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New hematological biomarkers in patients with atrial septal aneurysm

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Abstract

Mean platelet volume/platelet count (MPV/PC) and monocyte/lymphocyte (MLR), neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) ratios are new hematological markers showing systemic platelet activation and inflammation. The aim of this study was to compare new hematological markers in patients with atrial septal aneurysm (ASA) and to determine their relationship in patients with ASA. 70 ASA and 47 healthy subjects (as control group) were included in the study. Demographic, clinical, echocardiographic and hematological values of the groups were recorded. MPV/PC ratio and MLR were significantly higher in ASA group compared to control group (0.03 ± 0.013 vs 0.02 ± 0.009, P=0.02 and 0.27 ± 0.15 vs 0.22 ± 0.08, P=0.03). NLR and PLR were not different between the groups. The presence of ASA was positively correlated with MLR and MPV/PC, left atrium, left ventricular (LV) septum thickness and LV posterior wall thickness, while red blood cell (RBC) was negatively correlated. However, in multivariate linear regression analysis, there was an independent relation between the presence of ASA and MPV/PC, MLR, LV septum thickness and RBC. We found that MPV/PC ratio and MLR from new hematological biomarkers are independent predictors for the presence of ASA.

Keywords: Atrial septal aneurysm, inflammation, platelet

Introduction

Atrial septal aneurysm (ASA) is generally seen at the level of fossa ovalis and defined as the possible cambering of atrial septum towards the right & left atrium or both of them. It can be seen alone but also often can be seen together with other heart diseases such as patent foramen ovale, atrial septal defect and mitral valve prolapse. ASA prevalence in adult population was found to be 2.4% in studies performed with transthoracic echocardiography [1]. Previous studies have reported that ASA can cause atrial-induced arrhythmia and cryptogenic stroke [2-5].

Neutrophil/lymphocyte (NLR), platelet/lymphocyte (PLR), mean platelet volume/platelet count (MPV/PC) and monocyte/lymphocyte (MLR), ratios are new hematological markers showing systemic plaletlet activation and inflammation. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were also reported to be associated with inflammation and increased cardiovascular risk [6,7]. It was reported that the MLR is related to adverse clinical results in various cardiovascular diseases (i.e. heart failure, ST-segment elevation myocardial infarction) [8,9]. Increased MPV/PC ratio has been reported to be a better predictor for cardiovascular events [10]. Moreover, MPV and MPV/PC ratio are considered to be significant laboratory markers for the risk of acute ischemic stroke [11].

The aim of this study is to compare these NLR, PLR, MLR, MPV/PC ratio new hematological biomarkers in ASA and control cases and to determine their relationship with ASA.

Material and Methods

Selection of patients

70 study patients with ASA diagnosis (57 female, 13 male; mean age 44.5±16.4) and 47 individuals [control group] having normal echocardiographic parameters and with no any known disease (37 female, 10 male; mean age 40.0±10.1) were included in the study. Demographic and basic clinical properties and physical examination and blood-biochemistry parameters of both two groups were registered. Patients in sinus rhythm were taken to the study. Biochemical parameters (fasting blood sugar, lipid levels, complete blood count and kidney function tests) were examined in all patients.

Hypertension was defined as ≥140 mm Hg systolic and ≥90 mm Hg diastolic blood pressure or antihypertensive use. Diabetes mellitus

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diagnosis was determined as fasting blood glucose level ≥126 mg/dl or glucose level above 200 mg/dl in any measurement or active use and the available oral antidiabetic medicine or insulin use. If ejection fraction (EF) was <50%, it was accepted as left ventricular (LV) systolic dysfunction.

Exclusion criteria from the study were determined as coronary artery disease history, LV systolic dysfunction, hypertension, diabetes mellitus, hypertrophic cardiomyopathy, right or LV hypertrophy, serious valvular heart disease, chronic obstructive pulmonary disease, renal and hepatic failure, cancer, cerebrovascular disease, septicemia, thyroid dysfunction, hematologic diseases, acute or chronic infection or inflammatory state and antibiotic use.

Adhering to the working principles of the Helsinki Declaration, the study protocol was approved by the Sakarya University Ethics Committee.

Collection of laboratory parameters and blood samples

After 12 hours fasting, the forearm was squeezed to form a tiny venous stasis and peripheric venous bloods were taken from antecubital vessel. The blood samples were studied within 1 hour in the laboratory. The blood samples were taken into standard tubes including dipotassium ethylen dinitro tetraacetic acid (EDTA) complete blood count (CBC). By means of Abbott Cell-Dyn 3700 device, the complete blood cell numbers (hemoglobin, hematocrits, thrombocytes, neutrophils, lymphocytes, eosinophils and monocytes, basophils) were analysed. MPV/PC ratio, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and monocyte/ lymphocyte ratio (MLR) were calculated using data.

Echocardiographic Measurements

Transthoracic echocardiographic examination was made after at least 15-minute rest, at lateral position (2-dimensional, M-mode, coloured parasternal Doppler echocardiography), by using Philips (Philips Medical Systems, Amsterdam, Holland) and X5 probe, from parasternal and apical windows. Each participant was made transthoracic echocardiography by conforming to standard displays and techniques taking place in the guideline of American Society of Echocardiography [12]. The ejection fraction (EF) was calculated according to modified Simpson's rule. ASA was defined as the replacement of interatrial septum >10 mm from atrial septal plane towards left or right atrium and its base width being ≥15 mm [2].

Statistical Analysis

The analysis was evaluated using SPSS program (SPSS version 23; Armonk, NY, USA: IBM Corp). With the Kolmogorov Smirnov test, the normality analysis was made. By the aim of comparing the two groups showing normal distribution for numeric variables, Student's t test was used. The variables, in which it was determined that pre-conditions of parametric tests didn't come true, were assessed by nonparametric statistical analysis methods. Mann-Whitney U test was used in order to compare the two groups in terms of these variables. The results were expressed as ± mean standard deviation and mean value. Fisher Exact test was used in the analysis of categorical variables. Categorical variables were expressed as absolute value and %. $P<0.05$ level was accepted statistically meaningful. The relation between the two continuous variables was measured by Pearson or Spearman correlation. Independent factors related to the presence of ASA were investigated in multivariate linear regression analysis.

Results

Demographic and basic clinical properties were detected as similar among the two groups. Clinical baseline characteristics of the two groups were shown in the Table 1. When groups were compared according to echocardiographic parameters, left ventricular ejection fraction (LVEF), left ventricular LV diastolic diameter, right atrium diameter and systolic pulmonary artery pressure were similar in two groups. However, left atrium, left ventricular LV septum thickness and left ventricular LV posterior wall thickness were detected higher in the group with ASA (Table 1).

Table 1. Clinical and echocardiographic findings of two groups

	ASA group (n = 70)	Control group (n = 47)	P value
Age (years)	44.5 ± 16.4	40.0 ± 10.1	0.09
Female, n (%)	57 (81.4%)	37 (78.7%)	0.81
Cigarette (+), n (%)	15 (21.4%)	7 (14.8%)	0.47
Systolic BP, (mmHg)	111.2 ± 14.6	110.2 ± 13.5	0.70
Diastolic BP, (mmHg)	68.5 ± 9.8	67.7 ± 12.9	0.70
Heart rate, (pulse/min)	71.8 ± 14.1	71.5 ± 14.2	0.92
LVEF, (%)	61.7 ± 2.7	61.9 ± 2.8	0.61
LVEDD, (cm)	4.3 ± 0.4	4.2 ± 0.3	0.13
LA, (cm)	3.3 ± 0.4	3.1 ± 0.4	0.02
IVS, (cm)	1.0 ± 0.2	0.9 ± 0.1	<0.001
LVPW, (cm)	1.0 ± 0.2	0.9 ± 0.1	0.001
RA, (cm)	3.2 ± 0.5	3.1 ± 0.4	0.58
SPAP, (mmHg)	26.6 ± 2.3	25.3 ± 2.6	0.20

BP: blood pressure, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic diameter, LA: left atrial diameter, IVS: interventricular septum thickness, LVPW: left ventricular posterior wall thickness, RA: right atrium, SPAP: systolic pulmonary arterial pressure

In the Table 2 the comparison of hematological parameters of both two groups were shown. Hemoglobin, white blood cell, neutrophil count, monocyte count and MPV and platelet distribution width (PDW) were similar in both two groups. Red blood cell (RBC), lymphocyte and thrombocyte count were lower meaningfully in the group with ASA. NLR and PLR were not different between the groups. However, MPV/PC ratio and MLR were significantly higher in patients with ASA compared to control group (Table 2).

In the Pearson correlation analysis, the presence of ASA was positively correlated with MLR and MPV/PC, left atrium, left ventricular LV septum thickness and LV posterior wall thickness, while RBC was negatively correlated ($r = 0.226$, $p=0.01$; $r = 0.214$, $p=0.02$; $r = 0.199$, $p=0.03$; $r = 0.385$, $p<0.001$; $r = 0.341$, $p<0.001$ and r:-0.224, $p=0.01$) respectively). However, in multivariable linear regression analysis, there was an independent relation between the presence of ASA and MPV/PC ratio, MLR, LV septum thickness and RBC (Table 3).

Table 2. Laboratory values of two groups

	ASA group (n = 70)	Control group (n = 47)	P value
Glucose, (mg/dL)	90.4 ± 13.6	98.7 ± 14.3	0.40
Creatinine, (mg/dL)	0.7 ± 0.1	0.6±0.1	0.44
Total cholesterol, (mg/dL)	230.8 ± 51.9	199.4 ± 20.8	0.24
LDL, (mg/dL)	133.7 ± 34.5	112.6 ± 10.4	0.23
TG, (mg/dL)	101.8 ± 21.2	101.6 ± 54.7	0.99
Hb, (g/dL)	13.2 ± 1.1	13.6 ± 1.2	0.08
RBC, (106/L)	4.4 ± 0.5	4.6 ± 0.4	0.02
Leukocyte, (10^3/L)	7.3 ± 2.2	7.7 ± 2.2	0.20
PC, (10^3/L)	249.4 ± 52.5	279.3 ± 61.2	0.006
MPV, (f/L)	8.2 ± 1.5	7.8 ± 1.3	0.15
RDW, (%)	15.2 ± 1.5	15.3 ± 2.0	0.81
Lymphocyte, (10^3/L)	2.1 ± 0.5	2.5 ± 0.8	0.001
Monocyte, (10^3/L)	0.6 ± 0.3	0.5 ± 0.1	0.30
Neutrophil, (10^3/L)	4.3 ± 1.8	4.4 ± 1.6	0.54
MLR	0.27 ± 0.15	0.22 ± 0.08	0.03
NLR	2.29 ± 1.93	1.85±0.88	0.14
PLR	126.6 ± 64.2	114.9 ± 41.5	0.27
MPV/PC	0.03 ± 0.01	0.02 ± 0.001	0.02

LDL: Low density lipoprotein cholesterol, HDL: High density lipoprotein cholesterol, TG: triglyceride, Hb: hemoglobin, RBC: red blood cell, PC: platelet count, MPV: mean platelet volume, RDW: red cell distribution width, MLR: monocyte/lymphocyte ratio, NLR: neutrophil lymphocyte ratio, PLR: platelet count/lymphocyte ratio, MPV/PC: mean platelet volume/platelet count

Table 3. Results of the multivariate linear regression analysis for factors affecting the presence of ASA

	ßeta±SE	Confidence interval (%)	P value
MPV/PC ratio	0.19 ± 3.3	1.17-14.64	0.02
MLR	0.16 ± 0.3	0.006-1.23	0.04
IVS	0.37 ± 0.24	0.61-1.59	<0.001
RBC	-0.22 ± 0.08	-0.83-1.09	0.009

IVS: interventricular septum thickness, RBC: red blood cell, MPV: mean platelet volume, PC: platelet count, MLR: monocyte/lymphocyte ratio

Discussion

In our study, it was found that there was a significant relation between ASA, MPV / PC ratio and MLR compared to the controls. Besides, in multivariate linear regression analysis, only the thickness of the interventricular septum was found to be associated with the presence of ASA among echocardiographic parameters. As far as we know, our study is the first to discuss the relationship between ASA and MPV/PC ratio and MLR.

It has been reported in previous studies that ASA causes arrhythmia. Hanley et al. In their study, they reported that atrial arrhythmia was present in 20 (25%) of 80 ASA cases [3]. Although its exact mechanism is not known, it is argued that the excessive movement

in the atrial septum and the fluctuating motion of the aneurysmal structure induce arrhythmias [13]. In studies on ASA patients, atrial fibrillation (AF) was frequently detected [14]. The role of systemic inflammation has been demonstrated in the pathophysiology of AF, and systemic inflammation plays an important role in the development and recurrence of AF [15-16] and high NLR has been shown to be associated with the risk of formation and relapse [16]. MLR was shown to be associated with various heart diseases such as heart failure and coronary artery disease [8,9]. However, no data on MLR and AF were detected in the literature. In our study, no difference was found between the groups in terms of NLR, whereas the group with ASA had higher MLR, and an independent relationship was found between the presence of ASA and MLR. In ASA patients, atrial and ventricular fibrosis was detected, and in the studies it was determined that the inflammatory state caused fibrosis in myocard [17]. It was detected that in animal studies the monocytes played an important role in this fibrosis process [18,19]. In these patients, increased inflammatory state may be facilitating the development of arrhythmia like AF. In other studies, it was stated that NLR can be used as an AF determiner [20]. However, in our study, NLR was similar among the groups, so MLR may be more valuable in determining the risk of arrhythmia in these patients.

Another important complication of ASA is its ability to cause arterial embolism. It is reported that ASA causes arterial embolism with various pathophysiologic mechanisms. For example; left atrium may cause left atrium thrombus formation by causing an increase in the stability of blood flow [4-5] or thrombus formed within the aneurysm may directly cause embolization [2] or as a result of atrial arrhythmias [21]. Increased MPV is a useful biochemical indicator of platelet activity in cardiovascular diseases and stroke [22]. Moreover, MPV as a biomarker also predicts the risk of ischemic stroke. The MPV/PC ratio is a new marker and increased MPV/PC ratio is reported to be a better predictor for cardiovascular events than MPV [23]. In our study, MPV/PC ratio was significantly higher in the ASA group compared to the control group, and in the linear regression analysis, an independent relationship was detected between MPV/PC ratio and ASA. High MPV/PC ratio; suggests whether the PC is related to low detection, but it is stated that a low PC can be caused by the most common drug-related immune response or bleeding [24] and in our patient group, patients with chronic disease or drug use for any reason were excluded from the study. Therefore, the mechanism of PC abortion is not fully understood.

In our study, left atrium, LV septum thickness and LV posterior wall thickness were detected higher in the group with ASA. However, in logistic regression analysis, only the thickness of the interventricular septum was found to be associated with the presence of ASA among echocardiographic parameters. Previous studies have shown that increased left ventricular LV wall thickness is a factor that increases the risk of arrhythmia and stroke [25]. We think that this increase in left ventricular LV wall thickness may be another factor increasing the development of complications such as arrhythmia and stroke in patients with ASA. The mechanism of negative relationship between RBC and ASA in the regression analysis was not fully understood.

The most important restriction of this study is retrospective design and the limited number of patients. Moreover, other inflammatory markers such as C-reactive protein, interleukin-6 and tumor necrosis factor-alpha were not evaluated and any comparison between them was not performed; our study doesn't include AF and patients who have had a thromboembolic event or atrial thrombus detected and these patients couldn't be monitored for arrhythmia. In addition, stroke patients are not known because patients are not followed up.

Conclusion

In conclusion, we think that MLR and MPV/PC may be associated with increased thromboembolic status in ASA cases, and we think that this idea should be investigated by prospective studies involving much higher numbered and thromboembolic events.

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Conflict of interests
The authors declare that they have no competing interests.

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Ethical approval
This study was approved by University Education and Research Hospital Ethics Committee with decision number 27/3/2019 16214662/050.01.04/48.

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