Usefulness of the platelet-to-lymphocyte ratio in predicting the severity of carotid artery stenosis in patients undergoing carotid angiography

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Abstract Carotid artery stenosis (CAS) is primarily caused by atherosclerotic plaque. Progressive inflammation may contribute to the rupture of an atherosclerotic plaque. The platelet-to-lymphocyte ratio (PLR) is a new and simple marker that indicates inflammation. In this study, we aimed to investigate the use of the PLR to determine the severity of CAS. One hundred forty patients were chosen from among patients who underwent carotid angiography in our institution. Symptomatic patients with stenosis >50% in the carotid arteries and asymptomatic patients with stenosis >80% were diagnosed via carotid angiography as having critical stenosis. Patients were classified into two groups. Group 1 included patients who had critical CAS, whereas Group 2 included patients with noncritical CAS, as determined by carotid angiography. Correlations between the PLR and the severity of CAS were analyzed. There were no significant differences in sex and age between the two groups. The PLR was 162.5 ± 84.7 in the noncritical CAS group patients and 94.9 ± 60.3 in the critical CAS group patients ($p < 0.0001$). The PLR value of 117.1 had 89% sensitivity and 68% specificity for CAS [95% confidence interval, 0.043 –0.159; area under the curve, 0.101 ± 0.03]]. In this study, we have shown that PLR values may be associated with critical stenosis in at least one of the carotid arteries. Furthermore, PLR values may be used to predict critical stenosis in the carotid arteries.

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Introduction

Carotid artery stenosis (CAS) is an important arterial occlusive disease that may lead to the formation of cranial ischemic infarction and stroke. Atherosclerosis has a role in 90% of the etiologies of all extracranial carotid artery diseases [1-4]. Atherosclerosis is a systemic chronic inflammatory disease of the arterial intima. It affects overall systemic arterial circulation [3]. Increased inflammatory status is related to a poor prognosis for atherosclerosis [4].

Increased platelet activation has an important role in the initiation and progression of atherosclerosis [4]. Inflammatory mediators, such as interleukin 1 and 6, stimulate megakaryocytic proliferation and cause thrombocytosis. Thus, the platelet count may indicate inflammation. Studies have shown a relationship between coronary artery diseases and high platelet count [5-7]. In addition, lymphopenia is an indicator of physiologic stress and poor general health [8]. In this study, we aimed to reveal the relationship between CAS and platelet-to-lymphocyte ratio (PLR) values.

Materials and methods

Between January 2014 and May 2015, 140 patients who underwent carotid angiography were included in this study. An independent consultant neurologist evaluated all patients before the carotid intervention. Patients were considered asymptomatic if they had experienced a cerebral infarct, transient ischemic attack, or amaurosis fugax attributable to a lesion of the ipsilateral carotid artery within the preceding 6 months. Clinical data such as hypertension, previous stroke, diabetes mellitus, hyperlipidemia, current smoking status, coronary artery disease, peripheral vascular disease/abdominal aortic aneurysm, previous carotid stenting, previous carotid endarterectomy, and chronic kidney disease were recorded. Demographic data such as age and sex were also assessed. All patients underwent carotid Doppler ultrasound, magnetic resonance angiography, or computed tomography angiography of the carotid arteries before the angiography.

Premedication, which consisted of aspirin (100 mg/d) and clopidogrel (75 mg/d), was administered at least 2 days before the procedure. Experienced interventional cardiologists performed all carotid diagnostic and therapeutic interventional procedures. Vascular access was obtained via a 6 Fr sheath in the common femoral artery. Carotid and cerebral angiography was performed after an arch aortogram (40° left anterior oblique) using a pigtail catheter. A digital subtraction angiogram of the intracranial and extracranial carotid circulation was obtained for at least two projections.

The innominate and left subclavian arteries were engaged using a 6-F Judkins Right (JR) 4 diagnostic catheter. The JR catheter was advanced to the ascending aortic root, torqued counter-clockwise for turning its tip superiority, and then withdrawn into the vessel ostium. An angled glide catheter was used in a similar manner. In elderly patients and patients with Type III arches, a Simmons catheter (Cook, Bloomington, IN, USA) was used. We advanced the Simmons catheter into the left subclavian artery first with a 0.038-inch guide wire. We then withdrew the guide wire and advanced the catheter, thereby achieving an angled catheter tip in most patients. In some patients, we strangled the tip of the Simmons catheters in the ascending aorta. We repeatedly pulled back the catheter until selective engaging of the innominate and left common carotid arteries.

Standard anteroposterior and lateral projections were used to delineate the carotid bifurcation. Additional projections were used in some patients. Cerebral angiography was performed with standard anteroposterior and lateral projections in all patients. Independent interventional cardiologists retrospectively evaluated all angiographic images.

The degree of stenosis was assessed according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCA Guideline on the Management of Patients with Extracranial Carotid and Vertebral Artery Disease Criteria [5]. Internal carotid artery (ICA) stenosis of >50% in symptomatic patients and ICA stenosis >80% in asymptomatic patients were defined as critical for carotid angiography.

Patients were divided into two groups. Group 1 had critical ICA stenosis, whereas Group 2 had noncritical ICA stenosis as assessed by carotid angiography.

Data from all patients were collected from hospital medical records. Excluded from the study were patients with any hematologic disease, recent arterial thrombotic disease, cirrhosis, chronic pulmonary disease, chronic renal disease, any diagnosed cancer, chronic inflammatory or autoimmune diseases, active infection, or patients receiving antibiotic treatment. After 12-14 hours of fasting, venous blood samples were obtained from patients for biochemical and hemogram analysis. Complete blood cell counts and automated differential counts were determined via an automated hematology analyzer (Abbott CELL-DYN 3700 System, Ramsey, Minnesota, 55303, USA), which provided total white blood count, platelet, neutrophil, lymphocyte, monocyte, eosinophil, and basophils counts/ mL. The baseline PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. The institutional ethics committee approved the study protocol.

Statistical analysis

Data analysis was performed using SPSS for Windows 17.0 (Statistical Package for Social Science; SPSS Inc., Chicago, IL, USA). The mean differences of the continuous data were measured by the t test and the median differences of the categorical data were measured by the Mann-Whitney U and Fisher’s exact tests. A p value < 0.05 was accepted as statistically significant. The chi-square test was used to compare differences between categorical variables. Receiver operating characteristics curves (ROC) were conducted, when appropriate.

Results

One hundred forty patients were included in the data analysis. Patients were divided into two groups. Group 1 (n = 64) included patients with critical CAS, whereas Group
2 (n = 76) included patients with noncritical CAS on angiography. The groups were homogenous in demographic characteristics and past medical history (Table 1). The mean age of controls with noncritical stenosis was 68.5 ± 9.8 years, and the mean age of the patients was 67.0 ± 8.3 years. There were no significant differences in sex and age between the two groups. Clinical and demographic findings of groups are shown in Table 1.

The hemogram parameters of the controls with noncritical stenosis and critical carotid stenosis group are shown in Table 2. Total white blood cell count values were 8617 ± 2370 K/µL in the critical carotid stenosis group and 7688 ± 2095 K/µL in the noncritical carotid stenosis group at p = 0.417. Hemoglobin was 13.0 ± 1.7 gr/dL in the critical carotid stenosis group and 13.3 ± 1.6 gr/dL in the control group, respectively, at p = 0.544. Neutrophil counts were 4985 ± 1942 K/µL in the critical carotid stenosis group and 4850 ± 1851 K/µL in the control group at p = 0.993. Lymphocyte counts were 1882 ± 637 K/µL in the critical carotid stenosis group and 2956 ± 1404 K/µL in the control group at p < 0.0001. Platelet counts were 272,750 ± 87,235 K/µL in critical carotid stenosis group and 234,910 ± 58,952 K/µL in the control group at p = 0.012. The PLR was 162.5 ± 84.7 in the critical carotid stenosis group and 94.9 ± 60.3 in the control group at p < 0.0001.

The ROC analysis was performed to determine the PLR cutoff value to predict total thrombosis of one of the carotid arteries. The ROC curve is shown in Figure 1. The PLR was predictive at 117.1 with 89% sensitivity and 68% specificity for predicting critical stenosis in the carotid artery. A review of the literature shows that our study is the first showing a relationship between the PLR and CAS.

Cardiovascular disease is a progressive disease of atherosclerosis [5]. Atherosclerosis-related mortality remains the most common cause of death around the world. Atherothrombotic plaque is similar to inflammation in many respects. The role of inflammation has been detected at every stage of the atherosclerotic process [9]. At the histological level, immunoglobulins, T lymphocytes, plasma cells, and the presence of antigen-antibody complex in the atheroma plaque suggest the importance of inflammation in

### Discussion

The PLR values were higher in patients with critical CAS in our study. A preprocedural PLR of >117.1 had 89% sensitivity and 68% specificity for predicting critical stenosis in the carotid artery. A review of the literature shows that our study is the first showing a relationship between the PLR and CAS.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and demographic findings of the two groups.</th>
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<tbody>
<tr>
<td>Critical carotid stenosis group (n = 64)</td>
<td>Controls with no critical stenosis group (n = 76)</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>68.5 ± 9.8</td>
</tr>
<tr>
<td>Sex (m, %)</td>
<td>42 (67.7)</td>
</tr>
<tr>
<td>HT</td>
<td>54 (84.3)</td>
</tr>
<tr>
<td>DM</td>
<td>16 (25.8)</td>
</tr>
<tr>
<td>HL</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>CAD</td>
<td>25 (35.9)</td>
</tr>
<tr>
<td>Cigarette</td>
<td>13 (19.1)</td>
</tr>
<tr>
<td>PAD</td>
<td>7 (9.7)</td>
</tr>
</tbody>
</table>

The data are presented as mean (%) unless otherwise indicated.

CAD = coronary artery disease; DM = diabetes mellitus; HL = hyperlipidemia; HT = hypertension; m = male; PAD = peripheral artery disease; SD = standard deviation.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Hemogram parameters of patients with/without critical carotid stenosis.</th>
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<tbody>
<tr>
<td>Critical carotid stenosis group (n = 64)</td>
<td>Controls with no critical stenosis group (n = 76)</td>
</tr>
<tr>
<td>WBC (K/µL)</td>
<td>8617 ± 2370</td>
</tr>
<tr>
<td>Neu (K/µL)</td>
<td>4985 ± 1942</td>
</tr>
<tr>
<td>Lymp (K/µL)</td>
<td>1882 ± 637</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>13.0 ± 1.7</td>
</tr>
<tr>
<td>PLT (K/µL)</td>
<td>272,750 ± 87,235</td>
</tr>
<tr>
<td>MPV (fl)</td>
<td>7.6 ± 1.1</td>
</tr>
<tr>
<td>PLR</td>
<td>162.5 ± 84.7</td>
</tr>
</tbody>
</table>

The data are presented as mean ± standard deviation. Hb = hemoglobin; Lymp = lymphocyte; MPV = mean platelet volume; Neu = neutrophil; PLR = platelet-to-lymphocyte ratio; PLT = platelet; WBC = total white blood cell count.

Platelet counts and PLR levels are significantly higher and lymphocyte levels are significantly lower in the critical carotid stenosis group.

### Figure 1

The ROC curve for PLR to predict critical stenosis in a carotid artery. The PLR is predictive at 117.1 with 89% sensitivity and 68% specificity (95% CI, 0.043–0.159; AUC, 0.101 ± 0.03). AUC = area under the curve; CI = confidence interval; PLR = platelet-to-lymphocyte ratio; ROC = receiver operating characteristic curve.
the formation and progression of plaque [10]. Ongoing inflammatory conditions lead to megakaryocytic proliferation and thrombocytosis [11].

Platelets are 2–4 μm in diameter. They are small, non-nucleated, oval or round discoid blood cells. Platelets have an important role in the initiation of atherosclerotic lesions. Mediators released from platelets such as thromboxane A2, adenosine diphosphate, serotonin, platelet activating factor, and platelet-derived growth factor increase platelet activation and aggregation. They also stimulate the growth of vascular smooth muscle and chemotaxis for inflammatory cells and fibroblasts [12,13].

Cardiovascular events are primarily associated with a high platelet count [14–16]. There is a relationship between mortality and high platelet count in patients with acute coronary syndrome [16]. High baseline platelet counts demonstrate the instability of plaque and are associated with stent thrombosis on follow-up [17].

Lymphocytes are blood cells responsible for cellular and humoral immunity in the body. Recent studies have shown that lymphocyte counts decrease in acute coronary syndrome and congestive heart failure. This decrease is probably because of decrease in the cortisol secondary to stress [18,19]. A low lymphocyte count is associated with a worse prognosis [20].

The PLR has come into use recently as an indicator of the balance between inflammation and thrombosis. It may be more advantageous than platelet or lymphocyte counts alone. High PLR values are associated with cardiovascular diseases and adverse outcomes [18–21]. Oylumlu et al. found that high PLR levels before primary percutaneous coronary intervention with stent placement in patients presenting with acute ST segment elevation myocardial infarction may predict the development of future stent thrombosis [20]. A basal PLR of >150 showed 63% sensitivity and 70% specificity in predicting stent thrombosis [20]. An association between high PLR values and increased long-term mortality in patients with non-ST segment elevation myocardial infarctions was found in a previous study [18]. In another study, high PLR levels were a significant predictor for nondipper hypertension [21]. Gary et al. demonstrated that high PLR levels were associated with critical peripheral ischemia. The relationship between a high PLR and slow coronary flow phenomenon has been demonstrated by Oylumlu et al. [23].

In our study, we were able to demonstrate that high PLR values are related to critical stenosis in the carotid artery. The PLR may be a predictor marker evaluating the severity of CAS in patients who have undergone carotid angiography.

In conclusion, analysis of basal PLR values is a cheap and easy method that may be used in patients for the prediction of critical CAS. We reached this conclusion using a retrospective study. Larger prospective and multicenter studies must be performed to explain the relationship between the PLR and CAS.

References


