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Platelet to lymphocyte ratio predicts all-cause mortality in patients with carotid arterial disease

MUJGAN TEK*, MEHMET SERKAN ÇETİN, ERDEM DİKER, SAVAŞ ÇELEBİ, BASRİ AMASYALI, BERKTEN BERKALP

TOBB Economy and Technology University Cardiology Department, Ankara, Turkey

Background. Platelet to lymphocyte ratio (PLR) has been demonstrated as a risk and prognostic marker in many of cardiovascular diseases. A relationship between PLR and severity of carotid stenosis has been shown. The aim of our study was to investigate the relationship between PLR and all cause mortality in patients with carotid arterial disease.

Methods. This retrospective study included 146 patients who had been performed selective carotid angiography. Carotid stenosis were graded by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. Platelet to lymphocyte ratio was calculated as the ratio of platelets to lymphocytes. The end point of the study was all-cause mortality.

Results. During median follow-up of 16 months (0-65 months) 15 (10.3%) patients suffered all-cause mortality. 50 patients (34.2%) underwent carotid endarterectomy and 69 patients (47.3%) had non-carotid cardiac surgery. 38 patients (26.02%) had cerebrovascular events (stroke/transient ischemic attack) at admission. NASCET grades were not different between survivors and non-survivors. Non-survivors had significantly lower hemoglobin (Hb) levels (12.7 ± 1.6 g/dL *vs*. 13.7 ± 1.7 g/dL, p = 0.031) and they were older than survivors (74.2 ± 8.4 years *vs*. 68.6 ± 8.5 years, p = 0.029). Non-survivors had significantly higher PLR values compared with survivors (190.3 ± 85.6 and 126.8 ± 53.8, p = 0.017). In multivariate analysis, only PLR predicted all-cause mortality in patients with carotid artery stenosis.

Conclusion. In our study, higher PLR was associated with increased all-cause mortality.

Key words: platelet count, lymphocyte count, carotid artery disease, carotid stenosis, mortality.

INTRODUCTION

Previous studies showed that higher platelet and lower lymphocyte counts are associated with the formation of vascular diseases [1, 2]. The platelet to lymphocyte ratio (PLR) is a new widely used inflammatory marker that combines information from both pathways of hemostasis and inflammation [3, 4]. İt is suggested more useful than platelet and lymphocyte count alone. İncreased PLR has been shown to be associated with a number of clinical conditions involving cardiovascular diseases [5-8].

Stroke is one of the leading causes of death in the world. Carotid artery stenosis is an important atherosclerotic disease that may cause stroke [9]. The degree of carotid arterial stenosis is a risk factor for stroke development [10]. The relationship between PLR and severity of carotid stenosis and stroke has been shown [11, 12], but mortality relation is not known yet.

The aim of our study was to investigate the relationship between PLR and all cause mortality in patients with carotid arterial disease.

MATERIALS AND METHOD

This retrospective study included 146 patients who had been performed selective carotid angiography because of moderate to high extracranial internal carotid artery stenosis determined on Doppler carotids ultrasonography at TOBB ETÜ Hospital, Ankara, from January 2013 to June 2018. The majority of the study group were patients who were undergoing carotids Doppler ultrasonography before coronary artery bypass surgery.

Diagnostic Carotid angiographies had been performed by experienced interventional cardiologists using the conventional method. The degree of stenosis was assessed according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [13].

Clinical and demographic data were recorded from hospital medical records. Coronary artery disease was defined as angiographical presence of ≥ 50% stenosis in a major coronary artery or previous percutaneous coronary intervention/surgery for a stenotic coronary artery. Hypertension was

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defined as a previous diagnosis or current use of antihypertensive medications. Diabetes was defined as a previous diagnosis or current use of anti-diabetic medications. Smoking was defined as current, regular use of cigarettes. Cerebrovascular events (CVE) were diagnosed as past history of any ischemic cerebrovascular event with or without sequela and transient ischemic attack diagnosed by an expert neurologist.

Laboratory data of venous blood sampling including hematologic and biochemical parameters performed before angiography were recorded. Platelet to lymphocyte ratio was calculated as the ratio of platelets to lymphocytes obtained from the same blood samples.

Patients with vertebral artery/subclavian artery stenosis, arterial dissection or aneurysm, atrial fibrillation that would lead to stroke/TİA evidence of active infection, chronic inflammatory or auto-immune diseases, cancer or hematological diseases and patients receiving antibiotic and steroid therapy were excluded from the study.

The end point of the study was all-cause mortality. Survival status during follow-up period was assessed using the national death notification system. The institutional ethics committee approved the study protocol.

Statistical analysis

All statistical analyses were performed using the SPSS 25 (SPSS INC, Chicago, Illinois, USA). Categorical variables were expressed as frequencies and continuous variables as mean ± Standard deviation. The independent-sample t-test was used for continuous variables, and the chi-square test was used for categorical variables. Univariate Cox regression analysis was performed to assess the association of the variables with mortality and variables that had $p < 0.250$ in the univariate analysis were further analyzed with multivariate Cox regression model. ROC curve was used to detect the optimal cut-off point of PLR to estimate all cause mortality. The best cut-off value for PLR was selected by the use of the Youden index. Kaplan-Meier survival curves used to assess survival times and log-rank statistics were used to test survival time differences between upper and lower cut-off point of PLR. A calculated difference of $p < 0.05$ was considered to be statistically significant.

RESULTS

146 patients with carotid artery stenosis were included in the study (mean age 69.2 ± 8.6 years with 110 males). The median follow-up was 16 months (0-65 months). A total of 15 deaths occurred. Table 1 provides a comparison between survivors and non-survivors. Non-survivors had significantly lower Hb levels (12.7 ± 1.6 g/dL *vs*. 13.7 ± 1.7 g/dL, p = 0.031) and they were older than survivors (74.2 ± 8.4 years *vs*. 68.6 ± 8.5 years, p = 0.029). The rates of CVEs at admission were higher in non-survivors than in survivors (40% *vs*. 24.4%, p = 0.294). There was no statistically significant difference between the groups in terms of the degree of carotids artery stenosis according to NASCET classification . The rates of patients treated with carotid endarterectomy during follow-up period were similar between groups (35.1% in survivors and 26.6% in non-survivors, p = 0.366). Non-survivors had significantly higher PLR values compared with survivors (190.3 ± 85.6 and 126.8 ± 53.8, p = 0.017).

Univariate Cox regression analysis found that all-cause mortality was associated with age (p = 0.079), diabetes mellitus (DM) (p = 0.0229), smoking status (p = 0.219), ejection fraction (EF) (p = 0.128), high-density lipoprotein (HDL) (p = 0.140), Hb (p = 0.08) and PLR (p = 0.027). After multi-variate Cox regression analysis, only PLR was found to be an independent predictor of all-cause mortality (Table 2).

The ROC analysis was performed to determine the PLR cut-off value to predict all-cause mortality. The ROC curve is shown in Figure 1. The PLR was predictive at 131.07 with 64% sensitivity and 36% specificity (95%CI: 0.603-0.867, p = 0.004; area under the curve: 0.735).

Study population was dichotomized based on the cut-off PLR value of 131.07. Figure 2 shows Kaplan-Meier analysis of cumulative survival according to PLR value (≥ 131.07 or < 131.07) in patients with carotid artery disease. Patients with PLR ≥ 131.07 had a higher incidence of all-cause mortality compared with patients with PLR < 131.07 (log rank p = 0.062).

Table 1

Baseline Characteristics of Patients According to the Survival Status

Variables	Survivors n = 131	Non-survivors n = 15	P value
Age, years	68.6 ± 8.5	74.2 ± 8.4	**0.029**
Gender, male, n(%)	99(75.5)	11(73.3)	0.849
CAD, n (%)	110(83.9)	13(86.6)	0.698
HT, n(%)	105(80.1)	13(86.6)	0,468
Smoking, n(%)	39(29.7)	3(20)	0.431
DM, n (%)	48(36.6)	4(26.6)	0.771
LEAD, n (%)	33(25.1)	2(13.3)	0.487
CVE, n (%)	32(24.4)	6(40)	0.294
Glucose, mg/dL	139.4 ± 59.7	131.5 ± 56.6	0.632
GFR, mL/dk/1.73 m^2	73 ± 18.9	70 ± 23.5	0.768
CRP, mg/L	5.3 ± 6.6	7.8 ± 5.2	0.263
Total cholesterol, mg/dL	185.8 ± 56.7	187.3 ± 43.8	0.917
Triglyceride, mg/dL	151 ± 75.2	131 ± 60.8	0.330
LDL, mg/dL	119.3 ± 48.9	104.3 ± 43.4	0.243
HDL, mg/dL	40.7 ± 10.4	47.6 ± 22.2	0.336
Hemoglobin, g/dL	13.7 ± 1.7	12.7 ± 1.6	**0,031**
Platelet, 10^3 u/L	241.2 ± 77.7	221,5 ± 54.13	0,234
Lymphocyte, 10^3 u/L	2.2 ± 0.87	1.9 ± 0,89	0.194
PLR	126,8 ± 53.8	190.3 ± 85.6	**0.017**
LVEF, %	55.02 ± 9.2	50.6 ± 11.9	0.263
Carotid endarterectomy, n (%)	46(35.1)	4(26.6)	0.366
Non-carotid cardiac surgery, n (%)	60(45.8)	9(60)	0.221
Antiplatelet, n (%)	116(88.5)	12(80)	0.230
Statin, n (%)	87(66.4)	8(53.3)	0.736
NASCET, n (%)			
I-II-III (normal-50% stenosis)	56(42.7)	7(46.6)	0.655
IV-Va(50-85% stenosis)	31(23.6)	2(13.3)	0.627
Vb-VI(85%-occluded)	44(33.5)	6(40)	0,917

Abbreviations: CAD, Coronary artery disease; HT, hypertension; DM, Diabetes mellitus; LEAD, Lower extremity arterial disease; CVE, Cerebrovascular events; GFR, glomerular filtration rate; CRP, C reactive protein; LDL, low-density lipoprotein; HDL,high density lipoprotein; PLR, platelet to lymphocyte ratio; LVEF, left ventricular ejection fraction.

Table 2

Predictors of all-cause mortality in multivariate Cox regression analysis

Variables	OR (95% CI)	p
Age, years	1.070 (0.978-1.172)	0.141
DM, yes	0.706 (0.158-3.161)	0.649
Smoking, yes	0.434 (0.052-3.610)	0.440
LVEF, %	0.968 (0.906-1.035)	0.342
Hemoglobin, g/dL	1.042(0.678-1.601)	0.852
PLR	0.010 (1.002-1.018)	0.009
HDL, mg/dL	1.041 (0.998-1.086)	0.065

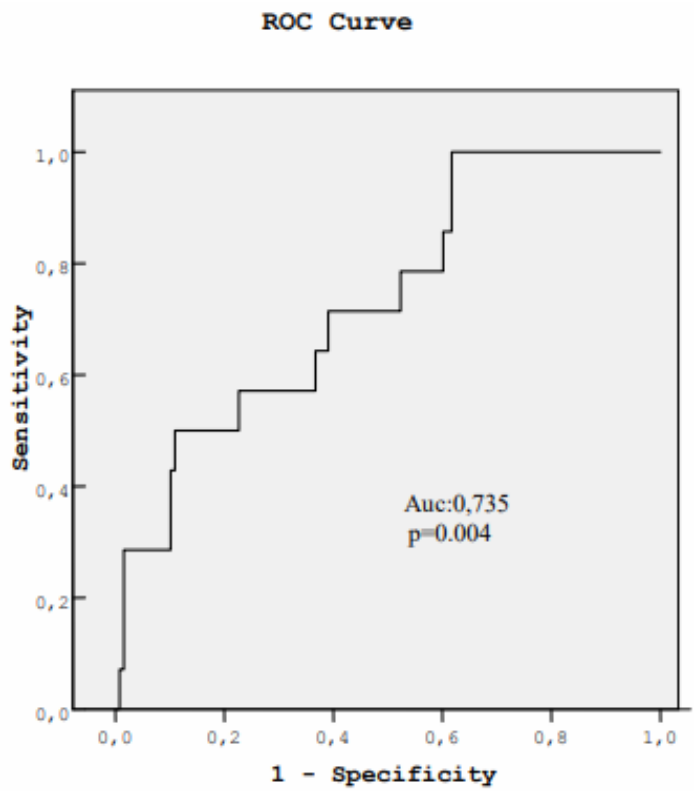

Figure 1. Receiver-operating characteristic curve of PLR for predicting all-cause mortality. Auc indicates area under the curve.

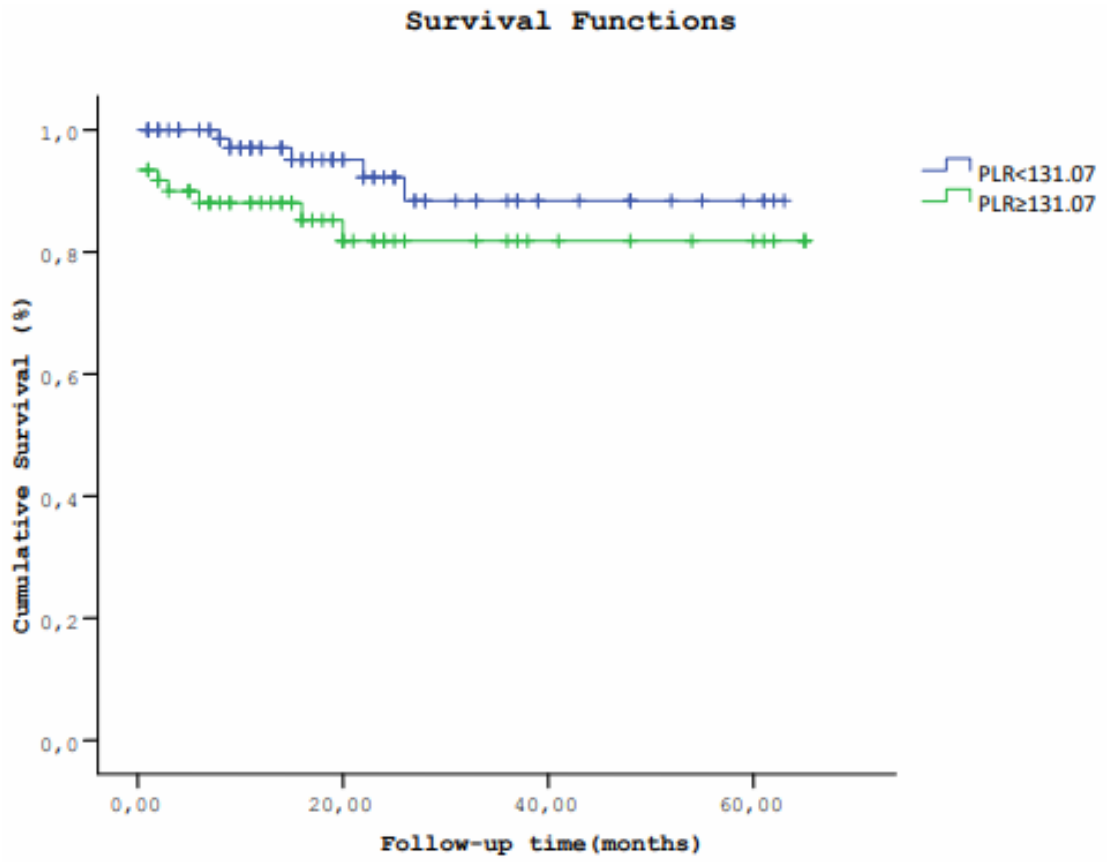

Figure 2. Kaplan-Meier survival curves according to cut-off PLR value.

DISCUSSION

In the present study, we found that PLR is an independent predictor of all-cause mortality in patients with carotid artery stenosis. We demonstrated that PLR predicts all-cause mortality independent of severity of carotid artery stenosis and associated risk factors.

PLR is a novel marker which indicates inflammation indirectly [14]. It has been demonstrated as an independent risk marker in many of cardiovascular diseases including coronary artery disease, heart failure, calcific aortic stenosis and atrial fibrillation [3, 15-17]. In addition to being a risk marker in cardiovascular field, PLR is also as a prognostic marker which shows mortality and other worse outcomes such as no-reflow phenomenon, impaired infarct artery patency, increased in hospital and short term mortality [18-22]. Lee *et al.* [4] demonstrated that elevated PLR is associated with long term all-cause mortality in patients at high risk of coronary artery disease who underwent coronary angiography in their study. Azab *et al.* [23] reported PLR > 176 is a significant independent predictor of long term mortality after NSTEMI. Osadnik *et al*. [24] reported PLR as a predictor of all-cause mortality in patients with coronary artery disease undergoing elective percutaneous coronary intervention and stent implantation.

Carotid artery stenosis is a serious condition that is usually caused by atherosclerosis [25]. As with coronary atherosclerosis, inflammation plays a pivotal role in carotid atherosclerosis from initiation through progression [26]. The association between increased PLR and carotid artery disease has been shown [11, 12]. Soylu *et al*. [11] reported that PLR has been associated with severity of carotid artery disease and is an independent predictor of stroke. However, in our study PLR was not associated with the degree of carotid stenosis. In the aforementioned study of Soylu *et al*. maximum stenosis was different between the PLR tertiles. The discrepancy between computed tomography and invasive angiography for quantification of stenosis degree may explain this result. Computed tomograpy enables assessment of plaque remodeling and, therefore, especially in cases with positive remodeling, it tends to overestimate stenosis degree in contrast to invasive angiography, which is also regarded as luminography [27].

Despite previous cross-sectional studies showing the relationship between PLR and carotid artery stenosis, there has been any study investigating the prognostic role of PLR in patients with carotid artery stenosis. Therefore, our study is the first in the literature evaluating this relationship. We showed the effect of PLR on all-cause mortality independent of platelet or lymphocyte counts alone. Increased PLR reflects the augmented status of inflammation and thrombosis which can be associated with increased mortality in this patient group.

Our study has several limitations. Firstly, it is a single center retrospective study. Secondly our patient population was mostly of preoperative coronary bypass surgery patients which constitutes a specific patient population. And lastly, the lack of longitudinal data suggesting progression of carotid atherosclerosis may add incremental value to the study.

In conclusion, in our study, higher PLR was associated with increased all-cause mortality. Assessment of this easy available marker may be helpful for risk assessment in carotid artery.

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Introducere. *Raportul plachete-limfocite (PLR) este demonstrat a fi factor de risc şi prognostic pentru mai multe patologii cardiovasculare. Relația dintre PLR şi stenoza carotidiană este demonstrată. Scopul studiului este de a investiga relația dintre PLR şi mortalitatea la pacienții cu stenoză carotidiană.*

Materiale şi metode. *A fost realizat un studiu retrospectiv pe 146 de pacienți ce au avut angiografie carotidiană selectivă. Stenoza carotidiană a fost evaluată conform criteriilor NASCET (North American Symptomatic Carotid Endarterectomy Trial). A fost calculat PLR. Efectul măsurat al studiului a fost mortalitatea de orice cauză.*

Rezultate. *Pacienții au fost urmăriți 16 luni în medie (0-65 luni). La 15 pacienți (10.3%) a survenit decesul. 50 de pacienți (34.2%) au suferit endarterectomie carotidiană şi 69 de pacienți au suferit chirurgie cardiacă non carotidiană. 38 de pacienți (26.02%) au suferit evenimente cerebrovasculare (atacuri vasculare*

ischemice sau tranzitorii). Pacienţii care nu au supravieţuit au avut niveluri semnificative statistic mai mici ale hemoglobinei (12.7 ± 1.6 g/dl vs. 13.7 ± 1.7 g/dl, p = 0.031) şi erau mai în vârstă decât pacienţii care au supravieţuit (74.2 ± 8.4 ani vs. 68.6 ± 8.5 ani, p = 0.029). Pacienţii care nu au supravieţuit au avut valori semnificativ mai mari ale PLR (190.3 ± 85.6 şi 126.8 ± 53.8, p = 0.017). În analiza multivariată numai PLR a prezis independent mortalitatea la pacienţii cu stenoză carotidiană.

Concluzii. *În acest studiu valori crescute ale PLR s-au asociat cu mortalitatea la pacienţii cu stenoză carotidiană.*

Correspondence to: Müjgan Tek, M.D, TOBB Economy and Technology University Cardiology Department, Ankara, Turkey,
Tel: +90-312-292 99 00
E-mail: drmujgantek@hotmail.com, mtek@tobbetuhastanesi.com.tr

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