartile range).
*** indicates statistical significance (p<0.05).**

Variables that differ between PCIS and VN included the following

GGT, NLR, PLR, leukocyte, and neutrophil levels were significantly higher in patients with posterior circulation stroke (PCIS) syndrome and lymphocyte levels were significantly higher in the VN group (p<0.05) (Table 1) (figure 1). The AUC and optimal cutoff values for NLR, PLR, and GGT were analyzed through ROC analysis (figure 2). According to these results, the diagnostic value of NLR was higher in predicting stroke (AUC: 0.741;95%CI: 0.652-0.829,p<0,001) (table 2).

Table 2. Diagnostic value of the independent factors for the distinction between PCIS and VN

	Cut of value	Sensitivity,(%)	Specificity,(%)	AUC (95%CI)	p-value
NLR	2.1	78	61	741 (652-829)	<0.001*
GGT	23.5	77	61	705 (612-797)	<0.001*
PLR	105	63	60	639 (542-736)	0.005*

NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; GGT :Gammaglutamyl transferase; AUC:Area under curve.
*** indicates statistical significance (p<0.05).**

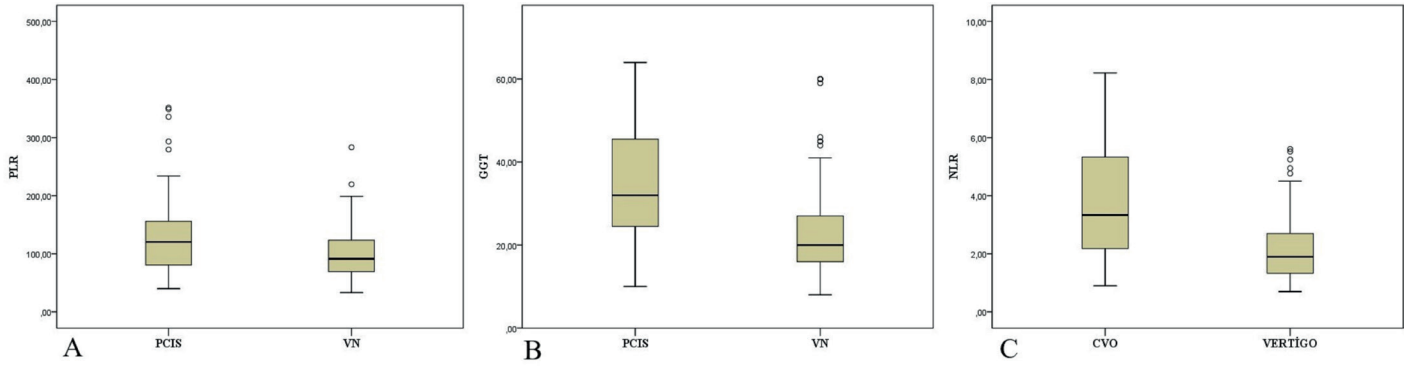

Figure 1. Comparison of Platelet-Lymphocite Ratio (PLR), Gamma Glutamyl Transferase (GGT) and Neutrophil / Lymphocite Ratio (NLR) Gamma Glutamyl Transferase(GGT) between two groups. (A) PLR. (B) GGT. (C) NLR.
PCIS: Posterior circulation ischemic stroke, VN: Vestibular neuritis.

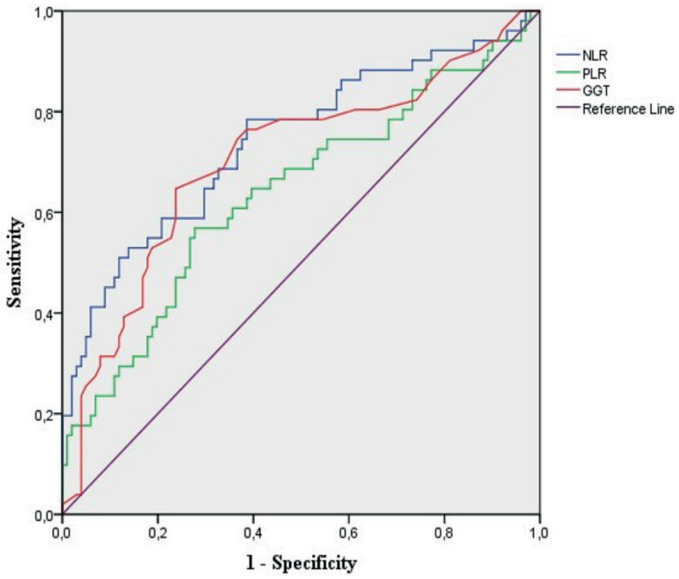

Figure 2. Prediction value of Neutrophil / Lymphocite Ratio (NLR), Platelet-Lymphocite Ratio (PLR) and Gamma Glutamyl Transferase (GGT) for the distinction of Posterior circulation ischemic stroke (PCIS) from Vestibular neuritis (VN)

DISCUSSION

In this study, we investigated the role of NLR, PLR, and GGT in the differential diagnosis of VN and PCIS. Our main results can be explained as follows: 1) NLR, PLR, and GGT levels were higher in stroke patients. 2) High NLR levels may indicate that the inflammatory response is more intense in stroke compared to VN. 3) High GGT and PLR levels may predict the underlying atherosclerotic and thrombotic processes in stroke patients.

The inflammatory response plays an important role in the pathogenesis of ischemic stroke. High levels of NLR, which can be easily calculated as a systemic inflammatory marker from neutrophil and lymphocyte count in peripheral blood samples, were to be an independent risk factor for ischemic stroke in previous studies (5, 9, 10). In our study, NLR levels were higher in the stroke group than in the group diagnosed with vestibular neuritis. In the light of the current literature, there are not many studies examining the relationship between NLR and vestibular neuritis. However, in two studies conducted so far, NLR was found to be higher in the VN group compared to the control group.

(11, 12). Many hypotheses were put forward for the VN etiology, such as vascular ischemia, various immunological mechanisms, and viral infections. Although the etiologic mechanisms focus on inflammation, the exact cause is uncertain (13). However, as a general rule, viral infections are associated with a decrease in neutrophil count and an increase in lymphocyte count (14). In these cases, lower NLR levels may be expected in viral infections. In our study, higher lymphocyte counts were detected in the VN group compared to the stroke group. Although these results do not provide a definitive judgment, they may suggest that viral infections are predominantly involved in the VN etiology. In another study, which is similar to our study, the correlation of NLR for central and peripheral vertigo discrimination was investigated. In the distinction of central and peripheral vertigo, the diagnostic cut-off value of NLR was found to be 2.8 (15). In our study, we excluded the patients with short-term episodic vertigo such as benign positional vertigo by creating a study group with patients having VN instead of the ones with peripheral vertigo. Moreover, we also excluded other patients having peripheral vertigo and diagnosed with Meniere or similar disorders because it might be challenging in clinical practice to differentiate the patients suffering from the infarction of posterior fossa and presenting to the hospital with isolated prolonged vertigo attacks from the patients with VN. This challenge may result in the misdiagnosis of the infarctions of the posterior fossa in the emergency departments. In a study that supports this outcome, prolonged spontaneous vertigo attacks without neurological and audiological pathological symptoms in peripheral vestibulopathies were attributed to VN within the scope of AVS (16). We also think that the values we obtained are more standardized by opting for the VN group instead of the peripheral vestibulopathy group. In this study, the optimal NLR cut-off value determined in favor of stroke was calculated as 2.1 (sensitivity: 78%, specificity: 61%). The fact that the NLR level, which is an indicator of the inflammatory response, is higher in stroke patients may indicate that inflammation is more severe in stroke patients.

GGT can be used as a biochemical marker that can cross the blood-brain barrier because it is released not only from the kidneys and liver but also from the cerebrovascular endothelium. (17). Previous studies have shown that increased GGT levels are associated with increased risk of ischemic stroke and increased mortality (18, 19). Still, the mechanisms to explain the relationship between the increase in stroke events and elevated GGT levels are unclear. However, the proinflammatory and prooxidant process resulting in atherosclerosis may indicate an elevated GGT level in stroke pathophysiology (18). There are sources in the literature stating that thrombotic and inflammatory processes are also involved in VN etiopathogenesis. In their study, Freedman and Loscalzo found a significant percentage of CD40-positive monocytes and macrophages in the vascular system of patients with VN compared to the control group (20). These inflammatory precursors may trigger an increase in thrombotic activation, disrupting microvascular perfusion, and causing loss of function in the vestibular organ (21). According to this theory, GGT elevation can be expected in the VN group. However, there is no data about the relationship between VN - GGT or vertigo - GGT in the literature. In our study, GGT levels were significantly higher in the PCIS group. We think that this result is due to the fact that atherosclerotic and thrombotic processes are more intense in the stroke group. In addition, our study is the first study examining the role of GGT levels in the distinction between VN and stroke.

PLR is considered to be a new, easily achievable, and repeatable systemic inflammatory marker that is believed to have prognostic value in a variety of diseases, especially for cardiovascular diseases. There are many studies in which the relationship of PLR with ischemic events were investigated in general, but its relationship with ischemic events in patients with the cerebrovascular disease has not yet been fully characterized (7, 22). It is believed that platelets have an important role in the pathogenesis of atherosclerosis and that high platelet count is related to cardiovascular events. Cortisol, catecholamine, and acetylcholine released as a result of activation of the hypothalamic-pituitary adrenal axis in ischemic stroke patients cause lymphocyte apoptosis with a definite reduction in lymphocyte counts and they are considered to form an immune suppression situation (23). For these reasons, considering the etiopathogenesis of stroke, an increase in PLR levels can be expected in ischemic stroke patients. The fact that PLR may reflect the status of both inflammatory and thrombotic pathways may be more valuable than platelet and lymphocyte counts alone. However, in the light of current knowledge in the literature, two studies analyzed how PLR values were affected in neuritis patients and illustrated that PLR levels were higher in the VN group compared to the control group (11, 12). In this study, we found that PLR levels were significantly higher in the stroke group compared to the VN group.

High levels of MPV can develop as a result of the pathophysiological interaction of risk factors for cerebrovascular diseases such as high cholesterol and smoking. Therefore, it offers a broad risk for cerebrovascular diseases (24). When the literature is reviewed, it is seen that some studies have found a significant relationship between high MPV level, high stroke risk, and high vascular mortality (25, 26). On the contrary, some other studies have stated that there is no such relationship (27, 28). When the relationship between VN and MPV is examined, it has been found that MPV has been significantly higher than the control group in a study conducted in the light of current information (11). In this study, no statistically significant difference has been found in terms of MPV levels in the differentiation of VN and ischemic stroke. In the light of the available data, we think that MPV is not a useful marker in differentiating these two groups.

Limitation

The retrospective design of this study can be considered

as its main limitation. Data on follow-up and outcome of patients could not be included in the study. Studies to be designed prospectively in the future may provide more robust evidence.

CONCLUSION

We demonstrated that NLR, PLR, and GGT are independent predictors of stroke in the differential diagnosis of acute VN and PCIS, especially in patients with normal cranial CT and no abnormal neurological findings. These results may result from the fact that inflammatory, atherosclerotic and thrombotic processes in stroke etiopathogenesis are more catastrophic than VN. However, new studies with larger patient groups are needed to clarify the reliability of these parameters.

Conflict of interest : The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: This study was approved by institutional review board and carried out in accordance with the "Helsinki Declaration". (Malatya İnönü University Ethics Committee Approval no: 2019 / 21-71).

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