The European Research Journal 2022;8(5):670-677 Original Article

DOI: 10.18621/eurj.1125452 *Cardiology*

The relationship of platelet to lymphocyte ratio with the presence and extent of coronary atherosclerosis detected by coronary computed tomography angiography

Hakan Çakır[1], Cüneyt Toprak[1], Ali Karagöz[1], Samet Uysal[1], Nuri Havan[2], Mustafa Kuzeytemiz[3], Cihangir Kaymaz[1], Mehmet Demir[3]

[1]Department of Cardiology, University of Health Sciences Turkey, Kartal Koşuyolu Cardiovascular Training and Research Hospital, İstanbul, Turkey; [2]Department of Radiology, University of Health Sciences Turkey, Kartal Koşuyolu Cardiovascular Training and Research Hospital, İstanbul, Turkey; [3]Department of Cardiology, University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

ABSTRACT

Objectives: Platelet-lymphocyte ratio (PLR) combines the predictive risk of platelet and lymphocyte counts into a single risk index. PLR has been studied as a predictive marker in a variety of cardiovascular diseases. However, our understanding of the link between PLR and coronary artery disease (CAD) remains limited. The present study aimed to evaluate the relationship between PLR and intensity of coronary atherosclerosis in patients with suspected CAD.

Methods: In this retrospective study, we included 221 patients undergoing dual-source 64-slice coronary computed tomography angiography (CCTA). Total and different types of leukocyte counts were measured with an automatic blood counter. Based on a modified version of the American Heart Association's categorisation, the coronary artery tree was divided into 16 segments. To assess the extent of coronary atherosclerosis, the number of affected coronary segments was counted. Coronary artery plaques were classified into three categories: (1) calcified plaque, (2) non-calcified plaque, and (3) mixed plaque.

Results: After multivariable backward stepwise regression analysis, PLR remained as an independent predictor for both the presence and extent of coronary atherosclerosis (OR = 2.38, 95% CI: 1.27-4.47 and OR = 1.66, 95% CI: 1.10-2.51, respectively). There was no significant relationship between PLR and plaque morphology. Conclusions: Higher PLR was associated with the intensity of coronary atherosclerosis detected by CCTA. Further research is necessary to determine the optimal approach to using PLR in medical practice.

Keywords: Platelet-lymphocyte ratio, coronary artery disease, atherosclerosis, computed tomography angiography

Coronary artery disease (CAD), which is pathologically characterized by atherosclerosis, is the leading cause of death worldwide. Chronic low-grade inflammatory state plays a central role in the onset and progression of atherosclerosis [1]. Inflammation's role in CAD has been thoroughly investigated, and a con-

***Received:* June 3, 2022; *Accepted:* June 19, 2022; *Published Online:* July 31, 2022**

How to cite this article: *Çakır H, Toprak C, Karagöz A, Uysal S, Havan N, Kuzeytemiz M, et al. The relationship of platelet to lymphocyte ratio with the presence and extent of coronary atherosclerosis detected by coronary computed tomography angiography. Eur Res J 2022;(5):670-677. DOI: 10.18621/eurj.1125452*

e-ISSN: 2149-3189

Address for correspondence: *Hakan Çakır, MD., University of Health Sciences Turkey, Kartal Koşuyolu Cardiovascular Training and Research Hospital, Department of Cardiology, İstanbul, Turkey. E-mail: dr.hcakir@gmail.com, Phone: +90 216 500 15 00, Fax: +90 216 459 63 21.*

sistent relationship between several pro-inflammatory markers and CAD has been established [2, 3]. Platelet (pro-inflammatory) and lymphocyte (regulatory and protective) counts have been identified as biological markers in a variety of cardiovascular diseases and inflammatory conditions [4-6]. Platelet-lymphocyte ratio (PLR), which is calculated by dividing the absolute platelet count by the absolute lymphocyte count, is an integrated manifestation of two considerable inflammatory pathways. Therefore, a raised PLR may play a more decisive role in forecasting CAD than each parameter alone.

Recently, the PLR has been investigated as a predictive marker for a variety of numerous cardiovascular conditions, such as acute coronary syndromes, peripheral vascular diseases, atrial fibrillation, and heart failure [7]. Moreover, PLR has been shown to be associated with the severity of atherosclerotic disease in stable angina pectoris [8]. In the majority of these studies, conventional angiography was preferred over coronary computerized tomography angiography (CCTA) to evaluate coronary artery lesions. CCTA can provide more accurate details about atherosclerotic plaque burdenas it allows direct assessment of the vascular wall, and thus positive remodeling.

This study aimed to investigate the association between PLR and the intensity of coronary atherosclerotic lesions in patients with suspected CAD undergoing CCTA. We hypothesized that higher PLR levels would be a reliable and independent risk factor for coronary atherosclerotic plaque burden. Meanwhile, we also examined the link between atherosclerotic plaque morphology and PLR levels.

METHODS

Study Population

In this retrospective study, we enrolled 295 consecutive patients undergoing CCTA for CAD from February 2018 to May 2020. All the patients had been referred to our outpatient clinic with the complaint of chest pain. A detailed physical examination was performed, and a detailed medical history was recorded for each patient. Patients with any history of CAD, acute/chronic kidney insufficiency, congestive heart failure, severe valvular heart disease, active infection or systemic inflammatory conditions, hematologic disorders, and active malignancy were excluded from the study. Following the application of the inclusion criteria, a total of 221 cases were admitted to the study. Diabetes mellitus was defined as a fasting plasma glucose level of more than 126 mg/dL on two separate tests, or the active use of any antidiabetic drug. Hypertension was considered to be a systolic blood pressure of ≥ 140 mm Hg and/or a diastolic blood pressure of ≥ 90 mm Hg, or the active use of any antihypertensive medication. Dyslipidemia was defined as a total cholesterol level of ≥ 200 mg/dL or the active use of any active lipid lowering medication. Body mass index (BMI) was calculated by the formula of weight (kg)/ height² (m²).

Ethics Committee Approval

All participants gave informed consent to participate in the research. The research protocol was approved by theInstitutional Research Ethical Committee (code: 2021/10/525).

Laboratory Analysis

Blood samples were drawn after an overnight fasting. Total and different types of leukocyte counts were measured with an automatic blood counter. PLR was calculated by dividing the platelet count by the lymphocyte count. All laboratory analyses, including biochemical parameters and lipid profiles, were performed using an automatic biochemistry analyzer (Cobas 8000; Roche Diagnostics, Basel, Switzerland).

CCTA and Assessment of Coronary Atherosclerosis

CCTA was performed with a dual-source 64-slice multidetector CT scanner (Aquilion; Toshiba Medical Systems, Japan). In case of heart rate higher than 65 beats per minute, an intravenous beta-blocker (metoprolol, 5-25 mg) was administered. Sublingual nitroglycerine (0.4 mg) was given just before scanning unless there were any contraindications. During scanning, 80-110 mL (weight-based dosing) of nonionic contrast agent (350 mgI/mL iomeprol; Bracco Imaging, Milan, Italy) was injected via venous route at a flow rate of 5.5 mL/s followed by 50 mL of isotonic bolus. A radiologist who specializes in cardiac imaging evaluated all angiographic images immediately after data collection. The relationship between PLR and CAD was studied separately based on the pres-

ence and extent of atherosclerotic lesions. Any apparently distinguishable structure attributed to the vessel wall in at least two different imaging planes was defined as coronary arterial plaque. Based on a modified version of the American Heart Association's categorisation, the coronary artery tree was divided into 16 segments [9]. To determine the extent of coronary atherosclerosis, the number of affected coronary segments was counted. Coronary artery plaques were classified into three categories: (1) calcified plaque (which has a higher Hounsfield unit (HU) than the contrast-enhanced coronary artery lumen); (2) non-calcified plaque (which has a higher HU than the adjacent connective tissue but a lower HU than the contrast-enhanced coronary artery lumen); and (3) mixed plaque (which has both calcified and noncalcified plaque components).

Statistical Analysis

The analysis was performed out using R software (version 4.0.1). Normality was analyzed using the Shapiro-Wilk's test. Continuous variables were expressed as mean ± standard deviation (SD) and categorical data as numbers and percentages (%). The

Table 1. Baseline clinical and laboratory characteristics of the study population

Variable	Coronary plaque (+) (n = 144)	Coronary plaque (-) (n = 77)	*p*value
Clinical characteristics			
Age (years)	57.2 ± 9.7	50.0 ± 9.8	**< 0.001**
Gender (male)	86 (59.7)	36 (46.8)	0.065
BMI (kg/m^2)	27.5 ± 3.4	27.1 ± 3.7	0.474
Cigarette smoking[a]	62 (43.1)	24 (31.2)	0.084
Hypertension	101 (70.1)	40 (51.9)	**0.007**
Diabetes mellitus	34 (23.6)	8 (10.4)	**0.017**
Dyslipidemia	94 (65.3)	36 (46.8)	**0.008**
Medication			
Acetylsalicylic acid	93 (64.6)	49 (63.6)	0.889
ACE inhibitors/ARBs	76 (52.8)	36 (46.8)	0.393
Beta blockers	64 (44.4)	32 (41.6)	0.680
Calcium antagonists	22 (15.3)	13 (16.9)	0.755
Statin	67 (46.5)	31 (40.3)	0.371
Laboratory characteristics			
Hemoglobin, g/dL	14.1 ± 1.6	13.7 ± 1.4	0.111
WBC count, ×10^3/mL	7.75 ± 1.75	7.39 ± 2.10	0.174
Platelet count, ×10^3/mL	257.9 ± 61.6	242.9 ± 56.2	0.079
Lymphocyte count, ×10^3/mL	2.15 ± 0.59	2.57 ± 0.84	**< 0.001**
Platelet–lymphocyte ratio	129.9 ± 50.6	100.8 ± 28.7	**< 0.001**
Creatinine, mg/dL	0.86 ± 0.17	0.84 ± 0.19	0.451
Total cholesterol, mg/dL	200.5 ± 47.6	183.1 ± 43.7	**0.008**
LDL cholesterol, mg/dL	133.1 ± 36.1	116.2 ± 35.5	**0.001**
HDL cholesterol, mg/dL	43.2 ± 12.8	46.6 ± 11.4	0.053
Triglyceride, mg/dL	161.5 ± 81.2	144.6 ± 76.5	0.134

[a]Active smokers. Data are expressed as mean ± SD and n (%). ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, BMI = body mass index, CAD = coronary artery disease, HDL = high-density lipoprotein, LDL = low-density lipoprotein, WBC = white blood cell.

students' t-test and the Mann-Whitney U-test were used to analyze continuous variables with normal and non-normal distributions, respectively. The chi-square test was used to analyze categorical variables and proportions. The Kruskal-Wallis test was used to compare the difference in PLR between coronary plaque morphology subgroups.Univariable and multivariable backward stepwise proportional odds regression analysis was performed to identify the predictive variables of coronary atherosclerosis. For backward elimination, a 0.20 alfa level was chosen. The results of regression analyses were reported as odds ratios (OD) with their respective 95% confidence intervals (CI). The partial effects plot was used to demonstrate the relative importance of some of the variables analyzed in the regression model. For all analyses, two-tailed statistically significant threshold was set at p - value < 0.05.

RESULTS

The baseline clinical and laboratory characteristics of the study population are shown in Table 1. The participants were divided into two groups based on the presence of coronary atherosclerotic plaque. Gender, BMI, and the frequency of cardiovascular medication were not significantly different between the two groups. The coronary atherosclerotic group had a higher prevalence of cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia. Among hematological parameters, patients with coronary atherosclerosis had higher platelet counts ($p < 0.001$) and lower lymphocyte counts ($p < 0.001$). PLR levels were also significantly different between the groups (129.9 ± 50.6 versus 100.8 ± 28.7, $p < 0.001$). The results of univariable and multivariable regression analyses to predict the independent variables associated with the presence and extent of coronary atherosclerosis are presented in Table 2 and Table 3, respectively. After multivariable backward stepwise regression analysis, PLR remained as an independent predictor for both the presence and extent of coronary atherosclerosis (OR = 2.38, 95% CI: 1.27-4.47 and OR = 1.55, 95% CI: 1.10-2.51, respectively). Apart from the PLR level, other variables including age, smoking, diabetes mellitus, hypertension, and low-density lipoprotein (LDL) level were found to be statistically significant (Figs. 1 and 2). Also, no significant relationship was found between the PLR and coronary plaque morphology (Fig. 3).

DISCUSSION

In this study, PLR was found to be an independent predictor of the presence and extent of CAD, independent of traditional cardiovascular risk factors. Moreover, there was no meaningful association between coronary plaque morphology and PLR levels. We evaluated the lesions with CCTA, which is a unique aspect of this study. In this regard, our results contribute to the cur-

Table 2. Univariable and backward stepwise multivariable analyses demonstrating the association between cardiovascular risk factors, including PLR and the presence of coronary plaque

Variable	Univariable		Stepwise multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p*value
Age (from 47 to 62)	3.09 (1.93-4.93)	< 0.001	3.51 (1.99-6.20)	**< 0.001**
Gender (male)	1.68 (0.96-2.95)	0.064		
Smoking	1.66 (0.93-2.99)	0.071	2.57 (1.25-5.26)	**0.010**
Hypertension	2.12 (1.22-3.84)	**0.001**	2.59 (1.29-5.20)	**0.007**
Diabetes mellitus	2.66 (1.16-6.09)	**0.001**	2.56 (0.95-6.90)	0.063
Creatinine	1.18 (0.76-1.81)			
LDL (from 104 to 151)	1.86 (1.27-2.74)	**0.001**	2.42 (1.50-3.92)	**< 0.001**
PLR (from 87.4 to 146.9)	3.09 (1.72-5.55)	**< 0.001**	2.38 (1.27-4.47)	**0.006**

CI = confidence interval, LDL = low-density lipoprotein, OR = odds ratio, PLR =platelet-lymphocyte ratio

Table 3. Univariable and backward stepwise multivariable analyses demonstrating the association between cardiovascular risk factors, including PLR and the extent of coronary atherosclerosis

Variable	Univariable		Stepwise multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (from 47 to 62)	2.39 (1.66-3.43)	**< 0.001**	2.19 (1.49-3.21)	**< 0.001**
Gender (male)	1.52 (0.94-2.45)	0.083		
Smoking	1.62 (1.004-2.64)	**0.042**	2.22 (1.33-3.71)	**0.002**
Hypertension	2.00 (1.21-3.30)	**0.006**	1.75 (1.04-2.95)	**0.036**
Diabetes mellitus	2.81 (1.54-5.12)	**0.007**	2.63 (1.40-4.96)	**0.003**
Creatinine	1.26 (0.86-1.84)	0.244		
LDL (from 104 to 151)	1.66 (1.21-2.28)	**0.001**	1.72 (1.25-2.37)	**0.001**
PLR (from 87.4 to 146.9)	2.13 (1.42-3.18)	**<0.001**	1.66 (1.10-2.51)	**0.025**

CI = confidence interval, LDL = low-density lipoprotein, OR = odds ratio, PLR = platelet-lymphocyte ratio

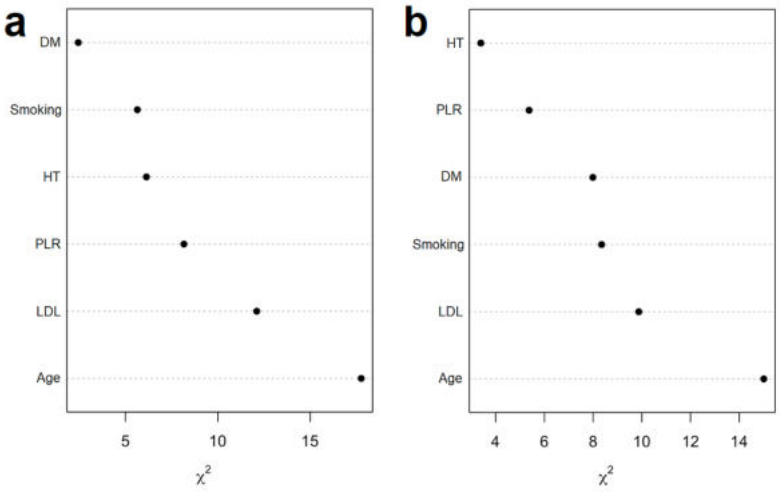

Fig. 1. The relative importance of each factor associated with the presence (a) and extent of coronary artery disease (b). DM = diabetes mellitus, HT = hypertension, LDL = low-density lipoprotein, PLR = platelet-lymphocyte ratio.

rent literature.

Platelet activation is a pivotal stage in the onset and progression of cardiovascular diseases [4]. During inflammation, platelets are stimulated by endothelial substances and secrete inflammatory mediators and cytokines [10]. Increased platelet count accelerates the formation, progression and instability of atherosclerotic lesions and has also been shown to be associated with adverse outcomes of CAD [11]. On the other hand, lymphocytes have been shown to play an active role in modulating inflammatory responses at each stage of the atherosclerotic process. Lymphopenia has been identified as a typical response to systemic stress, and has been linked to a poor prognosis, particularly in processes where inflammation is a major pathophysiological factor [12]. As an independent predictor, the PLR combines the predictive risk of platelet and lymphocyte counts into a single risk index. In this regard, some previous studies reported a positive correlation between PLR and commonly used inflammatory markers [13, 14].

Patients with high PLR levels have been shown to have an increased atherosclerotic burden on coronary angiography [15]. Akboğa *et al*. [16] investigated the association between high PLR and the presence/severity of coronary atherosclerosis; concluding that preprocedure PLR levels were independently associated with the Gensini score. Likewise, Yüksek *et al*. [8] reported the relationship between PLR and the severity of CAD in patients with stable angina pectoris. How-

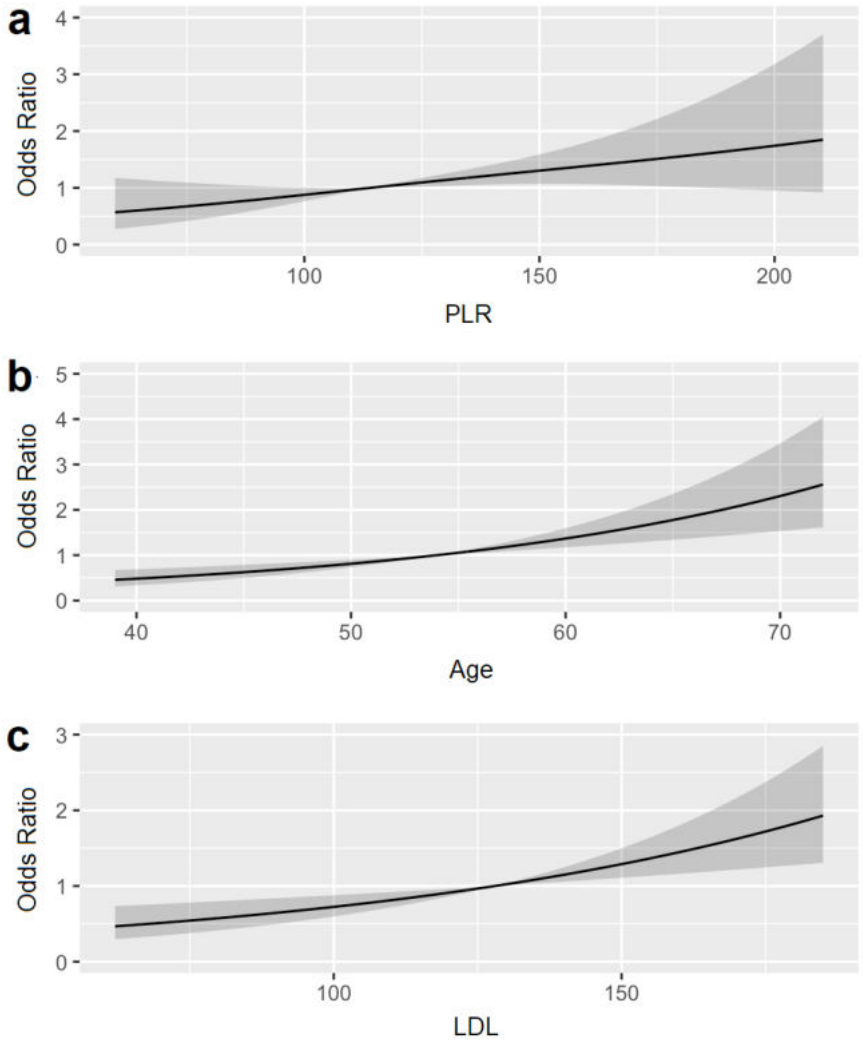

Fig. 2. Partial effect plots of PLR (a), age (b) and LDL (c) showing association with the extend of coronary artery disease in a multivariable model. LDL = low-density lipoprotein, PLR = platelet-lymphocyte ratio.

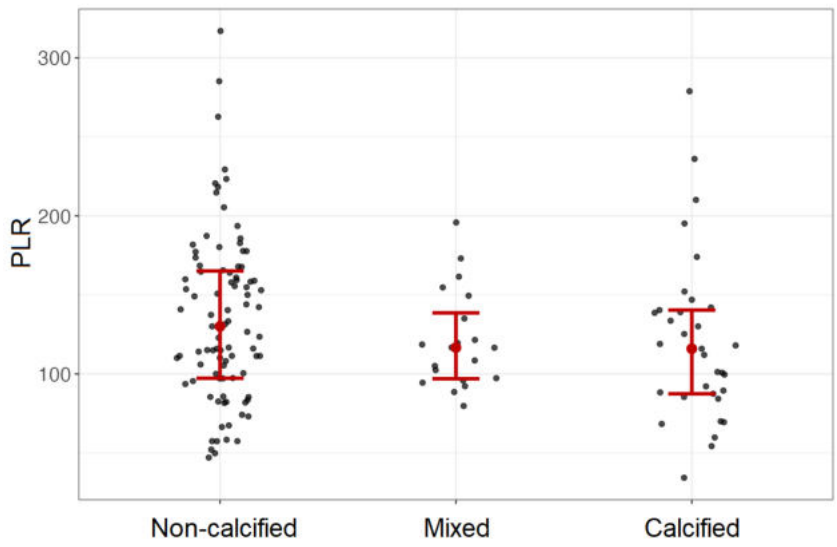

Fig. 3. Scatter plot of the relationship between PLR and plaque morphology (p> 0.05). PLR = platelet-lymphocyte ratio.

ever, the association between the PLR and CAD is not fully elucidated; the above-mentioned mechanisms related to platelets and lymphocytes in inflammation and atherosclerosis can shed light on these interactions. Our findings confirm and strengthen several previous studies consistently demonstrating PLR as a predictor of CAD. The identification of coronary artery lesions by CCTA helped us to make a more sensitive assessment compared to earlier studies, as CCTA provides more reliable qualitative and quantitative data about plaque morphology and the whole coronary system as compared to invasive approaches [17].

Coronary plaque content is a critical determinant of clinical progression and prognosis in CAD. However, the role of calcium deposits on plaque vulnerability is debatable, as several studies have shown inconsistent results regarding the effect of calcified plaques on major adverse cardiac event rates [18-20]. It has been previously shown that inflammatory markers are only weakly correlated with plaque composition and coronary calcification, and mostly determined by the existence of coronary risk factors [21]. The relationship between the coronary plaque morphology and PLR was also analyzed separately, but no association was detected. Further investigation of reliable and cost-effective inflammatory biomarkers predicting the presence of a vulnerable plaque with greater sensitivity and specificity is warranted.

Limitations

The present study had some limitations that have to be addressed. First, this research was conducted at a single center using a cross-sectional design with a small study sample size. Further randomized prospective studies are required to confirm our outcomes. Second, the presence or absence of calcification was the sole feature used to classify plaque morphology. As a result, we did not consider other plaque characteristics (such as a large lipid core and a thin fibrous cap) that could be assessed using imaging techniques like optical coherence tomography or intravascular ultrasonography. Third, our results are based on calculating PLR from a single blood sample before CCTA. Evaluating the change in PLR over time may provide useful information. Fourth, our study did not include all pro-inflammatory mediators associated with atherosclerosis, such as interleukin-1, C-reactive protein, and tumor necrosis factor. As a result, PLR could not be compared to these well-known inflammatory markers. Finally, additional longitudinal cohort studies investigating the associations of PLR with both cardiovascular events and mortality are required to support these findings.

CONCLUSION

According to the findings of the present study, increased PLR was found to be associated with the intensity of coronary atherosclerosis detected by CCTA in patients with no prior history of CAD. Thus, PLR can be useful in predicting the coronary atherosclerosis in addition to traditional cardiovascular risk factors. Further research is necessary to determine the optimal approach to using PLR in medical practice.

Authors' Contribution

Study Conception: HÇ, CT; Study Design: HÇ, NH; Supervision: HÇ, CT; Funding: N/A; Materials: SU, NH; Data Collection and/or Processing: SU, MK; Statistical Analysis and/or Data Interpretation: AK; Literature Review: HÇ; Manuscript Preparation: HÇ and Critical Review: CK, MD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685-95.
2. Ruparelia N, Choudhury R. Inflammation and atherosclerosis: what is on the horizon? Heart 2020;106:80-5.
3. Nam SH, Kang SG, Song SW. The neutrophil-lymphocyte ratio is associated with coronary artery calcification in asymptomatic Korean males: a cross-sectional study.Biomed Res Int 2017;2017:1989417.
4. Tsiara S, Elisaf M, Jagroop IA, Mikhailidis DP. Platelets as predictors of vascular risk: is there a practical index of platelet activity? Clin Appl Thromb Hemost 2003;9:177-90.
5. Akkurt Z, Türkçü F, Uçmak D, Yıldırım A, Yüksel H, Yüksel H, et al. [The neutrophil-to-lymphocyte ratio is increased in pa-

tients with Behçet's disease]. Kırıkkale Üniversitesi Tıp Fakültesi Dergisi 2016;16:4-11.[Article in Turkish]
6. Rodrigues SF, Granger DN. Leukocyte mediated tissue injury in ischemic stroke. Curr Med Chem 2014;21:2130-7.
7. Kurtul A, Ornek E. Platelet to lymphocyte ratio in cardiovascular diseases: asystematic review. Angiology 2019;70:802-18.
8. Yüksel M, Yıldız A, Oylumlu M, Akyüz A, Aydın M, Kaya H, et al. The association between platelet/lymphocyte ratio and coronary artery disease severity. Anatol J Cardiol 2015;15:640-7.
9. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation 1975;51(4 Suppl):5-40.
10. Yalçın KS, Tahtacı G, Balçık ÖŞ. [Role of platelets in inflammation]Dicle Tıp Dergisi 2012;39:455-7. [Article in Turkish]
11. Thaulow E, Erikssen J, Sandvik L, Stormorken H, Cohn PF. Blood platelet count and function are related to total and cardiovascular death in apparently healthy men.Circulation1991;84:613-7.
12. Núñez J, Miñana G, Bodí V, Núñez E, Sanchis J, Husser O, et al. Low lymphocyte count and cardiovascular diseases. Curr Med Chem 2011;18:3226-33.
13. Karagoz I, Yoldas H. Platelet to lymphocyte and neutrophil to lymphocyte ratios as strong predictors of mortality in intensive care population. Rev Assoc Med Bras (1992) 2019;65:633-6.
14. Soliman WM, Sherif NM, Ghanima IM, El-Badawy MA. Neutrophil to lymphocyte and platelet to lymphocyte ratios in systemic lupus erythematosus: relation with disease activity and lupus nephritis. Reumatol Clin (Engl Ed) 2020;16:255-61.
15. Zhou D, Wang G, Fan Y, Wan Z, Liu X. Platelet to lymphocyte ratio is associated with the severity of coronary artery disease and clinical outcomes of percutaneous coronary intervention in the Chinese Han population. Exp Ther Med 2017;13:731-8.
16. Akboga MK, Canpolat U, Yayla C, Ozcan F, Ozeke O, Topaloglu S, et al. Association of platelet to lymphocyte ratio with inflammation and severity of coronary atherosclerosis in patients with stable coronary artery disease. Angiology 2016;67:89-95.
17. Rodriguez-Granillo GA, Carrascosa P, Bruining N, Waksman R, Garcia-Garcia HM. Defining the non-vulnerable and vulnerable patients with computed tomography coronary angiography: evaluation of atherosclerotic plaque burden and composition. Eur Heart J Cardiovasc Imaging 2016;17:481-91.
18. Hadamitzky M, Täubert S, Deseive S, Byrne RA, Martinoff S, Schömig A, et al. Prognostic value of coronary computed tomography angiography during 5 years of follow-up in patients with suspected coronary artery disease. Eur Heart J 2013;34:3277-85.
19. Dedic A, Kurata A, Lubbers M, Meijboom WB, van Dalen BM, Snelder S, et al. Prognostic implications of non-culprit plaques in acute coronary syndrome: non-invasive assessment with coronary CT angiography. Eur Heart J Cardiovasc Imaging 2014;15:1231-7.
20. Hadamitzky M, Achenbach S, Al-Mallah M, Berman D, Budoff M, Cademartiri F, et al. Optimized prognostic score for coronary computed tomographic angiography: results from the CONFIRM registry (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry). J Am Coll Cardiol 2013;62:468-76.
21. Hamirani YS, Pandey S, Rivera JJ, Ndumele C, Budoff MJ, Blumenthal RS, et al. Markers of inflammation and coronary artery calcification: a systematic review. Atherosclerosis 2008;201:1-7.