J Surg Med. 2022;6(2):149-153.
DOI: 10.28982/josam.1055846

Journal of Surgery and Medicine
e-ISSN=2602-2079

Effect of systemic immune inflammation index on symptom development in patients with moderate to severe carotid stenosis

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Ethics Committee Approval
The study was approved with the protocol of Bursa YüksekİhtisasTraining and Research Hospital Clinical Research Ethics Committee dated 28.04.2021 and numbered 2011-KAEK-25 2021/04-01.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2022 February 4

Abstract

Background/Aim: Recent studies have shown that various inflammatory parameters obtained from routine blood tests can be used in the diagnosis and follow-up of cardiovascular diseases. Stroke is the second most common cause of death in the world. In this study, we aimed to investigate the role of systemic immune inflammation index (SII) value in predicting symptom development in patients with moderate to severe carotid artery stenosis (CAS).
Methods: Patients between the ages of 41 and 94 with moderate to severe CAS who were followed up and treated electively in our clinic between October 01, 2016 and October 31, 2021 were included in this retrospective observational cohort study. A total of 314 consecutive patients were included in the study. The patients were divided into two groups as asymptomatic (Group 1) and symptomatic group (Group 2).
Results: There were 245 and 69 patients in Groups 1 and 2, respectively. The median ages of patients in Groups 1 and 2 were 62 (41-86) years and 69 (49-94) years, respectively (P<0.001). In multivariate analysis, advanced age (OR: 1.692 CI 95%: 1.150-2.398 P=0.012), hypertension (OR: 1.114, CI 95%: 1.080-1.866, P=0.036) and SII (OR: 1.954, CI 95%: 1.090-2.942, P<0.001) values were determined as independent predictors of symptom development in patients with moderate-serious carotis artery stenosis. There was no statistically significant difference between the groups in terms of body mass index, gender, smoking, diabetes mellitus and chronic obstructive pulmonary disease rates (P>0.05 for all).
Conclusion: In this current study we demonstrated that high SII value detected in asymptomatic patients with stenosis of 50% or more in the carotid arteries may be a useful marker to predict symptom development.

Keywords: Inflammation, Carotid artery, Stenosis, Cerebrovascular event, Blood cells

How to cite: As AK, Abanoz M, Ozyazicioglu AF. Effect of systemic immune inflammation index on symptom development in patients with moderate to severe carotid stenosis. J Surg Med. 2022;6(2):149-153.

Introduction

Stroke is the second most common cause of death in the world [1]. Considering the etiology of stroke, it is seen that carotid artery stenosis causes stroke at a rate of approximately 30% [2]. In the presence of carotid artery stenosis (CAS), the symptoms are not always evident. It is of vital importance to recognize these patients and to predict the development of symptoms before the occurrence of conditions with high morbidity and mortality such as stroke.

Both the investigation of the etiopathogenesis of cardiovascular diseases, the examination of the progression of these diseases and the search for prognostic markers that can be used as biomarkers on these issues have been the subject of many recent studies [3]. Recent studies have shown that various inflammatory parameters obtained from routine blood tests can be used in the diagnosis and follow-up of cardiovascular diseases [4]. Two of the most important parameters checked for this purpose are the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR). There are studies showing that these parameters have a prognostic value for cardiovascular diseases [5, 6]. The systemic immune inflammation index (SII) value obtained by formulating neutrophil, lymphocyte and platelet values was determined in a recent study as an independent predictor of poor outcomes after coronary bypass operations [7]. In this study, we aimed to investigate the role of SII value in predicting symptom development in patients with moderate to severe CAS.

Materials and methods

Ethical approval for this study was obtained from Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee with date 28.04.2021 and number 2011-KAEK-25 2021/04-01. Patients between the ages of 41 and 94 with moderate to severe CAS who were followed up and treated electively in our clinic between October 01, 2016 and October 31, 2021 were included in this retrospective observational cohort study. Patients with a previous history of endovascular or surgical intervention to the carotid artery, a known systemic inflammatory disease, stroke with permanent sequelae, a history of intracerebral hemorrhage and hematological disease were excluded from the study. A total of 314 consecutive patients were included in the study. The data of patients were obtained from the hospital registry system. Demographic data and additional diseases (age, sex, smoking, hypertension, diabetes mellitus, hyperlipidemia, presence of chronic obstructive pulmonary disease) and routine laboratory data (hemogram [White blood cell (WBC)], neutrophil, lymphocyte, NLR, PLR, SII), biochemistry (creatinine, urea, [C-reactive protein (CRP)], albumin) were recorded.

The patients were divided into two groups as asymptomatic Group 1 and symptomatic group 2, and the factors affecting symptom development were examined.

Evaluation of carotid artery stenosis

All patients included in the study were first evaluated with Doppler ultrasonography (DUSG). All patients had 50% or more stenosis in the DUSG evaluation. These patients were then evaluated with digital subtraction angiography (DSA). Angiographic evaluations were performed according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) classification [8]. All patients with 50% or more lesions were included in the study.

Calculation of SII value

Blood parameters were obtained from the blood samples taken from the peripheral venous structures of all patients at the time of admission. SII values were obtained from the data in these parameters using the formula below.

SII=Platelet count (10^3/μL) x Neutrophil (10^3/μL) / Lymphocyte (10^3/μL)

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk,NY, USA). Data were expressed in mean (standard deviation (SD)) or median (minimum- maximum) or number and frequency. The Student's t-test was used for numerical values with normal distribution, while the Mann-Whitney U test was used for numerical data without normal distribution. The chi-square test was carried out to compare categorical variables. A multivariate logistic regression analysis was utilized to evaluate significant parameters in the univariate analysis for predicting symptomatic patients. The receiver operating characteristic (ROC) curve was used to evaluate the predictive value SII for symptoms and the area under the curve (AUC) was calculated. A *P*-value of <0.05 was considered statistically significant.

Results

There were 245 and 69 patients in Groups 1 and 2, respectively. The median ages of patients in Groups 1 and 2 were 62 (41-86) years and 69 (49-94) years, respectively ($P<0.001$). There was no statistically significant difference between the groups in terms of body mass index, gender, smoking, diabetes mellitus and chronic obstructive pulmonary disease (COPD) rates ($P>0.05$ for all). Hypertension and hypercholesterolemia rates were significantly higher in Group 2 ($P<0.001$ and $P=0.030$, respectively) (Table 1).

Table 1: Demographic and laboratory features of the patients

Variables	Group 1 (N= 245)	Group 2 (N= 69)	*P*-value
Age (years)	62 (41- 86)	69 (49- 94)	<0.001‡
Male gender, n(%)	139 (56.7%)	38 (55.1%)	0.806*
Smoking, n (%)	63 (25.7%)	21 (30.4%)	0.434*
BMI (kg/m^2)	26.8 (23.7- 36)	27.1 (23- 35)	0.197
Hypertension, n (%)	150 (61.2%)	59 (85.5%)	<0.001*
Diabetes mellitus, n (%)	52 (21.2%)	17 (24.6%)	0.545*
Hypercholesterolemia, n (%)	54 (22%)	24 (34.8%)	0.030*
COPD, n (%)	37 (15.1%)	13 (18.8%)	0.453*
White blood Cell (10^3/μL)	7.2 (4.6- 10.1)	7.7 (4.2- 9.9)	0.319‡
Hematocrit (%)	38.5 (34- 56)	41.2 (36- 54)	0.128‡
Platelet (10^3/μL)	272 (156.4- 450)	284 (144.8- 398)	0.071‡
Neutrophil (10^3/μL)	4.1(2- 9.6)	4.6 (1.9- 8.8)	0.094‡
Lymphocyte (10^3/μL)	1.9 (1- 4.1)	1.7 (0.9- 3.7)	0.119‡
NLR	2.1 (1.1- 6.1)	2.9 (1.2- 8.4)	<0.001‡
PLR	151.2 (121-238)	168.4 (119- 240)	<0.001‡
SII	690 (534-2328)	1190 (625- 2990)	<0.001‡

* Chi-square test, ‡Mann Whitney U test (Data is expressed as median (minimum-maximum)), BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, SII: Systemic immune inflammation index

Laboratory values of the patients are presented in Table 1. There was no difference between the groups in terms of hematocrit, platelet, white blood cell, neutrophil and lymphocyte levels ($P>0.05$ for all). NLR, PLR and SII values were significantly higher in Group 2 ($P<0.001$, for all).

Univariate and multivariate logistic regression analysis was applied to predict parameters supporting symptom development in patients with moderate- seriosus CAS (Table 2).

Table 2: Logistic regression analysis to identify factors affecting symptom onset in patients with moderate-serious carotis artery stenosis

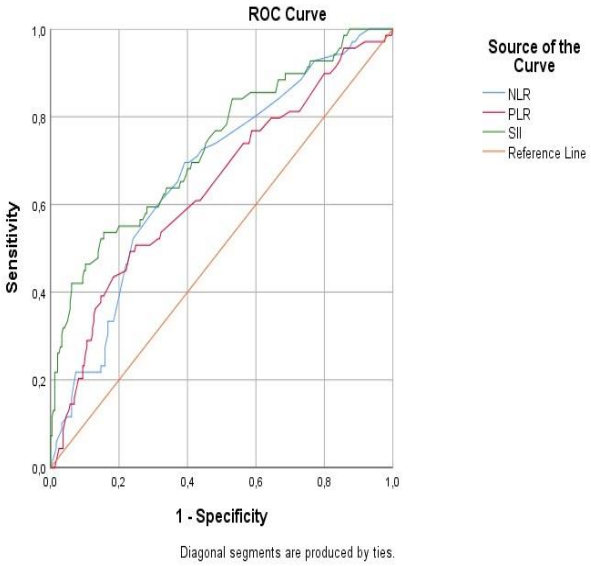
Variables	Univariate analysis			Multivariate analysis		
	P-value	Exp(B) Odds Ratio	95% C.I. Lower Upper	*P*-value	Exp(B) Odds Ratio	95% C.I. Lower Upper
Age	<0.001	1.992	1.364-2.869	0.012	1.692	1.150-2.398
Hypertension	<0.001	1.794	1.218-2.887	0.036	1.114	1.080-1.866
Hypercholesterolemia	0.034	0.790	0.660-0.894	0.347	1.112	0.796-1.236
Diabetes Mellitus	0.590	0.694	0.554-1.196	--	--	--
NLR	<0.001	1.125	1.096-1.956	--	--	--
PLR	<0.001	0.896	0.676-0.994	--	--	--
SII	<0.001	2.498	2.164-3.495	<0.001	1.954	1.090-2.942

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet lymphocyte ratio, SII: Systemic immune inflammation index

In univariate analysis, advanced age (OR [odds ratio]: 1.992, 95% CI [confidence interval]: 1.364-2.869, *P*<0.001), hypertension (OR: 1.794, 95% CI: 1.218-2.887, *P*<0.001), NLR (OR: 1.125, 95% CI: 1.096-1.956, *P*<0.001), PLR (OR: 0.896, 95% CI: 0.676-0.994, *P*<0.001), and high SII (OR: 2.498, 95% CI: 2.164-3.495, *P*<0.001) values were found to be significantly correlated with the development of symptom in patients with moderate-serious carotis artery stenosis. In multivariate analysis, advanced age (OR: 1.692 CI 95%: 1.150-2.398 *P*=0.012), hypertension (OR: 1.114, CI 95%: 1.080-1.866, *P*=0.036) and SII (OR: 1.954, CI 95%: 1.090-2.942, *P*<0.001) values were determined as independent predictors of symptom development in patients with moderate-serious carotis artery stenosis.

ROC curve analysis was applied to predict parameters supporting symptom development in patients with moderate-serious CAS. In this analysis, the cut-off value for preoperative NLR was 2.5 (AUC: 0.673, 95% CI: 0.603-0.743, *P*<0.001, 61.4% sensitivity and 58.7% specificity), cut-off value for PLR was 158.2 (AUC: 0.642, 95% CI: 0.566-0.718, *P*<0.001, 59.8% sensitivity and 56.6% specificity) and cut-off value for SII was 896.9 (AUC: 0.733, 95% CI: 0.663-0.803, *P*<0.001, 71.2% sensitivity and 61.7% specificity) (Figure 1).

Figure 1: Receiver operation characteristic (ROC) curve and area under the curve (AUC) for NLR, PLR and SII to predictsymptom onset in patients with moderate-serious carotis artery stenosis



Discussion

Carotid artery stenosis (CAS) has a high morbidity and mortality and it has an important place among cardiovascular diseases in which atherosclerosis plays a role in its etiology. CAS symptoms usually occur due to embolizations caused by plaque structure. These symptoms can be seen as amaurosis fugax, syncope and transient ischemic attack (TIA) or they can appear as stroke and death [9]. The most important parameter in making the decision to intervene in patients is the presence of symptoms. If the patient is asymptomatic, even if there is 90% or less stenosis, it is followed up medically. However, for patients with symptoms and radiologically detected stenosis exceeding 50%, there is an indication for invasive intervention [10]. In this study, we investigated possible factors that may affect the development of symptoms in patients with moderate to severe CAS. Our study results showed that advanced age, hypertension, and SII were independent predictors of symptom development in these patients.

Inflammation has a very important role in the development of cardiovascular diseases [11]. In fact, recent studies show that the risk of developing cardiovascular disease decreases with suppression of inflammation and immune-modulation treatments [4]. In addition, there are some blood parameters that can be routinely checked in practice in terms of showing vascular inflammation. These are mainly platelets, neutrophils and lymphocytes [12]. Neutrophils have a role in the development of atherosclerosis, plaque rupture, plaque remodeling and reperfusion injury. The number and density of neutrophils in the plaque causing stenosis can reveal both the risk of plaque rupture and the high probability of microembolization [13-15].

Platelets play a very active role both in the early stage of chronic vascular pathology associated with atherosclerosis and in plaque rupture [16, 17]. Platelets invading the atherosclerotic plaque cause leukocytes to proliferate through direct receptor interactions, and cause an increase in leukocyte activity through the pathways they activate. The role of platelets in CAS was also examined, and the relationship between mean platelet volume (MPV) and platelet distribution width (PDW), which are platelet activation markers and the rate of stenosis in the carotid artery was revealed [18, 19]. Similarly, there are some studies such as monitoring the severity of carotid artery disease and the development of symptoms, and predicting the development of stroke with the PLR value [20, 21]. In addition to platelets, it has been shown that neutrophils and lymphocytes play a decisive role in the development of symptoms, especially in stroke, in patients under medical follow-up and in patients undergoing carotid endarterectomy [22]. In our study, we found that NLR and PLR values were correlated with symptom development.

The SII value has recently been used as a prognostic marker in the clinical follow-up of some diseases. The SII value obtained by a formula from platelet, lymphocyte and neutrophil values was formerly used to evaluate the prognosis of malignancies [23-25]. After its weak efficacy in predicting malignancy-related clinical outcomes, its relationship with cardiovascular diseases, another inflammation-related condition, was investigated. In cases of heart failure, infective endocarditis, acute myocardial infarction, major cardiovascular adverse

events, and death from cardiovascular disease, SII was found to be significantly successful in predicting prognosis [7, 26-28]. In our study, we showed that a high SII value is an independent predictor of symptom development in patients with moderate to severe CAS.

Large multicenter studies show that interventions for stenosis, especially carotid endarterectomy (CEA), have significant advantages over medical treatment in symptomatic patients with CAS of 50% or more [29, 30]. However, in symptomatic patients, it is known that the main factor causing the development of symptoms is embolizations originating from the unstable plaque structure and the main mechanism causing these embolisms, especially plaque rupture, is inflammation occurring on the plaque [31]. In this case, it is very important to examine the plaque structure and detect the presence of inflammation in the plaque in asymptomatic patients. Being able to detect inflammation in the plaque will enable to predict the presence of carotid stenosis before the patient develops symptoms. In studies conducted for this purpose, magnetic resonance (MRI) imaging was used to detect the structure of atherosclerotic plaque to predict the risk of developing cerebrovascular attack. Plaque morphology has been shown to be directly related to embolization risk [32, 33]. In addition, it has been reported that it is possible to detect the existing inflammation on the plaque with advanced examinations such as 18 F-fluorodeoxyglucose-Positron emission tomography (18FDG/PET), thus providing a risk prediction in asymptomatic patients [34, 35]. As can be seen, detection of inflammation in the presence of atherosclerotic plaque is of vital importance. Our study showed that there is a significant relationship between inflammation and symptom development due to carotid artery stenosis, similar to previous studies. Unlike previous studies, we showed that a risky patient group can be detected without the need for expensive and advanced examinations such as MRI, 18FDG/PET, which are used for imaging plaque morphology or for radiological detection of inflammation. Inflammatory data such as SII obtained by cheaper and easily accessible blood parameters provide a prediction of risk in asymptomatic patients with 50% or more carotid artery stenosis.

Limitations

The most important limitations of our study are being single-centered, retrospective, and having low number of patients. More comprehensive publications with larger numbers of patients are needed to support existing data.

Conclusions

In this study, the relationship between SII and CAS-related symptom development was investigated in the literature for the first time. In the light of the analyzes performed, it has been shown that high SII values detected in asymptomatic patients with stenosis of 50% or more in the carotid arteries are an independent predictor of symptom development. This predictive ability will provide a great advantage to the physicians in terms of taking the necessary precautions before the development of adverse outcomes such as morbidity and mortality for the sensitive patient group mentioned.

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