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Original Article

The predictive value of platelet to lymphocyte ratio for procedural complications and mid-term mortality in aortic stenosis patients who underwent a transcatheter aortic valve implantation

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Abstract

Aim: Calcific aortic valve disease is an active cellular process including chronic inflammation, calcification, and lipid accumulation which issimilar to atherosclerosis. The platelet to lymphocyte ratio (PLR) is a hematologicalparameter which increases with the inflammation and vascular oxidative stress. In the present study, we aimed to evaluate whether the PLR had a prognostic role inprocedural complications and mid-term mortality ofaortic stenosis (AS) patients underwent transcatheter aortic valve implantation (TAVI).

Material and Methods: A total of 100 symptomatic severe AS patients undergone TAVI in atertiary heart center between June 2012 and June 2016 were retrospectively analyzed. The PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count before the TAVI procedure. The follow-up duration of the study was six months.

Results: The mean age of study population was 78 years (range: 65-85), and 35 patients were male. Of note, serum PLR level was significantly elevated in patients who developed vascular complication and stroke after the TAVI ($p<0.05$, for all). In addition, the patients with a high serum PLR had an elevated mortality during six months' follow-up ($p<0.05$).

Conclusion: High pre-procedural PLR level may have a predictive value for vascular complications and stroke in AS patients who underwent TAVI. Particularly, patients with a high serum PLR values after the TAVI should be closely followed up because total mortality among these patients washigh.

Keywords: Trans-Aortic Valve Implantation; Platelet To Lymphocyte Ratio; Inflammation; Mortality; Stroke; Vascular Complication.

INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart pathology (1), affecting 3% of adult population over 75 years old (2). The calcification of the valve is the most common reason of aortic stenosis, termed as a calcific aortic valve disease (CVAD) (3). CVAD is an active cellular process including a chronic inflammation, calcification, and lipid accumulation mimicking atherosclerosis (4-6). Also, the identification of lipid particles, the inflammatory cells, and the calcium crystal deposition support the idea that both calcific AS and atherosclerosis have a similar pathologic process (7,8). Moreover, an oxidative stress and endothelial dysfunction play an important role in the development of calcific AS (9-11). There are two available main treatment options in patients with symptomatic severe AS; surgical aortic valve replacement (SVAR) and transcatheter aortic valve implantation (TAVI). TAVI has emerged as a valuable treatment option in patients with inoperable and high-risk severe symptomatic AS.

Several previous studies have reported that increase of inflammatory markers is related with adverse outcomes in patients with cardiovascular disease (12-14).The platelet to lymphocyte ratio (PLR), which has been recently introduced as a new inflammatory index, increases concomitant with the inflammation and vascular oxidative stress (15,16). In previous studies, it was demonstrated that increase levels of PLR are related with elevated mortality rates among patients with cardiovascular diseases (17, 18). The investigators speculated that inflammation, oxidative stress, and endothelial dysfunction might have

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explained the association between PLR and cardiovascular diseases. Becausethe inflammation and oxidative stress play an important role in severe symptomatic AS, and the PLR as a marker of inflammation, in this study, weaimed toinvestigated whether the PLR level havea prognostic value with procedures complications, namely vascular complications and stroke, and mid-term mortality in AS patients who underwent TAVI.

MATERIAL and METHODS

Study population

This retrospective study was carried out in a total of 100symptomatic severe AS patients who underwent TAVI at tertiary heart center between June 2012 to June 2016. The patients withan acute or chronic infection, withan auto-immune disease, under any glucocorticoid therapywithin three months, witha hematologic disease, undergoing chronic peritoneal dialysis or hemodialysis treatment were excluded from the study. Baseline demographic characteristics and laboratory findings of each patient were retrieved from the hospital electronic database. The selection of the patients with severe symptomatic AS was based on the expected perioperative or short-term mortality that is calculated from the risk model of STS (The Society of Thoracic Surgeons Score) algorithm.Our multidisciplinary 'Heart–team' (cardiac surgeons, interventional cardiologists, and experts in echocardiography) assessed each of patients. The TAVI procedures were performed with the use of the Edwards-Saphien aortic valves (n: 75) and Boston Lotus aortic valves (n: 25). Ethical clearance was obtained from the Ethics and Research Committee of our hospital. Due to the retrospective design of the study, a written informed consent was not obtained from each patient.

Laboratory examination

All blood samples were obtained after anovernight fasting from the subjectsbefore the TAVI operation. The tubes with EDTA were used to evaluate automatic blood count. A Sysmex XT-1800i Hematology Analyzer device (Sysmex Corporation, Kobe, Japan) was used to measure the complete blood counts. The neutrophil to lymphocyte ratio (NLR) was calculated by dividing the number of neutrophil to lymphocytes; the PLR was calculatedby dividing the absolute platelet count by the absolute lymphocyte count, both of which obtained from the same automated blood sample prior to TAVI. An automatic biochemical analyzer divice (Roche Diagonistics Cobas 8000 c502) was used to measure C-reactive protein (CRP).

Defınations

In-hospital death was determined as all-cause of death during hospitalization. For the evaluation of mid-term mortality, hospital electronic data base and state-wide death registry database were used. Stroke was accepted as a neurologic deficit lasting <24 h as TIA or if longer as stroke. All vascular complications were defined as proposed by Valve Academic Research Consortium (19).

Statistical analyses

In this study, all statistical analysis was performed with SPSS 16.0 software (Statistical Package for the Social Sciences, SPSS Inc., Chicago IL). Fitness to normal distribution was analyzed with the Kolmogorov-Simirnov test. Data expressed as median (minimum-maximum) for variables with abnormal distribution. Differences among two groups were analyzed by Mann Whitney-U test. Categorical variables were analyzed by Fisher's exact test. The receiver operating characteristics (ROC) curve analysis was used to analyze the effect of NLR and PLR on vascular complications, stroke, and all-cause mortality. Differences were considered statistically significant at $p<0.05$.

RESULTS

The mean age of the study population was 78 years (range: 65-85), and 65 (65%) patients were females. Baseline demographic characteristics, laboratory, and interventional outcomes of all patients were listed in Table 1. In the study, a total of 6 deaths occurred in 100 patients during in-hospital stays and six months' follow-up. The patients who had experienced vascular complications had an elevated level of pre-procedural theNLR and PLR values in comparison to those who did not ($p<0.05$, for all) (Table 2). In addition, the patients who developed stroke after the TAVI had an elevated level of PLR value ($p<0.05$). In terms of all-cause mortality, we observed that the patients with a high PLR had a higher incidence of death compared to those without a high PLR ($p<0.05$).

Table 1. Baseline demographic characteristics, laboratory, and interventional outcomes of all patients

Total study population, n: 100	
Female gender, n (%)	64 (64)
Age, years	78 (65-85)
Diabetes mellitus, n (%)	56(56)
Hypertension, n (%)	55 (55)
BMI, kg/m2	23.5 (19.5-26.2)
Smoking, n (%)	6 (6)
Hyperlipidemia, n (%)	42 (42)
STS score	9.6 (6.5-16.2)
PLR	165.2 (113.5-198.6)
NLR	4.9 (2.2-6.5)
CRP, g/dL	1.6 (0.8-4.5)
Creatinine, mg/dL	0.8 (0.4-2.5)
Hemoglobin, g/dL	14.8 (12.5-16.9)
Vascular complication, n (%)	10 (10)
Stroke, n (%)	5 (5)
All-cause mortality, n (%)	6 (6)

Continuous variables are presented as median and nominal variables are presented as frequency (%). Abbreviations: BMI; Body Mass Index, STS; Society of Thoracic Surgeon, PLR; Platelet to Lymphocyte Ratio, NLR; Neutrophil to Lymphocyte Ratio, CRP; C-Reactive protein.

Table 2. Baseline demographic characteristics and laboratory findings of all patients with and without vascular complications, stroke, and all-cause mortality

	Vascular complication			Stroke			All-cause mortality		
	Absent, n=90	Present, n=10	P value	Absent, n=95	Present, n=5	P value	Survivors, n=94	Non-survivors=6	P value
Female gender, (%)	63.3	70	0.483	64.2	60	0.595	63.8	66.7	0.629
Age, years	78 (65-85)	81 (72-85)	0.079	78 (65-85)	79 (76-85)	0.382	78 (65-85)	81 (68-85)	0.435
Diabetes mellitus, (%)	54.4	70	0.276	55.8	60	0.614	56.4	50	0.540
Hypertension, (%)	55.6	50	0.496	53.7	80	0.250	53.2	83.3	0.156
BMI, kg/m^2	23.5 (19.5-26.2)	25.6 (19.5-26.2)	0.027	23.5 (19.5-26.2)	23.6 (19.5-24.2)	0.739	23.5 (19.5-26.2)	23.8 (20.5-25.6)	0.755
Smoking, (%)	6.7	0	0.522	6.3	0	0.729	5.3	16.7	0.317
Hyperlipidemia, (%)	42.2	40	0.585	40	80	0.098	43.6	16.7	0.195
PLR	165 (114-199)	181 (166-190)	<0.001	165 (114-199)	188 (174-192)	0.010	165 (114-196)	190 (176-199)	0.001
NLR	4.6 (2.2-6.5)	5.4 (4.9-6.1)	0.001	4.9 (2.2-6.5)	5.1 (4.2-5.3)	0.542	4.8 (2.2-6.5)	5.3 (4.2-6.1)	0.046
CRP, mg/dL	2 (1-5)	2 (1-4)	0.747	2 (1-5)	2 (1-4)	0.924	2 (1-5)	2 (1-3)	0.716
Creatinine, mg/dL	0.8 (0.4-2.5)	0.9 (0.5-1.8)	0.776	0.8 (0.4-2.5)	0.9 (0.8-1.3)	0.861	0.9 (0.4-2.5)	0.8 (0.6-1.8)	0.855
Hemoglobin, g/dL	14.9 (12.5-16.9)	14.6 (13.8-16.2)	0.703	14.8 (12.5-16.9)	14.3 (3.5-16.0)	0.793	14.8 (12.5-16.9)	14.8 (13.5-15.6)	0.531
STS score	9.6 (6.5-16.2)	8.9 (6.9-14.2)	0.216	9.5 (6.5-16.2)	13.5 (9.2-15)	0.028	9.6 (6.5-16.2)	9.6 (6.9-12.3)	0.711

Continuous variables are presented as median and nominal variables are presented as frequency (%).
Abbreviations: BMI; Body Mass Index, STS; Society of Thoracic Surgeon, PLR; Platelet to Lymphocyte Ratio, NLR; Neutrophil to Lymphocyte Ratio, CRP; C-Reactive protein

The incidence of stroke and vascular complications were 10% and 5%, respectively. Ofthese complications, 5 femoral lacerations were locally repaired. A total of 5 patients developed hematoma which resolved without any intervention. ROC analysis revealed that the PLR and NLR areas under the ROC curve (AUC) values for vascular complications were 0.867 and 0.808, respectively (Figure 1).

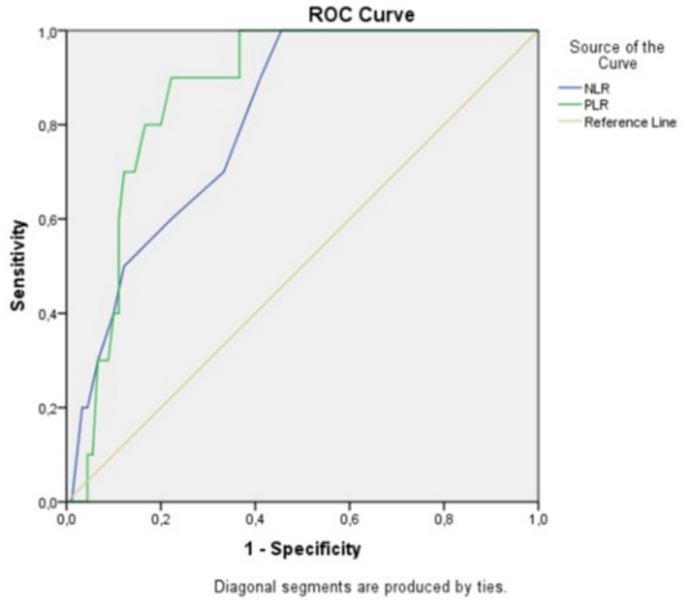

Figure 1. The receiver operating characteristic (ROC) curves of the PLR and NLR in predicting vascular complication in aortic stenosis (AS) patients after a transcatheter aortic valve implantation (TAVI)

The best cut-off value of PLR obtained from ROC analysis for stroke was 175.4 with sensitivity 90% and specificity 78%. The AUC value of PLR for stroke was 0.844 and the best cut-off value was determined to be 173.7 withsensitivity 100% and specificity 68% (Figure 2).

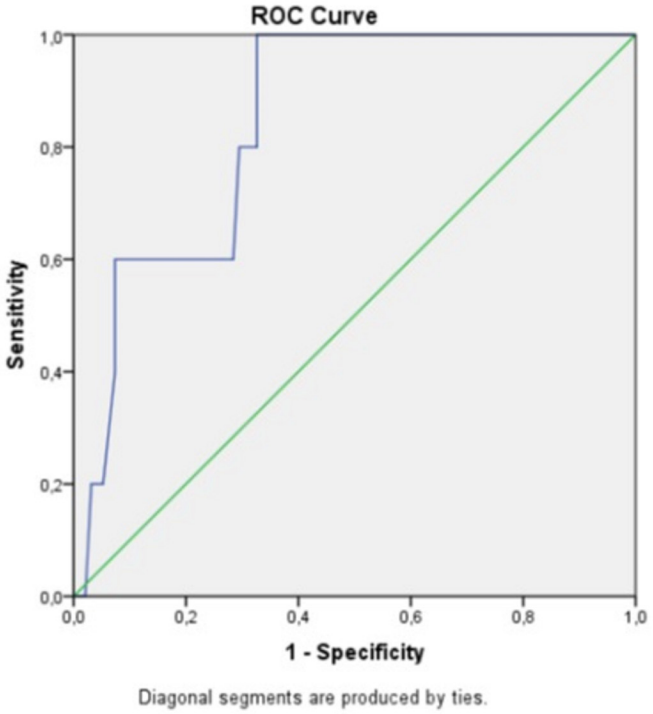

Figure 2. The receiver operating characteristic (ROC) curves of the PLR in predicting stroke in aortic stenosis (AS) patients after a transcatheter aortic valve implantation (TAVI)

The AUC values of the PLR and NLR for all-cause mortality were 0.743 and 0.921, respectively (Figure 3). The best cut-off valuewas determined to be 175.4 with sensitivity 100% and specificity 76%. A box plot was performed to demonstrate the difference between the PLR values of vascular complications (Figure 4).

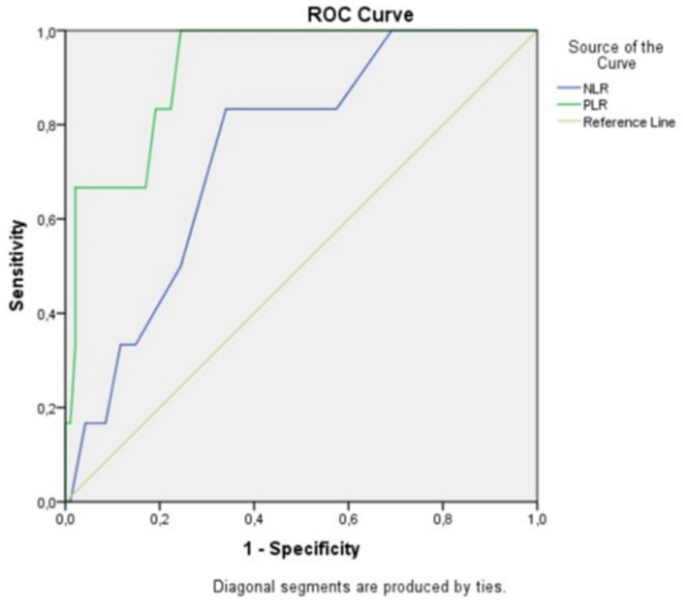

Figure 3. The receiver operating characteristic (ROC) curves of the PLR and NLR in predicting all-cause mortaliy in aortic stenosis (AS) patients after a transcatheter aortic valve implantation (TAVI)

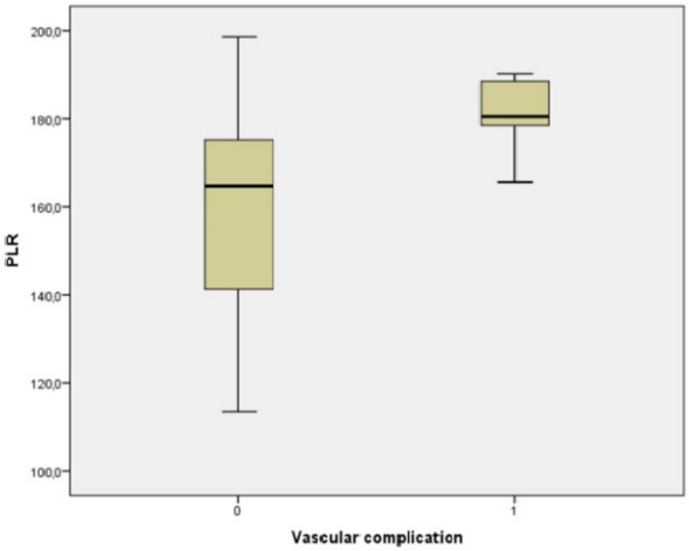

Figure 4. A box plot showing the difference between the PLR values of vascular complications

DISCUSSION

In the present study, we investigated whether the PLR level had a predictive value for all-cause mortality, stroke incidence, and vascular complicationsin TAVI. We showedthat increased levels of PLR were directly correlated with total mortality, vascular complications, and stroke incidence.

The AS is the most common valvular heart disease, and it is most commonly seen in patient with olderage (1,2). Risk factors associated with atherosclerosis are similar to the AS including older age, female gender, elevated low density lipoprotein (LDL), lipoprotein (a), hypertension, and smoking. Furthermore, the studies on early lesions of AS have demonstrated the similarity between subendothelial plaque lesions and aortic valve lesions. These lesions are composed of atherogenic lipoproteins including oxidized LDL, lipoprotein (a), and inflammatory cells (6). These pathogenic similarities between AS and atherosclerosis indicated a common mechanism as a general response to the tissue injury. Endothelial dysfunction, which plays a critical role in the pathogenesis of atherosclerosis, plays a key role in the pathogenesis of calcific aortic diseasesand it was verified by Poggianti et al. in patients with AS (10).

The NLR has been found to be associated with inflammation and oxidative stress. Because the inflammation and oxidative stress play a critical role in pathogenesis of severe AS, many studies have been used NLR as a marker of inflammation. Avci et al. studied the NLR in a total of 96 patients with mild, moderate, and severe AS patients (20). The researchers showed a notable higher level of NLR in severe AS patients. Moreover, Küçükseymen at al. demonstrated an elevated NLR in 220 mild, moderate, and severe AS patients compared to the 158 healthy subjects (21). Similar toprevious studies, we also demonstratedthat a higherNLR is associated with vascular complications and total mortality in AS patients who underwent TAVI.

Previously, some studies reported an association between elevated platelet counts and poor outcomes in patients with cardiovascular disease (22,23). Furthermore, elevated levels of platelet count may show a significant underlying inflammation because some inflammatory mediators may induce megakaryocytic proliferation and produce reactive thrombocytosis. Several previous studies have reported a relationship between PLR and inflammatory markers such as CRP, blood neutrophilcount, interleukin, and TNF-alpha (24,25). In a recent study, which including453 AS patients, the investigator demonstrated a significant relationship between the PLR and AS (26). Moreover, Akdag et al. demonstrated that increased PLR correlates with the severity of calcific AS (27). However, the suitability of the PLR for predicting vascular complications, stroke incidence, and all-cause mortality in AS patients undergoing TAVI remains unknown. The present study might be the first to demonstrate that PLR may have a good predictive value for predicting vascular complications, stroke incidence, and total mortality in AS patients undergoing TAVI.

The PLR is a simple marker of inflammation which can be easilyobtained from complete blood count parameters. Our study findings provided evidence for the association of higher PLR and increasedvascular complications, stroke, and all-cause mortality after TAVI. These findings revealed that the presence of high inflammatory status determined by PLR is an effective parameterin predicting vascular complications, stroke, and all-cause mortality after a TAVI. Besides, our findings provided evidence that in patients with a high PLR, closer follow-ups should be arranged after a TAVI.

Study limitations

Our study has some limitations. Firstly, this study hasa retrospective and observational design. Secondly, this study has a small sample size. Therefore, the limited number of patients who underwent a TAVI procedure may preventgeneralizability of our study. Thirdly, a spot laboratory value was used to estimate long-term mortality in the present study. Finally, some well-known inflammatory markers were not evaluated in our study.

CONCLUSION

The PLR is a simple and inexpensive parameterthat can be easily calculated from complete blood count parameters. Ourfindings showed that high preprocedural PLR may be a predictor of vascular complications, stroke, and all-cause mortality in AS patients after a TAVI. However, as it was a retrospective study, our findings warrant further prospective and multicenter studies with larger sample size to elucidate the association between PLR and vascular complications, stroke, and total mortality in AS patients after a TAVI.

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