Relationship between platelet-to-lymphocyte ratio and the presence and severity of coronary artery ectasia

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ABSTRACT

Objective: The aim of this study was to investigate the relationship between platelet-to-lymphocyte ratio (PLR), an easily available inflammatory marker, and coronary artery ectasia (CAE).

Methods: After applying the exclusion criteria, the retrospective study population consisted of 330 patients, including 110 patients with isolated CAE, 110 with obstructive coronary artery disease (CAD), and 110 with normal coronary artery angiograms (NCA). The severity of isolated CAE was determined according to the Markis classification. SPSS 22.0 statistical package program was used for data analysis.

Results: PLR was significantly higher in patients with isolated CAE than in those with NCA and obstructive CAD [123 (113–156), 100 (86–138), and 110 (102–141), respectively]. Logistic regression analysis showed that PLR and C-reactive protein level were significantly correlated with the severity of isolated CAE.

Conclusion: To the best of our knowledge, this study showed for the first time that PLR was significantly associated with CAE.

Keywords: coronary artery ectasia, inflammation, platelet-to-lymphocyte ratio

Introduction

Coronary artery ectasia (CAE) is characterized by dilation of the coronary arteries, particularly a localized or diffuse dilation with a luminal dilation over the normal adjacent segment or a vessel diameter 1.5-fold wider than the normal vessel (1). The prevalence of CAE has been reported as 0.3%–5% among patients who undergo coronary angiography (2). The isolated form of CAE, which has been defined as CAE without important coronary artery stenosis, constitutes a small portion of the total of CAE cases with a rate of 0.1%–0.8% (1, 3, 4). Abnormally dilated coronary arteries may cause angina pectoris and myocardial infarction due to vasospasm, as well as dissection or thrombus in patients without coronary artery disease (CAD) (5). Therefore, determining the factors associated with the presence and severity of CAE may be beneficial for management of those patients. Previous studies have shown that inflammation and atherosclerosis have major roles in development of CAE, although the underlying reasons for the ectasia formation have not still been fully understood (6). As CAE is associated with inflammation, and it frequently accompanies CAD, it has been supposed that CAE may be a variant of CAD. Based on the findings of previous studies, it has been suggested that a more severe inflammation could be involved in the pathogenesis of CAE (7).

Platelet-to-lymphocyte ratio (PLR) is a new prognostic and diagnostic marker in CAD (8). Increased PLR has been demonstrated to be associated with adverse outcomes in patients with acute coronary syndrome (9, 10). A high PLR was correlated with in-hospital mortality in patients with ST-elevated myocardial infarction (STEMI) (11), saphenous vein graft disease (12), severity of pulmonary embolism and CAD (13–15), and no reflow in patients with STEMI (16). To the best of our knowledge, no studies to date investigated PLR in patients with isolated CAE and compared the results with obstructive CAD and normal coronary artery angiograms (NCA).

The aim of this study was to investigate an easily available and relatively inexpensive inflammatory marker, PLR, in patients with CAE and compare the results with obstructive CAD and NCA.

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Methods

Study design
A total of 330 patients were included in this study after the study protocol was approved by local Ethics Committee of our hospital. We retrospectively analyzed the electronic patient data recording system of our hospital for the patients between January 2011 and June 2015. A total of 330 patients were included in the study, including 110 patients with isolated CAE, 110 with obstructive CAD without CAE, and 110 with NCA.

Inclusion and exclusion criteria
Based on clinical indications such as abnormal stress test results, dobutamine stress echo, positive treadmill tests, and myocardial perfusion scintigraphy or typical chest pain, a coronary angiography was performed to investigate ischemic heart disease. All of the patients were clinically stable. Patients with an acute coronary syndrome defined as STEMI or non-STEMI were excluded from the study. We also excluded patients with left ventricular systolic dysfunction [left ventricular ejection fraction (LVEF) <40%]; malignancy; and liver, kidney, or other acute or chronic inflammatory diseases, as well as patients who had undergone percutaneous coronary intervention and coronary artery bypass grafting before.

Data collection
The standard Judkins technique and 6-Fr catheters (Expo; Boston Scientific Corporation, Natick, Massachusetts, USA) were used to perform baseline angiography via the femoral artery, and Siemens Axiom Sensis XP (Munich, Germany) device was used. The vessel diameter was calculated quantitatively in case of conflicts about CAE. CAE was defined based on the criteria used in the Coronary Artery Surgery Study (17). According to the angiographic definition used in that study, segmental ectasia was considered when the diameter of the ectatic segment was ≥1.5 times that of the adjacent normal segment. When an identifiable normal adjacent segment could not be found, the mean diameter of the corresponding coronary segment in the control group was used as the normal value (1). CAE without coronary artery stenosis was considered as isolated CAE, and the severity of isolated CAE was determined according to the Markis classification (3).

Arterial hypertension was considered in patients with repeated blood pressure measurements >140/90 mm Hg or current use of antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glucose levels ≥126 mg/dl on multiple measurements, or current use of anti-diabetic medications. Hyperlipidemia was considered as a total serum cholesterol level >200 mg/dL or the use of a lipid-lowering medication. Family history of CAD was considered in case of 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.

Peripheral venous blood samples of the patients were obtained on their admission to the inpatient ward. An automated blood cell counter (Beckman Coulter analyzer, California, USA) was used for measuring complete blood count parameters. The levels of the following blood biochemistry parameters were measured: creatinine, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total bilirubin. C-reactive protein (CRP) measurement was done before the coronary angiography with nephelometric method, using an automatized analyzer (Beckman Coulter analyzer). PLR was calculated as the ratio of platelet to lymphocyte count, obtained from the same blood sample.

Transthoracic echocardiography was performed in all patients, and LVEF was calculated using Simpson’s method.

Table 1. Clinical and angiographic characteristics of the study population

| Variables | CAE  (n=110) | Obstructive CAD (n=110) | NCAs (n=110) | P |
|-----------|--------------|-------------------------|--------------|---|
| Male, n (%) | 56 (50.9) | 65 (59.1) | 47 (42.7) | 0.007* |
| Age, years, mean±SD | 62±12 | 64±13 | 58±11 | 0.001* |
| DM, n (%) | 27 (24.5) | 35 (31.8) | 19 (17.2) | <0.001* |
| Current smoker, n (%) | 26 (23.6) | 28 (25.4) | 25 (22.7) | 0.256 |
| Hypertension, n (%) | 58 (52.7) | 67 (60.9) | 50 (45.4) | 0.005* |
| Hypercholesterolemia, n (%) | 48 (43.6) | 51 (46.3) | 45 (40.9) | 0.155 |
| Family history of CAD, n (%) | 16 (14.5) | 18 (16.3) | 15 (13.6) | 0.455 |
| LVEF, %, mean±SD | 60±11 | 59±10 | 60±10 | 0.768 |
| Prior medication | | | | |
| Beta-blocker, n (%) | 41 (37.2) | 38 (34.5) | 43 (39.1) | 0.373 |
| ACE inhibitor or ARB, n (%) | 52 (47.2) | 55 (50.0) | 45 (40.1) | 0.115 |
| Statin, n (%) | 32 (29.1) | 36 (32.7) | 30 (27.2) | 0.245 |
| Markis classification | Distribution of ectasia | | | |
| Type 1, n (%) | 34 (30.9) | Left anterior descending artery, n (%) | 75 (68.1) |
| Type 2, n (%) | 19 (17.2) | Left circumflex artery, n (%) | 42 (38.1) |
| Type 3, n (%) | 15 (13.6) | Right coronary artery, n (%) | 82 (74.5) |
| Type 4, n (%) | 42 (38.1) | | | |

ACE - angiotensin-converting enzyme; ARB - angiotensin-receptor blocker; CAD - coronary artery disease; CAE - coronary artery ectasia; DM - diabetes mellitus; IQR - interquartile range; LVEF - left ventricular ejection fraction; NCAs - normal coronary arteries; SD - standard deviation; *=statistically significant. Group means for continuous variables were compared with the Student’s t-test, Mann–Whitney U test with/without Bonferroni correction, ANOVA, or Kruskal–Wallis test, where appropriate.
Statistical analysis

SPSS 22.0 statistical package program (SPSS Inc., Chicago, IL, USA) was used to analyze data. Kolmogorov–Smirnov test was used to analyze the distribution pattern of the variables. Normally distributed numerical variables were presented as mean±standard deviation, and non-normally distributed variables as median and interquartile range. Categorical variables were presented as the number (percentage). Group means of the continuous variables were compared with Student’s t-test, Mann–Whitney U test with/without Bonferroni correction, ANOVA, or Kruskal–Wallis test, where appropriate.

Results

A total of 330 patients were included in the study. Their clinical and angiographic characteristics as well as biochemical and hematological measurements are presented in Tables 1 and 2, respectively. There were no differences among the three groups for LVEF; number of current smokers; family history of CAD; hypercholesterolemia; and values of hemoglobin, total bilirubin, total cholesterol, creatinine, and LDL and HDL cholesterol. Compared to the NCA group, in isolated CAE and obstructive CAD

Table 2. Biochemical and hematological measurements of the study population

| Variables                  | Isolated CAE (n=110) | Obstructive CAD (n=110) | NCAs (n=110) | P       |
|----------------------------|----------------------|-------------------------|--------------|---------|
| Hemoglobin, g/dL, median (IQR) | 14.3 (12.7–15.8)      | 13.9 (12.1–16)          | 14.4 (13.1–15.7) | 0.184   |
| WBC, 10^3/μL, mean±SD     | 8.4±3.9              | 8.3±3.4                 | 7.2±3.7      | 0.062*  |
| Neutrophil, 10^3/μL, mean±SD | 6.5±3.8             | 6.2±4.4                 | 5.2±3.4      | 0.008** |
| Lymphocyte, 10^3/μL, mean±SD | 2.0±1.1             | 1.7±1.2                 | 2.2±1.1      | 0.035*  |
| Platelet, 10^3/μL, mean±SD | 254±65               | 245±63                  | 233±59       | 0.001*  |
| Total cholesterol, mg/dL, mean±SD | 180±59              | 179±58                  | 180±57       | 0.031   |
| LDL, mg/dL, mean±SD       | 116±37               | 118±36                  | 114±39       | 0.560   |
| HDL, mg/dL, mean±SD       | 39±13                | 41±12                   | 40±12        | 0.174   |
| Creatinine, mg/dL, mean±SD | 1.1±0.4             | 1.0±0.3                 | 1.1±0.4      | 0.655   |
| Total bilirubin, mg/dL, mean±SD | 0.56±0.3            | 0.56±0.3                | 0.57±0.3     | 0.873   |
| C-reactive protein, mg/dL, median (IQR) | 7 (2–12)            | 5 (2–7)                 | 3 (1–5)      |         |
| PLR, median (IQR)         | 123 (113–156)        | 110 (102–141)           | 100 (86–138) | <0.001* |

CAD - coronary artery disease; CAE - coronary artery ectasia; HDL - high-density lipoprotein; IQR - interquartile range; LDL - low-density lipoprotein; NCAs - normal coronary arteries; PLR - platelet-to-lymphocyte ratio; SD - standard deviation; TG - triglyceride; WBC - white blood cell; *=statistically significant

Group means for continuous variables were compared with the Student’s t-test, Mann–Whitney U test with/without Bonferroni correction, ANOVA, or Kruskal–Wallis test, where appropriate.

Table 3. Multiple logistic regression analysis showing independent predictors of isolated coronary artery ectasia

| Variables          | β  | 95% Confidence interval |
|--------------------|----|-------------------------|
| Age                | 0.290 | 1.010 | 0.990 | 1.030 |
| Male               | 0.132 | 1.056 | 0.976 | 1.136 |
| Diabetes mellitus  | 0.075 | 1.055 | 0.995 | 1.103 |
| WBC                | 0.065 | 1.015 | 0.990 | 1.040 |
| PLR                | <0.001* | 1.005 | 1.002 | 1.010 |
| C-Reactive protein | 0.001* | 1.009 | 1.003 | 1.015 |
| Neutrophil         | 0.088 | 1.025 | 0.974 | 1.075 |
| Hypertension       | 0.197 | 1.065 | 0.970 | 1.160 |

PLR - platelet-to-lymphocyte ratio; WBC - white blood cell; *=statistically significant

Figure 1. PLR values of the study groups
groups, the patients were significantly older; there was male predominance; the rates of hypertension and diabetes mellitus were higher; and the white blood cell, platelet, and neutrophil counts were greater. On the other hand, patients with isolated CAE and obstructive CAD had significantly lower lymphocyte counts than those with NCA. As shown in Figure 1, patients with isolated CAE had significantly higher PLR values compared to the other groups. In univariate logistic regression analysis, age, male gender, hypertension, diabetes mellitus, white blood cell and neutrophil counts, and PLR were significantly associated with isolated CAE. When those seven parameters were included in a multivariate logistic regression analysis, it was found that PLR and CRP were independently and significantly associated with isolated CAE (Table 3). In addition, there was a positive correlation between CRP levels and PLR (p<0.001, Fig. 2). We also demonstrated that PLR was significantly correlated with the severity of CAE (Fig. 3).

Finally, ROC analysis was performed in isolated CAE, obstructive CAD, and NCA groups to detect the cut-off value of PLR for predicting isolated CAE. The cut-off value of PLR on admission to predict an isolated CAE in all study population was 96, with a sensitivity of 69% and 68%, and a specificity of 65% and 66%, respectively (Area under curve=0.675 and 0.700, p<0.001, p<0.001 respectively; Fig. 4 a, b).

**Discussion**

In this study, we demonstrated that PLR, a relatively inexpensive and easily available test, could give relevant information for the presence of isolated CAE. We found that patients with isolated CAE had significantly higher PLR values than those with obstructive CAD and the control subjects with NCA. In previous studies, it was demonstrated that patients with isolated CAE had an increased risk of mortality, equal to that of patients with obstructive CAD (5).

Although a definitive link between atherosclerosis and ectasia has not been confirmed, it has been suggested that CAE is a variant of CAD (18). The tunica media the vascular wall, which includes the smooth muscle, has extracellular matrix proteins, elastin, and collagen. The molecules that are located in the tunica media can protect the vascular wall from stress and maintain integrity of vascular wall (19). Markis et al. (3) suggested that de-
struction of the tunica media is the cause of ectasia. Infiltration of this layer by inflammatory cells is another finding that can be seen in ectatic segments (18).

Several studies investigated the association between CAE and inflammation. Patients with isolated CAE have higher levels of adhesion molecules such as ICAM-1, VCAM-1, and E-selectin (20). High-sensitivity CRP (7), matrix metalloproteinase (MMP)-3, and interleukin-6 (21) levels were demonstrated in patients with isolated CAE when compared to patients with obstructive CAD. Kocaman et al. (22) also showed that the patients with isolated CAE had significantly higher leukocyte, monocyte, and neutrophil levels than did patients with non-obstructive CAD and NCA. Finally, Doğan et al. (23) reported that MMP-9 was significantly higher in the isolated CAE group than in obstructive CAD and NCA groups. Previous studies also showed that the presence of CAE was associated with cardiovascular mortality (24).

A number of inflammatory disorders, including various cardiovascular diseases, were shown to be closely associated with PLR. PLR may be used as an inflammatory marker in clinical practice. Balta et al. (25) and Kurtul et al. (14) showed that PLR was closely correlated with the severity of atherosclerosis. Azab et al. (9) reported that long-term mortality increased as PLR increased in patients with non-STEMI. Yılmaz et al. (26) reported that high pre-procedural PLR was a powerful and independent predictor of bare metal stent restenosis. Similarly, we demonstrated that high PLR was significantly associated with the severity of pulmonary embolism and saphenous vein graft disease (12, 13).

In fact, PLR gives information about both aggregation and inflammatory pathways. PLR can be superior to the platelet or lymphocyte counts alone for prediction of isolated CAE, since both inflammation and endothelial damage play a role in the pathogenesis of the disease.

Based on those findings and the pathophysiological role of inflammation in isolated CAE, we hypothesized that PLR could be associated with isolated CAE. Our findings suggested that a PLR of >96 was significantly correlated with isolated CAE. We also found that PLR was associated with the severity of isolated CAE.

Besides its close relation with the severity of isolated CAE, PLR also had a positive correlation with serum CRP level in our study, which supported its role in systemic inflammation. From a clinical point of view, PLR may be used as a predictor of isolated CAE as a new inflammatory marker in daily clinical practice.

Study limitations

Our study has some limitations. First, it is a retrospective study; therefore, we could not analyze the follow-up data adequately. Second, inflammatory markers other than CRP such as IL-6, TNF-α, and MMP were not analyzed and therefore not compared with PLR. A further limitation is evaluation of coronary angiography visually and calculating the vessel diameter quantitatively with quantitative coronary angiography in case of any conflict for CAE. We did not employ intravascular ultrasound or optical coherence tomography, and this is another limitation. The final limitation is the relatively small number of patients included in the study. Further studies on a larger patient population are needed to detect a causal relationship between PLR and CAE.

Conclusion

In conclusion, to the best of our knowledge, this is the first study showing that PLR is significantly associated with CAE. The present study demonstrates that PLR is significantly higher in patients with isolated CAE when compared to obstructive CAD and controls with NCA, and PLR is significantly correlated with the severity of CAE.

Conflict of interest: None declared.

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