Association between New Platelet Indices and Calcific Aortic Stenosis: Plateletcrit and Platelet to Lymphocyte Ratio

Yeni Platelet Belirteçleri ve Kalsifik Aort Darlığı Arasındaki İlişki: Plateletkrit ve Platelet Lenfosit Oranı

Hüseyin Altuğ Çakmak[1,*], Asım Enhoş[1], Mehmet Ertürk[2], Ali Kemal Kalkan[2], Muhammet Hulusi Satılmışoğlu[2], Mehmet Gül[2]

[1]*Mustafa Kemalpasa State Hospital, Department of Cardiology, Bursa, Turkey*
[2]*Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Department of Cardiology, Istanbul, Turkey*

ABSTRACT

Objective: Calcific aortic stenosis (AS) is the leading cause of death from valvular heart disease in worldwide. We aimed to evaluate the relationship between plateletcrit (PCT), platelet to lymphocyte ratio (PLR) and presence and severity of the calcific AS in the present study.

Materials and Methods: A total of 98 consecutive patients diagnosed with calcific AS and 30 healthy controls were included in this retrospective study. Patients with calcific AS were divided into three groups according to severity of disease as follows: mild AS (n=35), moderate AS (n=30) and severe AS (n=33).

Results: PCT and PLR were demonstrated to be significantly higher in the AS. Moreover, PCT and PLR were significantly highest in the severe AS group than in the mild and moderate AS groups. Correlation analysis indicated positive significant relationships between the PCT and maximal and mean transaortic gradients, and maximum jet velocities; but negative association with AVA. The same relations were obtained between PLR and echocardiographic parameters of severity of AS.

Conclusion: PCT and PLR, which reflect elevated inflammatory status and platelet activation and aggregation, are useful, cheap, easily available and simply calculated markers that have an ability to improve risk stratification of patients with calcific AS for treatment strategies.

Key Words: Plateletcrit, platelet to lymhocyte ratio, calcific aortic stenosis, echocardiography

ÖZET

Amaç: Kalsifik aort darlığı (AD) dünyada kalp kapak hastalıklarından ölümlerin önde gelen nedenidir. Biz bu çalışmada plateletkrit (PKT) ve platelet lenfosit oranı (PLO) ile kalsifik AD'nın varlığı ve şiddeti ile olan ilişkisini incelemeyi amaçladık.

Gereç ve Yöntem: Bu retrospektif çalışmaya sırasıyla 98 kalsifik AD tanısı olan hasta ile 30 sağlıklı kontrol dahil edildi. Kalsifik AD hastaları hastalığın şiddetine göre 3 gruba şu şekilde ayrıldı: hafif AD (n=35), orta AD (n=30) ve ileri AD (n=33).

Bulgular: PKT ve PLO aort darlığı grubunda anlamlı derecede yüksek bulundu. Ayrıca, PKT ve PLO ileri AD grubunda hafif ve orta AD gruplarına göre önemli derecede en yüksek saptandı. Korelasyon analizinde PKT ile maksimum ve ortalama transaortik gradyan ve maksimum jet akım hızı arasında önemli pozitif, aort kapak alanı ile anlamlı negatif ilişki saptandı. Benzer ilişkiler PLO ile AD şiddetinin ekokardiyografik parametreleri ile gösterildi.

Sonuç: Artmış inflamatuar durum ve platelet aktivasyon ve agregasyonunu yansıtan PKT ve PLO kalsifik AD olan hastalarda tedavi stratejileri için risk sınıflamasını iyileştirebilen kullanışlı, kolay elde edilebilen, ucuz ve basit hesaplanabilen belirteçlerdir.

Anahtar Kelimeler: Plateletkrit, platelet lenfosit oranı, kalsifik aort darlığı, ekokardiyografi

Introduction

Calcific aortic stenosis (AS), which is the worldwide leading cause of death from valvular heart disease, is the most common indication for aortic valve replacement. The prevalence of AS has been reported as 3% in general population, which has also seen more commonly aged over 75 years (1). Age, gender, hypertension, smoking, hyperlipidemia were presented as independent

significant risk factors for calcific AS (1,2). Increased platelet activation and aggregation due to raised shear stress in turbulent jet flow of AS were demonstrated in previous studies (3-4). Moreover, polisitemia vera has been reported as a possible cause of AS, which has not been related to severity of disease (5).

Plateletcrit (PCT), which is defined as platelet count x mean platelet volume / 10^7, is an indicator of total platelet mass. It is a part of the routine complete blood count (6). The associations and long term prognostic value of PCT have been reported in stable coronary artery disease (7), ST-segment (STEMI) (8) and non-ST segment elevation myocardial infarction (NSTEMI) (6), cardiac syndrome X (9). Moreover, clinical utility of PCT has been reported in both coronary slow flow phenomenon and saphenous vein graft disease (10,11).

Platelet to lymphocyte ratio (PLR) is defined as the ratio of the platelet to lymphocyte count obtained from the same blood sample (12). It has also been presented both as new inflammatory marker and a significant independent predictor of long-term prognosis in acute myocardial infarction (12) and peripheral arterial occlusive disease (13). Elevated PLR was demonstrated to be related with severity and complexity of coronary artery disease (14), coronary slow flow (15), poor coronary collateral development (16) in recent studies.

Since there is no information in the literature in terms of relation between PCT and calcific aortic stenosis and only one study has reported a significant independent association of increased PLR with presence and severity of calcific AS (17), we aimed to evaluate the relationship between both PCT and PLR and presence and severity of the calcific AS in the present study. We hypothesized that increased PCT and PLR, which are new indicators of severe chronic inflammation and platelet activity and aggregability, were related with the presence and severity of calcific AS.

Material and Methods

Ninety-eight consecutive patients, who admitted to outpatient cardiology clinic of state hospital with dyspnea, chest pain and/or syncope and diagnosed with calcific AS by using 2-D transthoracic echocardiographic examination between September 2013 and May 2015, and 30 healthy controls were included in this retrospective case-control study. Patients with calcific AS were divided into three groups according to severity of disease as follows: mild AS (n=35), moderate AS (n=30) and severe AS (n=33). The demographic, clinical and laboratory characteristics of the patients and controls groups were obtained from hospital records of the participants.

Presence of rheumatic or congenital AS, coronary artery disease, heart failure, peripheral artery disease, atrial fibrillation, congenital heart disease, myo-pericarditis, acute or chronic renal or hepatic dysfunction, concomittant moderate-severe valvular heart disease, acute coronary syndrome, malignancy, presence of prosthetic heart valve, primary or secondary hyperparathyroidism, acute or chronic infectious / inflammatory disease and use of medical therapy affecting platelet count or functions were exclusion criteria of the present study.

Definitions: Patients were defined hypertensive if systolic arterial pressure exceeded 140 mmHg and/or diastolic arterial pressure exceeded 90 mmHg, or had a history of use of antihypertensive drugs (18). Diabetes mellitus was defined whether patients with previous history of disease, use of diet, insulin or oral antidiabetic drugs, or had a fasting venous blood glucose level $\geq$126 mg/dl on two occasions in previously untreated patients. Hyperlipidemia was also defined as fasting total serum cholesterol >200 mg/dl, LDL >130 mg/dl, serum triglycerides (TG) >180 mg/dl, or the use of lipid-lowering drugs for a history of hypercholesterolemia (19). Height and weight of the study participants were recorded, and body mass index (BMI) was calculated as the weight divided by the square of height (kg/m2). Patients smoking 25 or more cigarettes daily at the time of diagnosis were recognized as active smokers.

Echocardiography: All study participants underwent comprehensive 2D, M-mode, conventional Doppler and color Doppler echocardiographic examinations to determine presence and severity of AS with a Vivid S5 (GE Vingmed, Horten, Norway) device using a 2.5- to 3.5-MHz probe by an experienced cardiologist, who was unaware of study participants data. The aortic valve area (AVA) was calculated using the continuity equation. The maximum aortic gradient was calculated with continuous-wave Doppler ultrasound scan over the aortic valve according to the peak velocities, whereas the mean aortic gradient was calculated according to time-velocity integrals. The classification of AS severity was done based on the American College of Cardiology/American Heart Association guidelines for valvular heart disease as follows:

(20): mild AS, AVA <1.5 cm2, mean gradient <25 mmHg, or jet velocity <3.0 m/s; moderate AS, AVA 1.0-1.5 cm2, mean gradient 25-40 mmHg, or jet velocity 3.0-4.0 m/s; severe AS, AVA <1.0 cm2, mean gradient >40 mmHg, or jet velocity >4.0 m/s. Moreover, left ventricular ejection fraction (LVEF) was determined using Simpson's method of discs in two dimensional echocardiography (20).

Laboratory Measurements: Blood samples were drawn by vacuteiner into tubes containing EDTA as anticoagulant. Samples were collected from the antecubital vein between 08:00 and 10:00 AM following 12-h fasting period. Hematological parameters including platelet indices were obtained using the Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland, Inc., Mervue, Galway, Ireland). Moreover, the biochemical parameters, including fasting blood glucose, creatinine, lipid profiles were measured using an Abbott Diagnostics C8000i (Abbott, Germany) auto-analyzer with commercial kits.

Statistical Analysis: Continuous, normally distributed variables will be expressed as mean ± standard deviation and non-normally distributed variables as median (interquartile range). Categorical variables will be expressed as frequencies and/or percentages. The variables will be investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov) to determine if they are normally distributed. Kruskal-Wallis and Mann-Whitney U-tests were used for continuous non-normally distributed variables, and one-way ANOVA and Tukey tests for continuous normally distributed variables. Categorical variables were compared by the likelihood ratio chi-square test. Correlations between variables were assessed using the Spearman rank correlations test. An overall 5% type-I error level was used to infer statistical significance and a p-value less than 0.05 was considered significant. Two-sided p-values <0.05 were considered to be statistically significant. All statistical analyses were carried out using SPSS statistical software, version 21.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline demographic, clinical and laboratory characteristics of the AS and the control groups were summarized in Table 1 and Table 2. Patients with AS tended to be significantly younger than the control subjects are. Moreover, incidence of hyperlipidemia, systolic and diastolic blood pressure, fasting glucose were found to be significantly higher in the AS group than in the controls. When the two groups were compared in terms of hematologic parameters, PCT, PLR, mean platelet volume (MPV) and platelet counts were demonstrated to be significantly higher in patients with the AS. However, hemoglobin and lymphocyte counts were decreased in the AS group compared to the control group. Furthermore, as expected, maximum and mean transaortic gradients and peak jet blood velocity were found to be significantly higher in the AS patients compared to control subjects. Aortic valve area (AVA) was significantly lower in the AS group.

When the demographic, clinical and laboratory characteristics of the AS patients based on subdivisions were investigated (Table 3 and 4); age was highest in the severe AS group than in the other groups. Moreover, BMI, systolic blood pressure, creatinine were demonstrated to be significantly highest in the severe AS patients. However, LVEF was significantly lowered, as the severity of stenosis raised. When the hematologic parameters were evaluated in subdivisions of the

Table 1. Baseline demographic and clinical characteristics of the AS and the control groups

	Aortic Stenosis (n = 98)	Control (n = 30)	p
Age, y	64.74 ± 2.81	66.17 ± 3.11	**0.037***
Gender, M/F, n (%)	49/49 (50/50)	12/18 (40/60)	0.337
BMI, kg/m2	27.72 ± 0.96	27.49 ± 1	0.506
Smoking, n (%)	27 (27.6)	11(36.7)	0.339
Diabetes mellitus, n (%)	27(27.6)	4(13.3)	0.112
Hypertension, n (%)	47(48)	12(40)	0.444
Hyperlipidemia, n (%)	53(54.1)	10(33.3)	**0.047***
SBP, mmHg	132.85 ± 5.87	122.4 ± 9.85	**<0.001***
DBP, mmHg	80.86 ± 3.86	71.63 ± 5.56	**<0.001***

AS: aortic stenosis; BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Table 2. Baseline laboratory and echocardiographic characteristics of the AS and the control groups

	Aortic Stenosis (n = 98)	Control (n =30)	p
Glucose, mg/dL	99.07 ± 26.62	80.33 ± 5.86	**<0.001***
Urea, mg/dL	31.41 ± 4.39	30.57 ± 3.45	0.365
Creatinine, mg/dL	0.93 ± 0.18	0.82 ± 0.17	**0.006***
LDL, mg/dL	107.15 ± 16.22	110.63 ± 13.43	0.288
HDL, mg/dL	46.96 ± 4.8	45.27 ± 5.01	0.097
TG, mg/dL	133.69 ± 36.8	132.53 ± 9.07	0.865
Hemoglobin, g/dL	12.08 ± 0.95	12.58 ± 0.64	**<0.001***
Platelet, ×10³	232.98 ± 28.67	203.9 ± 12.87	**<0.001***
MPV, fL	8.97 ± 0.89	8.46 ± 0.54	**0.005***
Lymphocyte, x10³	1.87 ± 0.14	2.06 ± 0.1	**<0.001***
PLR	125.85 ± 20.8	99.13 ± 8.18	**<0.001***
PCT	0.21 ± 0.04	0.17 ± 0.02	**<0.001***
LVEF, %	59.94 ± 2.07	60 ± 2.69	0.802
Maximal gradient, mmHg	55.71 ± 27.56	7.57 ± 1.33	**<0.001***
Mean gradient, mmHg	31.4 ± 16.26	3.95 ± 0.81	**<0.001***
Maximum jet velocity, m/s	3.29 ± 1.28	1.2 ± 0.2	**<0.001***
Aortic valve area, cm²	1.31 ± 0.44	3.63 ± 0.21	**<0.001***

AS: aortic stenosis; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; MPV: mean platelet volume; PCT: plateletcrit; PLR: Platelet to lymphocyte ratio; TG: triglyceride.

Table 3. Baseline demographic and clinical characteristics of the AS patients according to disease severity

	Mild AS (n = 35)	Moderate AS (n = 30)	Severe AS (n = 33)	p
Age, y	62.91 ± 2.32	64.87 ± 2.46	66.58 ± 2.37	**0.001***
Gender, M, n (%)	18 (51.4)	16 (53.3)	15 (45.5)	0.805
BMI, kg/m²	27.29 ± 0.97	27.76 ± 0.96	28.12 ± 0.77	**0.004***
Smoking, n (%)	7(20)	9(30)	11(33.3)	0.44
Diabetes mellitus, n (%)	12(34.3)	7(23.3)	8(24.2)	0.537
Hypertension, n (%)	14(40)	15(50)	18(54.5)	0.47
Hyperlipidemia, n (%)	16(45.7)	18(60)	19(57.6)	0.456
SBP, mmHg	131.63 ± 4.78	131.73 ± 4.83	135.15 ± 7.11	**0.045***
DBP, mmHg	80.46 ± 3.32	80.77 ± 3.59	81.36 ± 4.62	0.753

AS: aortic stenosis; BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure.

AS; PCT, PLR, MPV and platelet counts were demonstrated to be significantly higher in the severe AS group than in the mild and moderate AS groups. However, lymphocyte counts were lowest in the AS group compared to in the others. The maximal and mean transaortic gradients, and maximum jet velocities were significantly increased, while the AVAs were significantly decreased, as the degree of stenosis increased.

Correlation analysis indicated (Table 5) positive significant relationships between the PCT and the maximal and mean transaortic gradients, and maximum jet velocities; and negative association with AVA. The same relations were obtained between PLR (Table 6) and echocardiographic parameters of severity of AS respectively (all p values < 0.001). Furthermore, PCT, PLR, MPV and platelet counts were significantly directly correlated with themselves (all p values < 0.001). MPV, as one of the new platelet indices, was positively correlated with the maximal (r = 0.592, p < 0.001) and mean transaortic gradients (r = 0.591, p < 0.001), and maximum jet velocities (r = 0.590, p < 0.001); and inversely correlated with AVA (r = -0.546, p = 0.001). Platelet count was also directly correlated with MPV(r = 0.320, p < 0.001).

Table 4. Baseline laboratory and echocardiographic characteristics of the AS patients according to disease severity

	Mild AS (n = 35)	Moderate AS (n = 30)	Severe AS (n = 33)	p
Glucose, mg/dL	96.57 ± 23.32	98.23 ± 23.38	102.48 ± 32.49	0.583
Urea, mg/dL	30.91 ± 4	31.1 ± 3.38	32.21 ± 5.48	0.683
Creatinine, mg/dL	0.9 ± 0.18	0.88 ± 0.17	1 ± 0.18	**0.035***
LDL, mg/dL	108.17 ± 13.76	105.9 ± 15.08	107.21 ± 19.69	0.856
HDL, mg/dL	45.89 ± 5.5	47.97 ± 3.37	47.18 ± 5.01	0.209
TG, mg/dL	131.17 ± 40.94	134.37 ± 40.92	135.76 ± 28.21	0.872
Hemoglobin, g/dL	12.16 ± 1.04	12.09 ± 0.92	11.98 ± 0.88	0.966
Platelet, $\times 10^3$	216.97 ± 18.2	225.6 ± 21.98	256.67 ± 28.14	**<0.001***
MPV, fL	8.47 ± 0.42	8.64 ± 0.61	9.81 ± 0.9	**<0.001***
Lymphocyte, $\times 10^3$	1.92 ± 0.08	1.91 ± 0.13	1.77 ± 0.15	**<0.001***
PLR	112.97 ± 8.99	118.54 ± 13.88	146.16 ± 19.84	**<0.001***
PCT	0.18 ± 0.02	0.19 ± 0.02	0.25 ± 0.04	**<0.001***
LVEF, %	60.29 ± 1.62	60.8 ± 2.11	58.79 ± 2	**<0.001***
Maximal gradient, mmHg	28.06 ± 3.96	49.37 ± 3.59	90.82 ± 11.38	**<0.001***
Mean gradient, mmHg	14.23 ± 2.17	28.77 ± 1.91	52 ± 5.11	**<0.001***
Maximum jet velocity, m/s	1.82 ± 0.48	3.43 ± 0.25	4.71 ± 0.43	**<0.001***
Aortic valve area, cm^2	1.83 ± 0.11	1.26 ± 0.04	0.80 ± 0.10	**<0.001***

AS: aortic stenosis; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; MPV: mean platelet volume; PCT: plateletcrit; PLR: Platelet to lymphocyte ratio; TG: triglyceride.

Table 5. Correlation analysis between PCT and study variables in patients with the AS

	r	P
PLR	0.805	**< 0.001**
MPV	0.691	**< 0.001**
Platelet count	0.865	**< 0.001**
Aort$_{max}$	0.677	**< 0.001**
Aort$_{mean}$	0.679	**< 0.001**
Aort$_{maxjet}$	0.678	**< 0.001**
AVA	-0.620	**< 0.001**

AVA: aortic valve area; Aort$_{max}$: maximum transaortic gradient; Aort$_{mean}$: mean transaortic gradient; Aort$_{maxjet}$: maximum jet blood flow; MPV: mean platelet volume; PCT: plateletcrit; PLR: platelet to lymphocyte ratio.

Table 6. Correlation analysis between PLR and study variables in patients with the AS

	r	p
PCT	0.805	**< 0.001**
MPV	0.411	**< 0.001**
Platelet count	0.874	**< 0.001**
Aort$_{max}$	0.633	**< 0.001**
Aort$_{mean}$	0.650	**< 0.001**
Aort$_{maxjet}$	0.661	**< 0.001**
AVA	-0.595	**< 0.001**

AVA: aortic valve area; Aortmax: maximum transaortic gradient; Aortmean: mean transaortic gradient; Aortmaxjet: maximum jet blood flow; MPV: mean platelet volume; PLR: platelet to lymphocyte ratio.

Discussion

We reported that increased PCT and PLR are related to presence and severity of the calcific AS. This is the first study to demonstrate a strong significant relationship between PCT and severity of the AS. Moreover, PCT and PLR were found to be significantly correlated with other platelet indices such as mean platelet volume and platelet count. These results suggest that increased PCT and PLR have an impact on both prothrombotic and proinflammatory states.

The calcific AS and atherosclerosis share similar etiologies and pathophysiologic mechanisms, which are composed of chronic inflammation, endothelial damage, mechanical shear stress, deposition and oxidization of lipid-rich particles at vulnerable plaque sites, neoangiogenesis resulting

calcification (21). Platelets participate actively in the process of inflammation, atherogenesis and thrombus formation via production and release of several cytokines and chemokines, which are crucial mediators of vascular wall inflammation and shear stress (22). Severe chronic inflammation triggers megakaryocytic proliferation and lead to relative thrombocytosis (22). Platelets also have an important role in the transmigration of leukocytes, monocytes and macrophages into the sites of inflammation and vascular injury, which are significant pathophysiological pathways for developing of the calcific AS (21,22). An increased platelet reactivity, hyperaggregability and thrombus formation in the setting of the calcific AS was demonstrated in previous study (23). Prohaska et al. (4) reported a pre-operative marked platelet dysfunction in patients underwent isolated coronary artery bypass surgery and single aortic valve replacement. They suggested that platelets, after an initial activation due to impaired blood flow and shear stress, might participate in microvascular dysfunction and thrombotic events in the AS.

PCT indicates the number of circulating platelets in a unit volume of blood, which is analogous to the haematocrit for erythrocytes (24). It has been evaluated as a novel predictor of severe inflammation and raised cardiovascular risk. A clinical utility of PCT in predicting a slow coronary flow phenomenon was demonstrated in the study of Akpinar et al. (10). Moreover, a positive direct relation between PCT and critical saphenous vein graft stenosis was found in a recent study (11). Ugur et al. (8) reported that admission PCT was a significant independent predictor for long-term cardiovascular mortality in patients undergoing primary angioplasty for STEMI. The similar considerable prognostic value of PCT was reported in NSTEMI by the study of Gul et al. (6). Furthermore, Oylumlu et al. (9) demonstrated an increased mean PCT value in the cardiac syndrome X (CSX) patients and it was presented as a significant predictor of presence of the CSX with normal coronary arteries. In our study, PCT was found to be raised in the calcific AS patients, which was associated with severity of disease. It also directly correlated with other platelet indices such as PLR and MPV. It can be suggested that, raised PCT levels may due to severe chronic inflammation and increased platelet activity and aggregability, which play roles in the pathogenesis of the AS.

PLR, which is an indicator of increased inflammation, platelet activation and aggregation, combines the risk predictor effect of two parameters into a single risk factor (13). Previous clinical studies demonstrated a significant independent value of PLR in predicting long term major adverse outcomes in various cardiovascular diseases (12-17). Akdag et al. (17) reported that PLR was significantly higher in severe and mild-to-moderate AS groups when compared to the control subjects. Moreover, it was found to be higher in the severe AS group compared to mild-to-moderate group in subgroup analysis of the study. PLR was found to be significantly correlated with echocardiographic parameters of severity of AS. In our study, concordant with the Akdag et al. (17) study, similar findings were found in terms of relation between PLR and presence and severity of the AS. Kurtul et al. (14) demonstrated that elevated PLR was related with both severity and complexity of coronary artery disease and had an important prognostic value for in-hospital mortality in the setting of acute coronary syndrome. Temiz et al. (25) also reported a considerable prognostic significance of PLR for early cardiovascular mortality in STEMI.

The possible theory for these findings may be an increased blood viscosity and thrombus formation due to exaggerated platelet activity and aggregability resulting in increased PCT and PLR. Chronic inflammation, endothelial dysfunction and oxidative processes, which are seen both in the atherosclerosis and calcific AS, further increases platelet functions and responses causing severe form of disease. Turbulent jet blood flow and increased shear stress, occurred in the setting of calcific AS, may destruct endothelium of vascular wall around or near aortic valves and may trigger an increase of platelet activation, aggregation and coagulation cascade results in raised PCT and PLR values.

Study Limitations: The present study has some limitations. First, this is a single center and retrospective study, which has not data about future major adverse cardiovascular events of patients to determine prognostic significance of PCT and PLR in this setting. Second, because of single measurement of PLR and PCT on admission, serial changes in response to medical or interventional treatment could not be evaluated. Third, although this study has a relatively small sample size, we were able to demonstrate strong relationship between PCT, PLR and presence and severity of AS respectively. A lack of data about levels of specific markers for oxidative stress, inflammation and endothelial

dysfunction was the last limitation of the present study.

We demonstrated, for the first time, a strong significant relation between PCT and presence and severity of AS in our study. Moreover, similar findings were presented for PLR in patients with calcific AS. PCT and PLR, which are part of routine complete blood count and reflect elevated inflammatory status and platelet activation and aggregation, are useful, cheap, easily available and simply calculated markers that have an ability to improve risk stratification of patients with calcific AS for treatment strategies. Further studies with prospective design and larger population size are needed to elucidate precise relationship between the new platelet indices and presence and severity of the AS.

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