Acta Medica Alanya

Research Article

Araştırma

Acta Medica Alanya 2023;7(3): 213-218
Doi: 10.30565/medalanya.1291772

Comparison of the Relationship Between Inflammatory Markers and Saphenous Vein Graft Disease in Patients With Stable Angina Pectoris

Stabil Anjina Pektorisli Hastalarda İnflamatuvar Belirteçler ile Safen Damar Grefti Hastalığı Arasındaki İlişkinin Karşılaştırılması

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ABSTRACT

Aim: Coronary artery bypass graft surgery is one of the most commonly used strategies to revascularization of occlusive coronary atherosclerotic lesions. Atherosclerosis is known to be a chronic inflammatory process. Many inflammatory cells and mechanisms are active in this process. Markers such as mean platelet volume-to-lymphocyte ratio (MPVLR) and C-reactive protein-to-albumin (CAR) which may be associated with the severity of inflammation. In this study, it was aimed to determine the relationship between these parameters and saphenous vein graft (SVG) diseases.

Methods: In this retrospective study, 314 patients SVG disease with stable angina pectoris were included. Patients were divided into two groups according to the severity of SVG disease. We compared 159 patients who had severe stenosis in SVG and 156 patients who did not,in terms of CAR, NLR, PLR, MPVLR.

Results: Patients who ≥50% stenosis in SVG had significantly higher CAR, MPVLR, NLR, and PLR (respectively 9.1 (4.2-16.8) p<0.001, 4.5)0.68) p<0.001, 2.4 (0.69) p=0.002, 153)6) p=0.048). In line with these data, CAR and MPVLR values were also higher in the group with ≥50% stenosis in SVG, which was highly statistically significant (respectively 3.2 (0.9-4.4) vs 9.1 (4.2-16.8); p<0.001 and 3.64)0.43) vs 4.53)0.68); p<0.001).

Conclusion: C-reactive protein-to-albumin and MPVLR can be a useful and easily accessible markers to predict severity SVG stenosis.

Key Words: C-reactive protein-to-albumin ratio, mean platelet volume-to-lymphocytes ratio, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, saphenous vein graft diseases.

ÖZET

Amaç: Koroner arter baypas greft cerrahisi, tıkayıcı koroner aterosklerotik lezyonların revaskülarizasyonu için en sık kullanılan stratejilerden biridir. Aterosklerozun kronik bir inflamatuar süreç olduğu bilinmektedir. Bu süreçte birçok enflamatuar hücre ve mekanizma aktiftir. Enflamasyonun ciddiyeti ile ilişkili olabilecek biyobelirteçler; ortalama trombosit hacmi-lenfosit oranı (MPVLR) ve C-reaktif protein-albümin (CAR), nötrofil-lenfosit oranı (NLR) ve platelet-lenfosit oranı (PLR)'dir. Bu çalışmada bu parametreler ile safen ven grefti (SVG) hastalıkları arasındaki ilişkinin belirlenmesi amaçlanmıştır.

Yöntem: Bu retrospektif çalışmaya stabil anjina pektorisli SVG hastalığı olan 314 hasta dahil edildi. Hastalar SVG hastalığının şiddetine göre iki gruba ayrıldı. SVG'de ciddi darlık olan 159 hasta ile darlık olmayan 156 hastayı CAR, NLR, PLR, MPVLR açısından karşılaştırdık.

Bulgular: SVG'de ≥%50 darlığı olan hastalarda CAR, MPVLR, NLR ve PLR anlamlı olarak daha yüksekti (sırasıyla 9.1 (4.2-16.8) p<0.001, 4.5(0.68) p<0.001, 2.4 (0.69) p=0.002, 153 (6) p=0.048). Bu veriler doğrultusunda SVG'de ≥%50 darlık olan grupta CAR ve MPVLR değerleri de istatistiksel olarak anlamlıydı (sırasıyla 3,2 (0,9-4,4) ve 9,1 (4,2-16,8); p<0,001 ve 3,64 (0,43) - 4,53(0,68); p<0.001)

Sonuç: C-reaktif protein-albümin ve MPVLR, SVG stenozunun ciddiyetini tahmin etmek için yararlı ve kolay erişilebilir bir belirteç olabilir.

Anahtar Kelimeler: C-reactive protein-albumin oranı, ortalama platelet hacmi- lenfosit oranı, nötrofil-lenfosit oranı, platelet-lenfosit oranı, safen ven greft hastalığı

Recieved Date: 03.05.2023 / **Accepted Date:** 17.10.2023 / **Published (Online) Date:** 31.12.2023

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To cited: Zorlu Ç, Ömür SE, Yılmaz S. Comparison Of The Relationship Between Inflammatory Markers And Saphenous Vein Graft Disease In Patients With Stable Angina Pectoris Acta Med. Alanya 2023;7(3): 213-218 doi: 10.30565/medalanya.1291772

Introduction

Saphenous vein grafts (SVG) degenerate more than arterial grafts over time. Despite this, they are still used in coronary artery bypass surgery[1]. SVG degeneration negatively affects long-term outcomes in CABGs. In SVG stenosis < 1 month period, thrombosis is seen as the leading cause. In the period of 1-12 months, neointimal hyperplasia may be the cause of stenosis. Atherosclerosis occurs in SVG stenosis after 12 months.[2-4]

It is known that inflammatory conditions predispose to vascular thrombosis. The neutrophil-to-lymphocyte ratio (NLR), whose association with atherosclerosis has recently been frequently investigated, is a marker of inflammation.[5] The platelet-to-lymphocyte ratio (PLR) is used as a biomarker in atherosclerosis.[6] Also, platelets play a leading role in thrombosis, and increased mean platelet volume (MPV) has been found to be associated with negative consequences in cardiovascular diseases. Mean platelet volume-to-lymphocyte ratio (MPVLR), a relatively newer inflammatory biomarker than others, has also been investigated in some studies and has been shown to predict adverse cardiovascular outcomes.[7,8] In addition, high C-reactive protein (CRP) levels and low albumin levels are inflammatory biomarkers and CRP-to- albumin ratio (CAR) is a valuable prognostic marker of heart disease.[9,10]

Previous studies have investigated the importance of NLR, PLR or CAR in SVG diseases, but no study has yet been conducted that compares and evaluates all these markers simultaneously. In this study, the relationship between NLR, PLR, MPVLR and CAR and the development of SVG disease was investigated.

Patients and Method

Study Population: Between January 2017-September 2020 who underwent coronary angiography due to stable angina patient data were collected. Three hundred and fourteen patients who had CABG operation involving SVG were enrolled in the study. Coronary angiography indication was made according to the presence of typical angina despite maximal anti-ischemic and antianginal medical therapy or positive non-invasive screening tests for myocardial ischemia. Coronary angiography images were evaluated by 3 different cardiologists. Patients were divided into two according to whether there was ≥50% stenosis in SVG. The criteria for not receiving the study were as follows: inflammatory disease, active infection, hematologic disorders, malignancy, connective tissue disease, advanced liver disease, receiving dialysis and thyroid diseases. Transthoracic echocardiography were performed in all patients. The patients and their laboratory data were evaluated separately with their anamnesis and physical examination. The ethics committee approval of the study was obtained from the local university board with the application dated 28.01.2021 and numbered 21-KAEK-007.

Demographic and laboratory data: Routine biochemical datas were calculated and evaluated with the Coulter LH-780 Hematology Analyzer (Beckman Coulter, Inc, California). Hemogram panel (white blood cell, neutrophil, platelet, MPV etc.) and albumin, CRP were measured at the time before the elective coronary angiography. The PLR was defined as the ratio of the platelet count to the lymphocyte count, the NLR was defined as the ratio of the neutrophil count to the lymphocyte count, and the MPVLR was evaluated as the ratio of the MPV to the lymphocyte count, in CAR calculation, the method of ratio of CRP (mg/dL) to albumin (g/dL) and then multiplying the result by 100 was used. The other biochemical parameters were performed using appropriate methods. Hypercholesterolemia is defined as a previous diagnosis of hypercholesterolemia and being under statin treatment or having an LDL value above 130 mg/dL. Diabetes mellitus and hypertension were defined as receiving appropriate medical therapy for the treatment of these diseases. Also, a fasting blood glucose ≥126 mg/dL in a few consecutive values or >200 mg/dL in any time period was considered as diabetes mellitus. The presence of hypertension was accepted in patients whose repetitive blood pressure ≥ 140/90 mmHg. The patient was defined as being a smoker at the time of admission or smoking in the previous 6 months.

Echocardiographic Examination: All echocardiographic examinations (EPIQ 7, Amsterdam, Philips, Netherlands) were performed using a 2.5-3.5 MHz transducer with all participants. Evaluations were made in the presence of at least two cardiologists, in accordance with the criteria of the American Society of Echocardiography. Left ventricular ejection fraction (LVEF) was evaluated by Simpson method.[11]

Angiographic Evaluation: Coronary angiography (General Electric Optima; Wisconsin, ABD) was performed via the radial/femoral route using the standard Judkins technique and was examined by two experienced angiographers. All images were calibrated with a guide catheter (6-7 french). SVGs were evaluated from at least 2 different angles following contrast material injection. Thus, the patients included in the study; those with less than 50% stenosis in the SVG and those without less than 50% stenosis were divided into 2 groups.

Statistical Analysis: Statistical evalution of the data was done using the SPSS 21.0 (SPSS INC, Illinois, USA). The probability value of $p < 0.05$ was taken in the tests for statistical significance. Student-T test was used to evaluate parametric data and Mann-Whitney U test was used to evaluate nonparametric data. Categorical variables were evaluated by Chi-square test. The Kolmogorov-Smirnov test was used

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to evaluate the normality of the data and was verified on all data. Receiver-operating characteristic (ROC) curves were estimated for NLR, PLR, MPVLR, and CAR. ROC analysis was used to determine the cut-off values of PLR, NLR, MPVLR, and CAR in predicting SVG disease.

Results

Three hundred fourteen patients presenting 'with stable angina pectoris were' included in this study. Mean age of the patients in the study was 64.1 (±9.5) years and 28.6% of patients were female. There was ≥50% stenosis in SVG in 159 of the patients in the study. Table 1 shows the clinical data and demographic information of the patients.

İn Table 2, laboratory data of the patients are given comparatively. In line with these data, CAR and MPVLR values were also higher in the group with ≥50% stenosis in SVG, which was highly statistically significant (respectively 3.2 (0.9-4.4) vs 9.1 (4.2-16.8); p<0.001 and 3.64 (0.43) vs 4.53(0.68); p<0.001).

Figure 1 shows MPVLR, CAR, PLR, NLR roc curves to foresee significant stenosis in SVG. The AUC of CAR was the highest of all parameters (0.864, p<0.001) in predicting significant stenosis in the SVG, with 82% sensitivity and 72% specificity. It was found that the AUC of MPVLR was significantly higher than both AUC of NLR (0.795 vs 0.680, p < 0.001) and PLR (0.795 vs 0.584, p<0.001) for predicting significant stenosis in SVG. According to the this data MPVLR value of >4.53 could be used as a predictor of >%50 stenosis in SVG with a sensitivity of %80 and a specificity of %66.

In univariate analyses (Table 3), ≥50% stenosis in SVG was positively and significantly correlated with lymphocyte count (p <0.001), hemoglobin (p <0.001), neutrophil count (p <0.001), MPVLR (p <0.001), and CAR (p <0.001). ≥50% stenosis in SVG was associated with CAR and MPVLR in univariate logistic regression analysis (table 3). When 'multivariate regression analysis results are evaluated, CAR and MPVLR were also identified as an independent predictor for ≥50% stenosis in SVG (OR 1.096, 95%CI 1.054 to 1.132 and OR 1.536, 95%CI 1.206-1.635) (Table 3).

Discussion

This study is the first study comparing NLR, PLR, MPVLR, and CAR that predict SVG disease in patients with CABG

Table 1. Baseline characteristics of the study groups

Variables	<50% stenosis in SVG n = 155	≥50% stenosis in SVG n =159	P Value
Age, years	63.5)9.31)	64.8)9.72)	0.068
Female, % (n)	30.30 (47)	27 (43)	0.210
BMI, kg/m2	27.50)4.8)	27.60)3.84)	0.804
Smokers, % (n)	41.29 (64)	45.91 (73)	0.389
Diabetes Mellitus, % (n)	45.80 (71)	61.63 (98)	<0.001
Hypertension, % (n)	66.45 (103)	76.10 (120)	0.005
Hyperlipidemia, % (n)	72.90 (113)	76.72 (122)	0.402
Time after CABG, months	64.40)37.42)	71.30)26.43)	0.192
LVEF, %	45.10)7.1)	54)5.8)	<0.001
Aspirin, % (n)	80 (124)	84.9 (135)	0.194
P2Y12 inhibitors, % (n)	32.25 (50)	28.93 (46)	0.508
Statins, % (n)	63.87 (99)	59.11 (94)	0.298
Beta-blockers, % (n)	83.87 (130)	86.79 (138)	0.405
ACEI/ARB, % (n)	70.96 (110)	74.84 (119)	0.309
CCB, % (n)	19.35 (30)	18.23 (29)	0.852
Nitrate, % (n)	16.12 (25)	26.41 (42)	0.001
Ranolazine, % (n)	18.70(29)	16.98 (27)	0.698
Trimetazidine, % (n)	23.87 (37)	25.78 (41)	0.452

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft;CCB, calcium channel blocker; LVEF, left ventricular ejection fraction; SVG, safen vein graft

Table 2. Laboratory Characteristics of the Study Patients

Variables	<50% stenosis in SVG n = 155	≥50% stenosis in SVG n =159	P Value
Glukose (mg/dL)	162)92)	170)104)	0.391
Creatinine (mg/dL)	1.11)0.29)	1.18 (0.32)	0.052
WBC (x 103/mm3)	7.7)1.6)	8.1)2)	0.118
Lymphocyte count (x109/L)	2 (0.4)	1.8)0.5)	<0.001
Neutrophil count (x109/L)	4.2)0.9)	4.4)1.1)	0.048
Hemoglobin (g/L)	14.4)1.5)	12.9)1.5)	<0.001
Platelet count (x103/mm3)	266)61)	296)60)	0.154
MPV (fL)	7.5)0.4)	8.4)0.7)	<0.001
CRP (mg/dL)	0.12 (0.06-0.2)	0.48 (0.3-0.7)	<0.001
Albumin (g/dL)	4)0.2)	3.9 (0.1)	0.05
NLR	2)0.32)	2.4)0.69)	0.002
PLR	129)54)	153)6)	0.048
MPVLR	3.64)0.43)	4.53)0.68)	<0.001
CAR X100	2.6 (0.9-4.5)	9.1 (4.2-16.8)	<0.001
Low-density lipoprotein cholesterol (mg/dL)	142)19)	144)22)	0.624
HDL (mg/dL)	42)6)	39)5)	0.213
Triglycerides (mg/dL)	228)65)	211)61)	0.595

CAR, C-reactive protein to albumin ratio; CRP, C-reactive protein; MPV, mean platelet volume; MPVLR, mean platelet volume to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelets to lymphocyte ratio WBC: White blood cell count, HDL: High-density lipoprotein cholesterol.

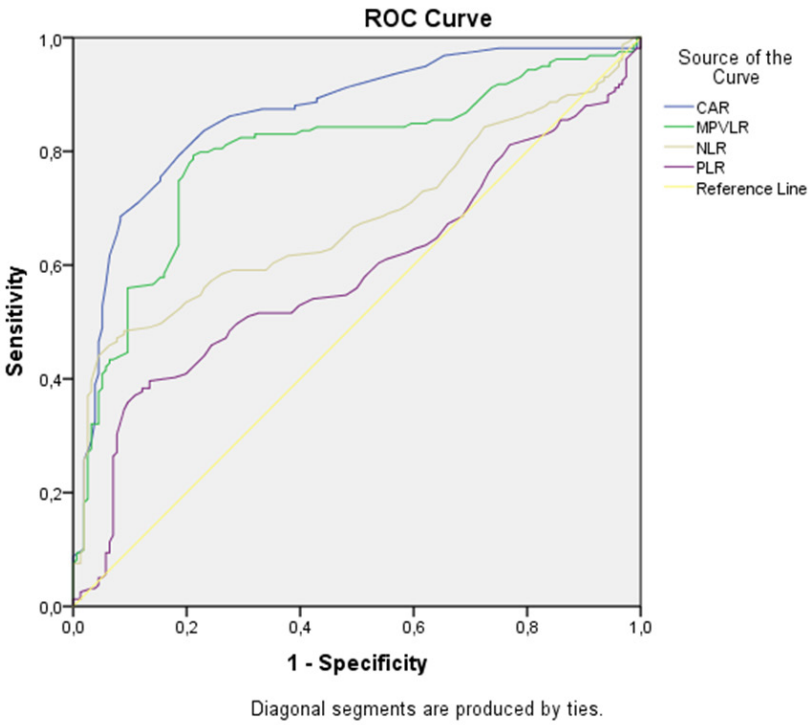

Figure 1. ROC curve of inflammatory parameters for predicting the presence of >50% stenosis in SVG.

Acta Medica Alanya 2023;7(3): 213-218
Doi: 10.30565/medalanya.1291772

Table 3. Univariate and Multivariate Predictors of ≥50% stenosis in SVG

Variables	Univariate	P value	Multivariate	P value
	OR, 95% CI		OR, 95% CI	
Hemoglobin	0.941 (0.923-0.959)	<0.001	0.949 (0.920-0.989)	0.007
Lymphocyte count	0.178 (0.136-0.236)	<0.001	0.317 (0.152-0.515)	<0.001
Neutrophil count	0.902 (0.886-0.962)	0.001	1.102(0.964-1.286)	0.064
Mean platelet volume	1.316 (1.118-1.1564)	<0.001	1.198 (0.954-1.339)	0.102
CAR	0.989 (0.942-1.036)	<0.001	1.096 (1.054-1.132)	<0.001
MPVLR	1.746 (1.488-1.920)	<0.001	1.536 (1.206-1.635)	<0.001
NLR	0.996 (0.958-1.210)	0.002	0.991(0.945-1.002	0.221
Female	0.802 (0.548-0.956)	0.008	0.903 (0.751-1.048)	0.003
Diabetes mellitus	0.928 (0.874-0.982)	0.001	0.938 (0.908-0.966)	0.006

CAR, C-reactive protein to albumin ratio; MPVLR, mean platelet volume to lymphocyte ratio; NLR, neutrophil to lymphocyte.

who underwent CAG due to stable angina. We found a more significant relationship between SVG with MPVLR and CAR than NLR and PLR in these patients. Saphenous vein graft diseases are a problem that negatively affects prognosis in patients with CABG. Therefore, it is important to identify inexpensive and easily detectable markers that predict SVG lesions. Many traditional risk factors for SVG lesions have taken place in the literature such as DM, HT. On the other hand, the relationship between inflammatory markers such as NLR, PLR, CRP, albumin with SVG has also been investigated in previous studies.[12,13] Determining which of these markers associated with the degree of SVG stenosis is more effective is important to eliminate time loss and confusion.

It is known that atherosclerosis is a chronic inflammatory process and therefore blood elements such as lymphocytes, neutrophils and platelets play a role in this process.[14] There are already numerous studies examining CRP in atherosclerosis and coronary artery disease.[15-16] The relationship between CAR and various coronary artery diseases has also been investigated in various studies and the relationship has been shown.[9,17]

Increased platelet activation has been shown to be associated with inflammation and therefore with atherosclerosis.[18] MPV is often used to evaluate immature platelets, and they are more prone to platelet aggregation and adhesion due to the substances they secrete.[19] Lymphocytes also play a major role in the inflammatory response, and lymphocyte count and activity affect and reflect the course of atherosclerosis and coronary artery disease.[20] PLR has been shown to be a useful marker in demonstrating systemic inflammatory response and in various forms of atherosclerosis and coronary artery disease.[21] In a previous meta analysis by Örnek et al., MPVLR was found to be associated with atherosclerosis and inflammation.[8] Increased NLR another systemic inflammatory is a marker and is associated with poor prognosis in coronary artery diseases.[22] CRP and albumin are also markers that have been shown to be associated with atherosclerosis, indicating a systemic inflammatory response.[23,24] CRP levels are expected to be high in inflammation, while plasma albumin levels are expected to be low.[25] Nutrition influences the state of inflammation and also some known infective parameters can be used as biomarkers for inflammation. Therefore, hypoalbuminemia may be a useful marker to indicate the severity of atherosclerosis. In addition, hypoalbuminemia leads to decreased antiplatelet activity, resulting in increased blood viscosity, leading to cardiovascular complications. studies have shown that serum albumin levels are inversely correlated with the severity of coronary artery stenosis in patients with myocardial infarction.[26] CAR has been shown in several studies to be a better marker than CRP and albumin in reflecting the severity of coronary artery stenosis and showing systemic inflammatory response.[27]

According to the results of this study, it was found that CAR and MPVLR reflect the severity of SVG stenosis better than PLR and NLR. Also found CAR to be the best indicator.

Limitations: Limitation of the study is that it is an observational, single-center study. Our research is multicenter and should be repeated with more participants. Another limitation of ours is that patients with acute coronary syndrome were not included in the study.

Conclusions: Patients who underwent CABG have major cardiovascular event risks in long-term follow-up. Identifying patients at the high risk of graft stenosis is challenging and also important in terms of future outcomes. In this context, inflammatory markers such as mentioned above have important role in preventing cardiovascular mortality and morbidity.

Conflict of Interest: The authors declare no conflict of interest related to this article.

Funding sources: The authors declare that this study has received no financial support.

Ethics Committee Approval: In this study,national and international ethical rules are observed.

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Peer-review: Externally peer reviewed.

Acknowledgement: Authors, thanks to parents for their contribution.

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