The association between platelet/lymphocyte ratio and coronary artery disease severity

Murat Yüksel, Abdulkadir Yıldız, Mustafa Oylumlu, Abdurrahman Akyüz, Mesut Aydın, Hasan Kaya, Halit Acet, Nihat Polat, Mehmet Zihni Bilik, Sait Alan

Department of Cardiology, Faculty of Medicine, Dicle University; Diyarbakır-*Turkey*

Abstract

Objective: In this study, we aimed to explore the association between platelet-to-lymphocyte ratio (PLR) and the severity of atherosclerosis in coronary artery disease (CAD).

Methods: Clinical and laboratory data of 388 patients who underwent coronary angiography were evaluated retrospectively. Gensini score, which indicates the severity of atherosclerosis, was calculated for all of the patients. Patients with CAD were categorized as mild and severe atherosclerosis, according to their Gensini score. Eighty patients with normal coronary arteries formed the control group. Mean PLR values of the three study groups were compared. Also, PLR value was tested for whether it showed a positive correlation with Gensini score.

Results: The mean PLR of the severe atherosclerosis group was significantly higher than that of the mild atherosclerosis and controls groups ($p<0.001$). Also, PLR was positively correlated with Gensini score in CAD patients. A cut-off value of 111 for PLR predicted severe atherosclerosis with 61% sensitivity and 59% specificity. Pre-procedural PLR level was found to be independently associated with Gensini score, together with WBC, age, and low HDL level, in the multivariate analysis.

Conclusion: Our study suggests that high PLR appears to be additive to conventional risk factors and commonly used biomarkers in predicting severe atherosclerosis. *(Anatol J Cardiol 2015; 15: 640-7)*

Keywords: atherosclerosis, coronary artery disease, Gensini score, platelet-lymphocyte ratio

Introduction

Cardiovascular diseases (CVDs) are still the leading cause of death all over the world, despite modern therapeutic advances. It is known that inflammation plays a substantial role in the initiation and propagation of the complex atherosclerotic process (1) that lies beneath CVD. The role of inflammation in CVD has been studied extensively, and a consistent relationship between various inflammatory markers and CVD has been established in the past (2-4). A low blood lymphocyte count has been shown to be related with worse cardiovascular consequences in patients with CAD and chronic heart failure (5-7). In cases of sustained inflammation, lymphocyte counts decrease due to increased lymphocyte apoptosis. Lymphocytes represent a more convenient immune response, while neutrophils cause a destructive inflammatory reaction. Also, ongoing inflammatory conditions lead to increased proliferation in megakaryocytic series and relative thrombocytosis. Previous studies demonstrated an association between high circulating platelet count and major adverse cardiovascular outcomes in patients with coronary artery disease (CAD) and also in healthy adults (8-10). Platelet-to-lymphocyte ratio (PLR) is a new prognostic marker that integrates the risk prediction of these 2 parameters into 1. It gives an idea about both the aggregation and inflammation pathways, and it may be more valuable than either platelet or lymphocyte count alone in the prediction of coronary atherosclerotic burden. PLR was found to be useful in predicting poor prognosis in cancer population (11-13) and in predicting critical limb ischemia in peripheral artery disease (14) previously. Moreover, higher PLR value emerged as a significant independent predictor of long-term survival in patients presented with acute coronary syndrome (15) and as an independent predictor of no-reflow development in patients undergoing primary PCI (16). In line with these findings, a high PLR tertile of a recent study population

Address for Correspondence: Dr. Murat Yüksel, Dicle Üniversitesi Kalp Hastanesi, 1. Kat Kardiyoloji Kliniği, 21280, Sur-Diyarbakır-*Türkiye*
Phone: +90 412 248 80 01 Fax: +90 412 248 85 23 E-mail: yukselmurat@yahoo.com
Accepted Date: 10.06.2014 **Available Online Date:** 11.07.2014

DOI:10.5152/akd.2014.5565

that presented with STEMI showed poorer outcomes compared to the low PLR group, and PLR was found to be an independent predictor of in-hospital mortality in patients with STEMI (17).

Gensini score was established to expose the severity and extent of coronary atherosclerosis. There are many studies demonstrating the relationship between systemic inflammation and coronary atherosclerosis; however, to our knowledge, there are no data about the relationship between PLR and severity of coronary atherosclerosis yet. In this context, we aimed to investigate the usefulness of a recently defined cardiovascular risk marker, PLR, in predicting the severity of coronary atherosclerosis.

Methods

Study population

The present study is a single-center and retrospectively designed study, consisting of 388 eligible consecutive patients who underwent selective coronary angiography between May and July 2013 in our clinic. Informed consent was obtained from all of the participants, and the study was approved by the local ethics committee.

A thorough physical examination was performed for all of the patients included in the study, and they were asked for their history of previous myocardial infarction, hypertension, diabetes mellitus, smoking and non-cardiac diseases and family history of CAD. Arterial hypertension was considered in patients with at least three repeated measurements of blood pressure above 140 mm Hg systolic and 90 mm Hg diastolic or active use of antihypertensive medication. Diabetes mellitus was defined as fasting plasma glucose levels above 126 mg/dL in at least two different measurements or active use of anti-diabetic drugs. Smoking was defined as current smoking or ex-smokers who forwent smoking in the past 6 months. A positive family history for CAD was considered a history of CAD or sudden cardiac death in a first-degree relative before the age of 55 years for men and 65 years for women.

Patients with moderate or advanced valvular heart disease, clinically decompensated congestive heart failure, malignancy, hematological disorder, severe renal or hepatic insufficiency, active infection or systemic inflammatory conditions, or autoimmune disorders and patients using steroids were excluded.

Biochemical and hematological parameters

After an overnight fasting, peripheral venous blood samples were drawn from patients. Total and differential leukocyte counts were measured by an automated hematology analyzer (Abbott Cell- Dyn 3700; Abbott Laboratory, Abbott Park, Illinois, USA). Absolute cell counts were used in the analyses. PLR was computed as platelet count divided by lymphocyte count. Total and high-density lipoprotein cholesterol (HDL), triglycerides, and fasting plasma glucose levels were measured using the Abbott Architect C16000 auto-analyzer (Architect C16000 auto-analyzer; Abbott Laboratory, Abbott Park, Illinois, USA). Plasma low-density lipoprotein cholesterol (LDL) concentrations were calculated using the Friedewald equation (18).

Coronary angiography and assessment of coronary atherosclerosis severity

Selective coronary angiography was performed for all patients enrolled in the study by Judkins technique through the femoral artery using the Allura Xper FD10 (Philips, Amsterdam, the Netherlands). All of the coronary angiograms were evaluated by 2 interventional cardiologists who were blinded to the patient information and to each other. A thorough review of each coronary angiogram established the lesion location and percentage of luminal stenosis among all coronary artery lesions.

CAD was defined as the presence of stenosis of at least 50% of the vessel diameter in any of the main coronary arteries, according to the American College of Cardiology/American Heart Association (ACC/AHA) lesion classification (19). The Gensini scoring system was used to identify the severity of CAD (20). This method classifies and scores the degree and extent of the stenosis of the coronary arteries. This system scores 1 point for 1% to 25% stenosis, 2 points for 26% to 50%, 4 points for 51% to 75%, 8 points for 76% to 90%, 16 points for 91% to 99% stenosis, and 32 points for total occlusion. The score is then multiplied by a factor representing the importance of the lesion's location in the coronary arterial system. For the location, scores are multiplied by 5 for a left main lesion; 2.5 for the proximal left anterior descending (LAD) or left circumflex (LCX) artery; 1.5 for the mid-segment LAD and LCX; 1 for the distal segment of the LAD and LCX, first diagonal branch, first obtuse marginal branch, right coronary artery, posterior descending artery, and intermediate artery; and 0.5 for the second diagonal and second obtuse marginal branches.

According to their coronary angiograms, patients were categorized into three groups. The first group consisted of 80 patients with normal coronary arteries (control group). The rest of the patients with coronary artery disease were divided into two according to their Gensini score: (21, 22) those with mild atherosclerosis (n=156; Gensini score <25 points) and severe atherosclerosis (n=152; Gensini score ≥25 points).

Statistical analysis

Continuous variables were defined as means and standard deviation; categorical variables were given as percentages. The normality of distribution for continuous variables was confirmed with the Kolmogorov-Smirnov test. According to the distribution pattern of the continuous variables, the independent-sample t-test or the Mann-Whitney U test was used for continuous variables, and the chi-square test was used for categorical variables. One-way analysis of variance (ANOVA) or Kruskal-Wallis test was used to compare 3 groups. When there was a significant difference between the three study groups, the comparison of two groups in terms of the relevant

Table 1. Comparison of baseline demographic characteristics and cardiovascular risk factors of the study population*

	Control group (n=80)	Mild atherosclerosis (n=156)	Severe atherosclerosis (n=152)	*P*
Age, years	57.8±10.5	59.8±10.8	63.7±12.2	<0.001[a]
Male, n (%)	47 (60)	92 (59)	102 (67)	0.288
Coronary risk factors				
Family history, n (%)	6 (8)	15 (10)	19 (13)	0.473
Smoking, n (%)	27 (34)	39 (25)	49 (32)	0.237
Hypertension, n (%)	27 (34)	56 (36)	70 (46)	0.105
Diabetes, n (%)	20 (25)	37 (24)	46 (30)	0.412
Biochemical parameters				
Total cholesterol, mg/dL	180 (154-213)	178 (152-212)	175 (146-206)	0.810*
LDL, mg/dL	110 (85-128)	113 (89-139)	109 (87-136)	0.793*
HDL, mg/dL	40 (33-48)	36 (31-42)	34 (29-39)	<0.001*, [b]
Triglyceride, mg/dL	125 (92-201)	140 (105-190)	136 (91-197)	0.456*
Glucose, mg/dL	108.9±27.8	129.7±61.8	146.1±69.5	<0.001[c]
Creatinine, mg/dL	0.79±0.15	0.87±0.20	1.01±0.55	<0.001[d]
Hematologic parameters				
Hemoglobin, g/dL	13.5±1.6	13.6±1.5	13.7±1.6	0.548
WBC, x10^9/L	8.3±2.4	8.5±2.6	10.1±3.4	<0.001[e]
Platelet, x10^9/L	248±63	241±57	279±58	<0.001[f]
Lymphocyte, x10^9/L	2.5±0.9	2.4±0.9	2.3±1.1	0.337
PLR	106.2±36.9	113.8±60.8	141.7±73.1	<0.001[g]
MPV, fL	8.3±1.3	8.3±1.5	8.4±1.4	0.715

HDL - high-density lipoprotein; LDL - low-density lipoprotein; MPV - mean platelet volume; N/S - non-significant, PLR- platelet-to-lymphocyte ratio; SD-standard deviation; WBC- white blood cell count;
*Values are mean±SD; median (25-75 percentiles), or n (%). Comparison between three groups was performed with one-way ANOVA or *Kruskal-Wallis test.
For the results of post hoc tests or Mann-Whitney U test with Bonferroni correction, the significance levels are:
P_1 (control vs. mild atherosclerosis); P_2 (control vs. severe atherosclerosis); P_3 (mild vs. severe atherosclerosis)
[a] P_1=0.450 (N/S); P_2=0.001; P_3=0.010
[b] P_1=0.006; P_2<0.001; P_3=0.027 (N/S due to Bonferroni correction)
[c] P_1=0.044; P_2<0.001; P_3=0.058 (N/S)
[d] P_1=0.317 (N/S); P_2<0.001; P_3=0.005
[e] P_1=0.797 (N/S); P_2<0.001; P_3<0.001
[f] P_1=0.509 (N/S); P_2=0.004; P_3<0.001
[g] P_1=0.729 (N/S); P_2<0.001; P_3=0.001

parameter was performed with post hoc tests in one-way ANOVA and with Mann-Whitney U test after Bonferroni correction in Kruskal-Wallis test. Correlations were assessed using either Pearson's correlation test or Spearman's rank test according to the distribution pattern of the variable. Independent associations between Gensini score and independent variables were assessed by backward stepwise multiple linear regression analysis by including all parameters showing p value of less than 0.1 on univariate analysis [patient age, PLR, white blood cell (WBC), high-density lipoprotein (HDL), serum creatinine]. Standardized β regression coefficients and their significance from the multiple linear regression analysis were reported. Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cut-off level of preprocedural PLR values to predict severe coronary atherosclerosis. Statistical analyses were performed using SPSS 16.0 (SPSS Inc, Chicago, Illinois, USA). A two-tailed p value <0.05 was considered statistically significant.

Results

A total of 308 patients with coronary artery disease (men 63%, mean age: 62±12 years) and 80 control subjects (59% male, mean age: 59±10 years) with normal coronary arteries were enrolled in the study. Baseline demographic, biochemical, and hematological characteristics of the groups are outlined in Table 1. The study groups were comparable in terms of gender and traditional coronary risk factors, while patients in the severe atherosclerosis group were older compared to the mild atherosclerosis group and controls (p=0.038 and p=0.033, respectively).

Fasting serum glucose was significantly higher in the severe atherosclerosis group than the mild atherosclerosis group

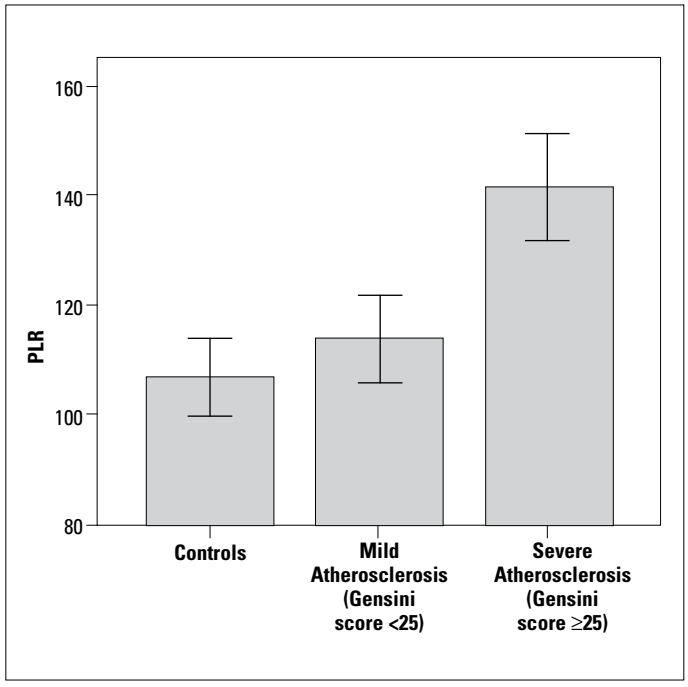

Figure 1. Mean platelet-to-lymphocyte ratio (PLR) of controls and mild and severe atherosclerosis groups

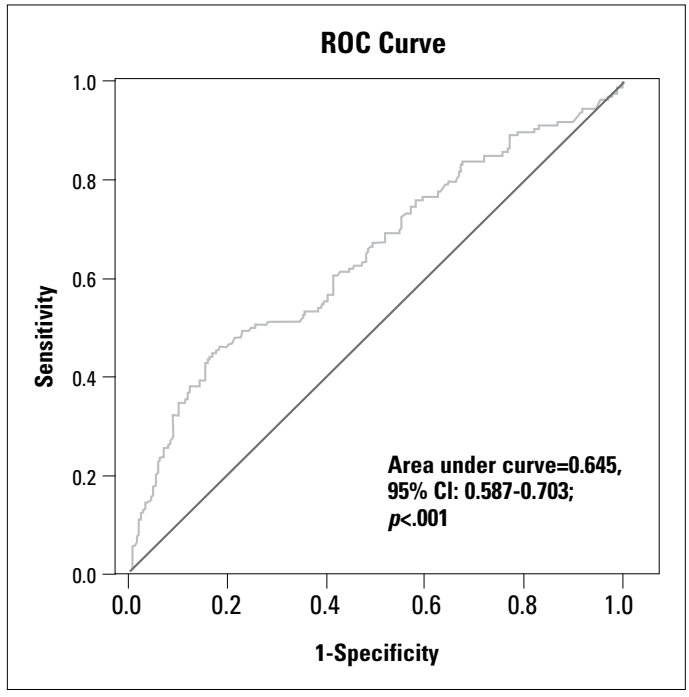

Figure 2. The receiver operating characteristic (ROC) curve analysis of platelet-to-lymphocyte ratio for predicting severe atherosclerosis

(p=0.045) and controls (p<0.001); also, it was significantly higher in mild atherosclerosis than control subjects (p=0.033). The mean serum creatinine level of the severe atherosclerosis group was significantly higher than that of the mild atherosclerosis and control groups (p=0.003 and p<0.001, respectively), while it was comparable between the latter two groups (p=0.284). The severe atherosclerosis group had significantly lower HDL levels compared to controls (p<0.001), whereas it was similar between the severe and mild atherosclerosis groups (p=0.137).

Among hematological parameters, hemoglobin levels were similar between all three groups. WBC was significantly higher in the severe atherosclerosis group than in the other two groups (p<0.001 for both), whereas it was similar between the mild atherosclerosis and control groups (p=0.779).

The severe atherosclerosis group had significantly higher platelet counts compared to the mild atherosclerosis group (p<0.001) and controls (p=0.001), though platelet counts of the last two groups were similar (p=0.671). Lymphocyte count was comparable between all three groups (p=0.337). PLR was significantly higher in the severe atherosclerosis group compared to the mild atherosclerosis (p<0.001) and control groups (p<0.001) (142±73, 114±61, and 106±37 respectively, p<0.001 for ANOVA; Fig.1). PLR was also significantly higher in patients with CAD (n=308) compared to controls (n=80) (128±68 vs. 106±37, p<0.001).

PLR was found to be correlated with age (r=0.285; p<0.001), CRP (r=0.245; p=0.001) (CRP was available for only 144 participants), fasting serum glucose level (r=0.187; p=0.014), and neutrophil count (r=0.922; p<0.001). Also, PLR values of patients with CAD (n=308) correlated significantly with their Gensini scores (r=0.268, p<0.001). Using a cut-off level of 111, PLR predicted severe atherosclerosis with a sensitivity of 61% and specificity of 59% (area under ROC curve=0.645, 95% CI: 0.587-0.703; p<0.001; Fig. 2). Also, fasting plasma glucose was positively correlated with Gensini score (r=0.256, p<0.001). This correlation was valid after the exclusion of 92 diabetic cases from the study population (r=0.221, p<0.001).

Table 2. Multivariate linear regression analysis to determine independent variables significantly associated with Gensini score

Dependent variable	Independent variables	B	β	t	*P*	VIF
Gensini	Age	0.574	0.192	3.891	<0.001	1.112
	PLR	0.076	0.141	2.873	0.004	1.097
	WBC	3.019	0.265	5.514	<0.001	1.055
	Glucose	0.036	0.064	1.284	0.200	1.127
	Creatinine	8.678	0.097	1.953	0.052	1.123
	HDL	-0.505	-0.133	-2.787	0.006	1.044

HDL - high-density lipoprotein; PLR - platelet-to-lymphocyte ration; WBC - white blood cell count. B - standardized β regression coefficients

Independent associations between Gensini score and independent variables were assessed by multivariate linear regression analysis by including all parameters showing correlation with a p value of less than 0.1 on univariate analysis (patient age, PLR, WBC, HDL, serum creatinine, fasting serum glucose). Pre-procedural PLR was independently associated with Gensini score (β=0.141, p=0.004), together with WBC (β=0.265, p<0.001), HDL (β=-0.133, p=0.006), and age (β=0.192, p<0.001; Table 2).

In addition, the patients with CAD (n=308) were further divided into three tertiles based upon their PLR values (lower than 97.8, higher than 131.7, and those in between). The mean Gensini score of patients in the high PLR tertile was significantly higher than that of the middle and lower tertiles (p=0.002 and p<0.001, respectively), while mean Gensini scores of the middle and lower PLR tertiles were similar (p=0.564; Fig. 3).

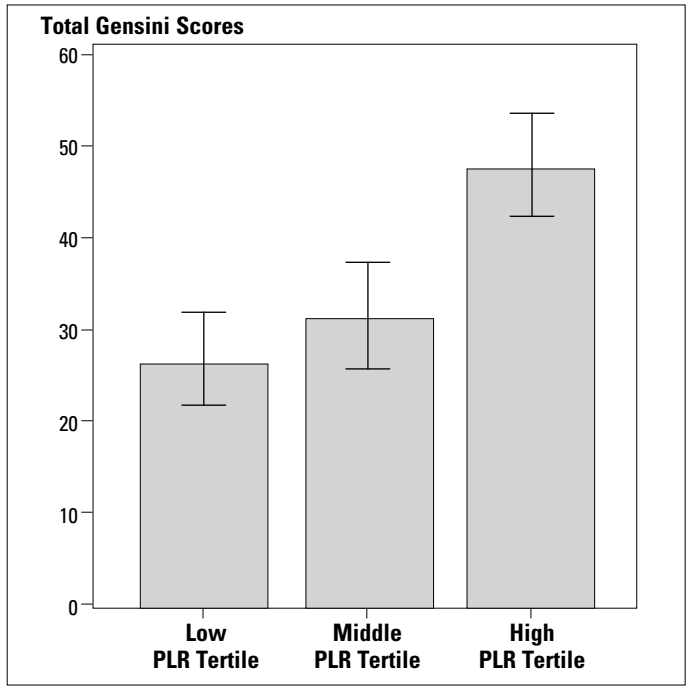

Figure 3. Mean Gensini scores of patients in each PLR tertile
PLR - platelet-to-lymphocyte ration

Discussion

The association between neutrophil-to-lymphocyte ratio, a novel hematological indicator of inflammatory status in the body, and various cardiac disorders has been studied extensively in previous researches (23-30), including the prediction of severe atherosclerosis in patients undergoing coronary angiography (22, 31, 32). Similarly, PLR, a recent hematological parameter indicating the inflammatory and prothrombotic state, has been shown to be associated with poor prognosis in patients with cardiovascular diseases; however, there are limited data about the association between PLR and coronary artery disease severity.

In the present study, we found that high PLR level was independently associated with the severity of coronary atherosclerosis. Patients with high pre-procedural PLR had significantly higher Gensini scores, and there was a positive correlation between PLR values and Gensini scores of patients with CAD. Additionally, this study showed that pre-procedural PLR >111 predicted severe atherosclerosis with a sensitivity of 61% and specificity of 59%. PLR was independently associated with Gensini score, together with age, WBC, and low HDL, in the multivariate analysis. To our best knowledge, this study is the first report investigating the relationship between PLR and severity of atherosclerosis.

The initiation, progression, and propagation of atherosclerosis in the coronary arterial wall are influenced by multiple factors. Inflammation plays a crucial role at all stages of atherosclerosis, from initiation through progression and, finally, in the thrombotic consequences of this disease (1, 22, 32, 33). Lymphocytopenia is a common finding in chronic inflammatory states because of increased lymphocyte apoptosis. Moreover, the leukocyte production in bone marrow makes a shift towards increasing neutrophils and decreasing lymphocytes in response to stress. Lymphocytes represent a more convenient immune response, while neutrophils cause a destructive inflammatory reaction (7). The diagnostic and prognostic usefulness of a low lymphocyte count was demonstrated in patients with acute coronary syndrome and stable CAD, respectively (6, 34). Low lymphocyte count was found to be significantly related with the survival in a population-based analysis of patients with known or suspected stable CAD by Ommen et al. (6), and they suggested that low lymphocyte count is a potential addition to clinical prognostic models in patients with stable CAD and that it may have possible independent prognostic value. The pathophysiologic mechanisms underlying these findings are speculative. However, it is reasonable that the lymphocyte count indicates an early marker of physiologic stress and systemic inflammation. In our study, the PLR values of participants were positively correlated with CRP levels, and they showed a significant positive correlation with neutrophil count, supporting that PLR may indicate an inflammatory state in the body.

Increased proliferation in megakaryocytic series and relative thrombocytosis are two results of the ongoing inflammatory state in the body, which results in a prothrombotic condition. It is reported that healthy adults with increased platelet counts have an augmented risk of thrombotic complications. The circulating platelets may contribute to the initiation of atheromatous plaque formation and trigger its complications (10). High platelet and low lymphocyte counts in the circulation have been suggested to be risk indicators of worse cardiovascular outcomes in previous studies (6-10, 34, 35). A recently developed new prognostic marker, high PLR, integrates the predictive risk of these 2 parameters into 1. The advantage of PLR calculation could be that it reflects the condition of both aggregation and inflammatory pathways, and it may be more valuable than either platelet or lymphocyte count alone in the prediction of coronary atherosclerotic burden. Several new studies suggesting a relationship between PLR and CAD have been published. Azab et al. (15) have shown that higher PLR values are associated with an increase in long-term all-cause mortality in patients admitted with non-ST-segment elevation myocardial infarction (NSTEMI). In a recent study by Acar et al. (36), PLR was found to be independently related with coronary collateral development in patients with chronic total occlusions. In our previous study, we

showed that high pre-procedural PLR value is a significant and independent predictor of no-reflow development in patients undergoing primary coronary angioplasty (16). In the present study, we found that pre-procedural PLR value correlated positively with the amount of coronary atherosclerotic burden in CAD patients. Also, we showed that patients with high pre-procedural PLR value are more likely to exhibit severe atherosclerosis on coronary angiography. We found that PLR is independently associated with Gensini score, with a β coefficient of 0.141 in the multivariate analysis. It means that a 10-unit increase in PLR value is associated with a 1.41-point increase in Gensini score.

Diabetes mellitus (DM), a systemic disease characterized by hyperglycemia, is a well-known major risk factor for CAD. High serum glucose is associated with earlier micro- and macrovascular complications of DM. Furthermore, it has been demonstrated that fasting glucose may also be independently associated with the development and severity of atherosclerosis in non-diabetic patients (37, 38). Patients in all 3 groups of our study had similar DM rates, and fasting plasma glucose was positively correlated with Gensini score. After the exclusion of 92 diabetic cases from the study population, fasting plasma glucose was still correlated significantly with Gensini score. This indicates that the initiation and progression of coronary atherosclerosis accelerate with increases in fasting plasma glucose, even in non-diabetic patients. So, our results are in line with the literature.

HDL works for protection against CAD, and low plasma level of HDL is another important risk factor for the initiation and progression of coronary atherosclerosis. The inverse association between HDL level and coronary artery disease is strong and consistent in population-based studies (39). Thus, in our patient population, it is reasonable to find that plasma HDL level was significantly lower in the severe atherosclerosis group. Our results were compatible with the results of a recent study by Karan et al. (40), in which they showed a positive correlation of fasting glucose and a negative correlation of HDL with the severity of coronary atherosclerosis.

Study limitations

Our study has some limitations, including the limited number of study participants from a single center and the cross-sectional design. The amount of coronary atherosclerosis was evaluated only by coronary angiography; since it displays only the lumen of coronary arteries, it does not provide extensive data about the coronary plaque burden. Therefore, further studies performed with intravascular ultrasound and/or coronary CT may provide more accurate information about the amount of coronary atherosclerosis. Lack of other established inflammatory markers, such as C-reactive protein, interleukin-6, and tumor necrosis factor-α, is another limitation of the study. Another limitation of this study is that it does not give an idea about the cause-and-effect relationship between PLR and coronary atherosclerosis. Although we found significant associations, further large-scale, prospective studies are needed to clarify and confirm the association between PLR and coronary artery disease severity and whether it is a result or cause of severe atherosclerosis. Despite these limitations, to our knowledge, this is one of the first studies evaluating the relationship between PLR on admission and the severity of coronary atherosclerosis assessed by Gensini score.

Conclusion

In conclusion, we suggest that high PLR appears to be additive to conventional risk factors and commonly used biomarkers in predicting severe atherosclerosis, and PLR value correlates positively with Gensini score. When we consider that PLR is a calculation of routine complete blood count parameters that does not require any additional expense and is a readily available marker, it can help to identify individuals at high risk for advanced CAD who might need a more aggressive therapeutic approach and closer clinical follow-up.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - M.Y., A.Y., H.K.; Design - M.Y., H.K., A.A., M.A., N.P.; Supervision - S.A., M.Y., M.Z.B.; Resource - S.A.; Material - M.Z.B., N.P., H.A., M.A.; Data collection and/or processing - A.A., H.A., N.P., M.Z.B., M.Y.; Analysis and/or Interpretation - M.Y., M.O., H.K.; Literature search - M.Y., M.O.; Writing - M.Y.; Critical review - H.K., M.O., A.Y.

References

1. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352: 1685-95. [CrossRef]
2. Han YC, Yang TH, Kim DI, Jin HY, Chung SR, Seo JS, et al. Neutrophil to lymphocyte ratio predicts long-term clinical outcomes in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Korean Circ J 2013; 43: 93-9. [CrossRef]
3. 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: 653-7. [CrossRef]
4. Duffy BK, Gurm HS, Rajagopal V, Gupta R, Ellis SG, Bhatt DL. Usefulness of an elevated neutrophil to lymphocyte ratio in predicting long-term mortality after percutaneous coronary intervention. Am J Cardiol 2006; 97: 993-6. [CrossRef]
5. Acanfora D, Gheorghiade M, Trojano L, Furgi G, Pasini E, Picone C, et al. Relative lymphocyte count: a prognostic indicator of mortality in elderly patients with congestive heart failure. Am Heart J 2001; 142: 167-73. [CrossRef]

6. Ommen SR, Gibbons RJ, Hodge DO, Thomson SP. Usefulness of the lymphocyte concentration as a prognostic marker in coronary artery disease. Am J Cardiol 1997; 79: 812-4. [CrossRef]
7. Zouridakis EG, Garcia-Moll X, Kaski JC. Usefulness of the blood lymphocyte count in predicting recurrent instability and death in patients with unstable angina pectoris. Am J Cardiol 2000; 86: 449-51. [CrossRef]
8. Nikolsky E, Grines CL, Cox DA, Garcia E, Tcheng JE, Sadeghi M, et al. Impact of baseline platelet count in patients undergoing primary percutaneous coronary intervention in acute myocardial infarction (from the CADILLAC trial). Am J Cardiol 2007; 99: 1055-61. [CrossRef]
9. Iijima R, Ndrepepa G, Mehilli J, Bruskina O, Schulz S, Schomig A, et al. Relationship between platelet count and 30-day clinical outcomes after percutaneous coronary interventions. Pooled analysis of four ISAR trials. Thromb Haemost 2007; 98: 852-7.
10. 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. Circulation 1991; 84: 613-7. [CrossRef]
11. Smith RA, Ghaneh P, Sutton R, Raraty M, Campbell F, Neoptolemos JP. Prognosis of resected ampullary adenocarcinoma by preoperative serum CA19-9 levels and platelet-lymphocyte ratio. J Gastrointest Surg 2008; 12: 1422-8. [CrossRef]
12. Smith RA, Bosonnet L, Raraty M, Sutton R, Neoptolemos JP, Campbell F, et al. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg 2009; 197: 466-72. [CrossRef]
13. Proctor MJ, Morrison DS, Talwar D, Balmer SM, Fletcher CD, O'Reilly DS, et al. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. Eur J Cancer 2011; 47: 2633-41. [CrossRef]
14. Gary T, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, et al. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PloS One 2013; 8: e67688. [CrossRef]
15. Azab B, Shah N, Akerman M, McGinn JT Jr. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. J Thromb Thrombolysis 2012; 34: 326-34. [CrossRef]
16. Yıldız A, Yüksel M, Oylumlu M, Polat N, Akyüz A, Acet H, et al. The Utility of the platelet-lymphocyte ratio for predicting no reflow in patients with ST-segment elevation myocardial infarction. Clin Appl Thromb Hemost 2014 Jan 14. Epub ahead of print. [CrossRef]
17. Temiz A, Gazi E, Güngör Ö, Barutçu A, Altun B, Bekler A, et al. Platelet/lymphocyte ratio and risk of in-hospital mortality in patients with ST-elevated myocardial infarction. Med Sci Monit 2014; 20: 660-5. [CrossRef]
18. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18: 499-502.
19. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB 3rd, Loop FD, et al. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). Circulation 1988; 78: 486-502. [CrossRef]
20. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983; 51: 606. [CrossRef]
21. Oishi Y, Wakatsuki T, Nishikado A, Oki T, Ito S. Circulating adhesion molecules and severity of coronary atherosclerosis. Coron Artery Dis 2000; 11: 77-81. [CrossRef]
22. Kaya H, Ertaş F, İslamoğlu Y, Kaya Z, Atılgan ZA, Çil H, et al. Association between neutrophil to lymphocyte ratio and severity of coronary artery disease. Clin Appl Thromb Hemost 2014; 20: 50-4. [CrossRef]
23. Polat N, Yıldız A, Yüksel M, Bilik MZ, Aydın M, Acet H, et al. Association of neutrophil-lymphocyte ratio with the presence and severity of rheumatic mitral valve stenosis. Clin Appl Thromb Hemost 2013 Dec 11. Epub ahead of print.
24. Karavelioğlu Y, Karapınar H, Yüksel M, Memiç K, Sarak T, Kurt R, et al. Neutrophil to lymphocyte ratio is predictor of atrial fibrillation recurrence after cardioversion with amiodarone. Clin Appl Thromb Hemost 2014 Jan 14. Epub ahead of print.
25. Yıldız A, Kaya H, Ertaş F, Oylumlu M, Bilik MZ, Yüksel M, et al. Association between neutrophil to lymphocyte ratio and pulmonary arterial hypertension. Turk Kardiyol Dern Ars 2013; 41: 604-9. [CrossRef]
26. Yıldız A, Oylumlu M, Yüksel M, Aydın M, Polat N, Acet H, et al. The Association between the neutrophil-to-lymphocyte ratio and the presence of ventricular premature contractions in young adults. Clin Appl Thromb Hemost 2013 Nov 6. Epub ahead of print. [CrossRef]
27. Acet H, Ertaş F, Akıl MA, Oylumlu M, Polat N, Yıldız A, et al. New inflammatory predictors for non-valvular atrial fibrillation: echocardiographic epicardial fat thickness and neutrophil to lymphocyte ratio. Int J Cardiovasc Imaging 2014; 30: 81-9. [CrossRef]
28. Arıbaş A, Akıllı H, Gül EE, Kayrak M, Demir K, Duman C, et al. Can neutrophil/lymphocyte ratio predict recurrence of non-valvular atrial fibrillation after cardioversion? Anatol J Cardiol 2013; 13: 123-30.
29. Koza Y, Taş MH, Şimşek Z, Ateş ES. The relationship between neutrophil-to-lymphocyte ratio and coronary artery disease. Anatol J Cardiol 2014; 14: 99-101.
30. Yıldız A, Yüksel M, Oylumlu M, Polat N, Akıl MA, Acet H. The association between the neutrophil/lymphocyte ratio and functional capacity in patients with idiopathic dilated cardiomyopathy. Anatol J Cardiol doi: 10.5152/akd.2014.5131. [CrossRef]
31. Arbel Y, Finkelstein A, Halkin A, Birati EY, Revivo M, Zuzut M, et al. Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography. Atherosclerosis 2012; 225: 456-60. [CrossRef]
32. Sönmez O, Ertaş G, Bacaksız A, Taşal A, Erdoğan E, Asoğlu E, et al. Relation of neutrophil-to-lymphocyte ratio with the presence and complexity of coronary artery disease: an observational study. Anatol J Cardiol 2013; 13: 662-7.
33. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002; 105: 1135-43. [CrossRef]
34. Thomson SP, Gibbons RJ, Smars PA, Suman VJ, Pierre RV, Santrach PJ, et al. Incremental value of the leukocyte differential and the rapid creatine kinase-MB isoenzyme for the early diagnosis of myocardial infarction. Ann Intern Med 1995; 122: 335-41. [CrossRef]
35. Ommen SR, Hodge DO, Rodeheffer RJ, McGregor CG, Thomson SP, Gibbons RJ. Predictive power of the relative lymphocyte concentration in patients with advanced heart failure. Circulation 1998; 97: 19-22. [CrossRef]
36. Acar G, Kalkan ME, Avcı A, Alizade E, Tabakçı MM, Toprak C, et al. The relation of platelet-lymphocyte ratio and coronary collat-

eral circulation in patients with stable angina pectoris and chronic total occlusion. Clin Appl Thromb Hemost 2013 Oct 18. [CrossRef]

37. Nielson C, Lange T, Hadjokas N. Blood glucose and coronary artery disease in nondiabetic patients. Diabetes Care 2006; 29: 998-1001. [CrossRef]
38. Yan Q, Gu WQ, Hong J, Zhang YF, Su YX, Gui MH, et al. Coronary angiographic studies of impaired glucose regulation and coronary artery disease in Chinese nondiabetic subjects. Endocrine 2009; 36: 457-63. [CrossRef]
39. Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013 Nov 7.
40. Karan A, Güray Y, Güray U, Demirkan B, Astan R, Baysal E, et al. Mean platelet volume and the extent of coronary atherosclerosis in patients with stable coronary artery disease. Turk Kardiyol Dern Ars 2013; 41: 45-50. [CrossRef]