Original Article

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The Predictive Value of the Systemic Immune Inflammation Index for one-year Major Adverse Cardiovascular and Cerebrovascular Events in Patients with Coronary Artery Disease who Underwent Carotid Stenting

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Abstract

Aim: The study aimed to examine and contrast the ability of a systemic immune inflammation index (SII) to predict major adverse cardiovascular and cerebrovascular events (MACCEs) that occurred one year after carotid artery stenting (CAS) in patients with established coronary artery disease (CAD).

Methods: The data of 157 patients with CAD who underwent CAS between April 2015 and January 2020 were retrospectively evaluated. Before the index procedure, blood samples were taken and SII values were calculated and analyses were performed. Measurement of the degree of carotid stenosis was performed according to the North American Symptomatic Carotid Endarterectomy Study. The patients were split into two groups based on whether they experienced MACCEs or not.

Results: One hundred-fifty seven patients made up the study population, and their average age was 66.9 +/- 8.7 years. Multivariate Cox regression analysis revealed platelet to lymphocyte ratio (PLR) [hazard ratio (HR): 1.006, p=0.033] and SII [HR: 1.000, p=0.027] independently predicted the MACCEs but neutrophil to lymphocyte ratio did not. Compared with other inflammatory parameters evaluated in the study including C-reactive protein, platelets, and PLR, SII had a better and adequate discriminatory performance for MACCEs (area under the curve: 0.762, p<0.001). An SII ≥615 predicted the one-year MACCEs with 81% sensitivity and 63% specificity.

Conclusion: High SII may be a helpful diagnostic for CAS patients with CAD who need to be risk-stratified.

Keywords: Coronary artery disease, carotis artery stenting, systemic immune inflammation index

Introduction

Atherosclerosis is a systemic disease that is not confined to a single artery region and affects arteries in different regions simultaneously, but with varying degrees of progression. The prevalence of major carotid lesions in patients undergoing coronary artery bypass grafting has been reported as high as 8% to 14%. Co-existing carotid artery stenosis and coronary artery disease (CAD) are prevalent. On the other hand, the prevalence of CAD in patients undergoing carotid endarterectomy (CEA) has been reported to be between 40% and 50% (1). In addition, there is literature data that the co-existence of significant CAD and carotid stenosis is an unfavorable prognostic factor in patients undergoing interventional treatment of the carotid artery stenosis (2,3).

Carotid artery stenosis constitutes an important part of ischemic stroke. Patients with symptomatic carotid artery stenosis can significantly reduce their risk of having an ischemic stroke by undergoing invasive CEA or carotid artery stenting (CAS) treatments. In-hospital and long-term unfavorable outcomes that may occur after CAS can be affected by many factors such as diabetes, smoking, age, underlying CAD, chronic kidney failure and lung diseases, and symptomatic condition, along with technical

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and procedural parameters (4). Inflammation has a crucial part in all stages of the atherosclerotic process, including start and progression, as shown by a wealth of experimental and clinical data, which further supports the notion that atherosclerosis is typically recognized as a chronic inflammatory disease (5). C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are a few inflammatory indicators linked to poor outcomes in CAD and carotid artery stenosis patients (4). Additionally, it has been suggested that the NLR and PLR are also associated with symptomatic internal carotid artery (ICA) stenosis, can predict atherosclerosis progression in carotid artery disease, and carotid stenosis tends to become symptomatic with post-CAS morbidity (6,7). Based on platelet, neutrophil, and lymphocyte counts, systemic immune inflammation index (SII), a recently developed inflammatory marker, evaluates the patient's inflammatory and immune status simultaneously. It has also been suggested to be associated with adverse outcomes in several malignancies, cardiovascular disorders such as CAD, and chronic heart failure and in patients undergoing CAS. However, to our knowledge, there is no specific literature yet on patients with proven CAD who underwent CAS. We also know that examination of each risk factor for survival in patients with CAD undergoing CAS is incredibly rare because of the dearth of literature data and the highly diverse patient group in individual publications (8). Considering everything said above, there is still debate over the prognostic factors for these patients' survival, and more study is required.

Considering this, the current study examined the predictive value of the SII in patients who underwent CAS and had a history of CAD.

Materials and Methods

Study Population

In this observational analysis, we evaluated the medical records of 195 consecutive patients with proven CAD at our tertiary center for CAS between April 2015 and January 2020. The following inclusion criteria were used for the study: (1) Those who have documented stable CAD with a history of PCI or CABG or with at least 50% stenosis in at least one vessel, (2) age ≥18 years old, (3) having symptomatic ICA stenosis (50-99%) or asymptomatic ICA stenosis (≥60-99%) by digital subtraction angiography.

Patients were treated as symptomatic if they had recently experienced a transient ischemic attack (TIA), retinal ischemic event, or an ischemic stroke that originated from a restricted carotid artery. Measurement of the degree of carotid stenosis was performed according to the North American Symptomatic Carotid Endarterectomy Study (9).

Those with acute coronary syndromes such as unstable angina or myocardial infarction (n=7), uncontrolled diabetes mellitus defined as glucose >300 mg/dL (n=6), coagulopathy (n=0), active infection (n=5), who are pregnant or in the perinatal period (n=0), a severe comorbid disease with a life expectancy of <1 year (n=3), those with previous CAS or CEA (n=6), and those with missing data (n=11) was not included in the study. Finally, 157 of 195 patients stayed and were a part of the study cohort.

Clinical and Laboratory Assessment

The demographic and biochemical parameters of the patients were evaluated and noted. Blood values taken from venous blood samples at hospitalization were recorded from health reports and were collected in standardized EDTA tubes for total blood count analysis and measurements. Absolute neutrophil count/absolute lymphocyte count and absolute platelet count/absolute lymphocyte count were used to calculating NLR and PLR, respectively. Systemic immunological inflammation index was calculated using the following formula: NLR x total platelet count in peripheral blood. Acceptable blood pressure readings were those with a diagnosis of hypertension, anti-hypertensive drug use, or mean readings between 140 and 90 mmHg. Diabetes mellitus, the use of hypoglycemic medications, such as insulin therapy, or blood glucose levels of less than 126 mg/dL during fasting and/or 200 mg/dL after meals were identified. Smoking was defined as current smoking in the past 6 months. Transient ischemic attacks were classified as TIAs attacks (focal cerebral ischemia) that are not accompanied by persistent cerebral infarction (10). In addition, an episode of neurological impairment brought on by a focal cerebral, spinal, or retinal infarction was referred to as an ischemic stroke (11). These embolic incidents are the medical symptoms of the illness. A neurologist made the clinical diagnosis of TIA or stroke, and imaging modalities were used to confirm the diagnosis (magnetic resonance imaging with or without computerized tomography angiography).

CAS Protocol and Medical Treatment

All patients received acetylsalicylic acid (ASA) 100 mg and clopidogrel 75 mg 5 days before stenting. Unfractionated heparin (100 units/kg) was administered to provide prolongation of activating clotting time to 250-300 s in all processes. All CAS procedures were performed under local anesthesia using an 8 F introducer sheath via the femoral artery. Diagnostic carotid angiography was performed, and a size 8 F guiding catheter was used for the intervention. Carotid artery anatomy, location and degree of stenosis, and intracranial vascular anatomy of

the carotid artery were evaluated. Self-expanding stents were used for treating carotid artery stenosis in all study cohorts. In all study cohorts, distal filters were used to protect against emboli, but just like with predilatation and post-dilatation, distal filter use was left to the operator's discretion. To prevent hypotension and bradycardia before balloon inflation, intravenous atropine (0.5-1 mg) was usually given to the patients if predilatation and/or post-dilatation were planned. Following the last round of imaging, all patients were sent to the critical care unit, where they underwent at least 48 h of intense observation. For the first six weeks, all patients were instructed to take ASA 100 mg/day and 75 mg/day of clopidogrel, followed by 100 mg/day of aspirin for the rest of their lives.

Primary Endpoint

Initially, the goal was to determine the presence of major adverse cardiovascular and cerebrovascular events (MACCEs) defined as cardiovascular death (comprising myocardial infarction, significant cardiac arrhythmia, heart failure, and any stroke), non-fatal myocardial infarction, or non-fatal cerebrovascular accident (ischemic stroke or TIA) during the 1 year follow-up period. A stroke was defined as a neurological deficit lasting more than 24 h. A TIA was defined as a new onset or exacerbation of pre-existing neurological symptoms with complete resolution within 24 h. The diagnosis of myocardial infarction was based on the 4th universal definition of myocardial infarction. Major adverse cardiovascular and cerebrovascular events-related information was obtained using the hospital records or the national death notification system or by follow-up interviews with patients or their relatives (directly or by telephone). An impartial group of physicians who were not aware of the patients' pre-event test results independently reviewed each event. Patients with and without MACCEs were separated into two groups within the study cohort.

Compliance with Ethical Standards

Because of the retrospective nature of our investigation, written informed consent from participants could not be acquired; however, the Ethics Committee of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (date: 28.09.2022, approval no: 175-2022) accepted the study methodology.

Statistical Analysis

The continuous variables were given as means ± standard deviations (if normal distribution) and medians (interquartile ranges) (if not normal distribution). The categorical variables were given as percentages. The chi-squared (χ^2) test was used to compare the categorical variables between the groups. The Kolmogorov-Smirnov test was used to assess whether the variables were normally distributed. The Student's t-test or Mann-Whitney U test was used to compare the continuous variables between the groups according to whether they were normally distributed or not. To determine the independent predictors of one-year MACCEs, variables found to be associated at a $p<0.05$ level according to univariate analysis, were included in the multivariate Cox regression analysis with the results reported as the hazard ratios (HR) and 95% confidence intervals (CI). Receiving operating characteristic (ROC) curve analysis was carried out to see whether there was an additional benefit of using the SII index to identify the MACCEs as well as to assess the sensitivity and specificity of the SII index and its cutoff value for MACCEs. Additionally, using ROC analysis and a 95% CI, the area under the curve (AUC) or C-statistic was employed as a measure of the discrimination ability and predictive accuracy of SII, PLR, platelets, and CRP. Predictive power was classified as "good" if the AUC was 0.70 or greater and as inadequate if the AUC was less than 0.70 (12). Time-to event data were presented graphically by using the Kaplan-Meier survival curves and long-rank tests. The threshold of statistical significance was established at $p<0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences version 24.0 software (IBM Corp., Armonk, NY, USA).

Results

A total of 157 patients made up the study population, with a mean age of 66.98.7 years. Of these, 114 (72.6%) were men. One-year MACCEs were observed in 41 (26.1%) patients, including 25 (15.9%) deaths, 11 (7%) non-fatal strokes or TIAs (7 of them within the first 30 days and 4 of them after 30 days), and 5 (3.2%) non-fatal myocardial infarction. The left ventricular ejection fraction (LVEF) was discovered to be considerably lower in the MACCE group in terms of clinical and demographic factors (p=0.007), although there was no statistical difference between the two groups for the metrics other than LVEF. When laboratory parameters were analyzed, patients with MACCEs had statistically higher CRP levels (p=0.001), higher platelet and neutrophil counts (p=0.002, and p=0.001, respectively), and higher neutrophil counts. Although the group with MACCEs tended to have low lymphocyte counts, this was not statistically significant (p=0.078). Additionally, the MACCEs group had greater inflammation-based scores than the other groups, including SII, NLR, and PLR (p=0.001 for all). Table 1 provides comprehensive information on the demographic, clinical, and laboratory characteristics of all research participants and comparisons between those who had and did not have MACCE. Considering the procedural parameters, it was observed that patients with MACCEs were more symptomatic (p=0.039), had higher carotid artery tortuosity (p=0.007), and had more open cell stenting (p=0.028).

The procedural characteristics of the study population are summarized in Table 2.

The factors independently associated with MACCEs in the univariate cox regression analysis are given in Table 3a. Also, to determine the independent predictors of MACCEs, we performed multivariable cox regression analysis by using variables that showed statistically significant associations in the univariate analysis. Since platelet, neutrophil, and lymphocyte counts are a part of the SII, NLR, and PLR, we believe that they may have a negative impact on the outcomes of the regression study. Four different models used multivariate cox regression analysis to predict MACCEs. While lymphocytes with a p-value >0.05 in the univariate analysis were excluded from the multivariate cox regression analysis, platelets and neutrophils were included in Model 1. On the other hand, Model 2 (NLR), Model 3 (PLR), and Model 4 (SII) cox regression analyses included scores based on inflammation.

Table 1. Baseline demographic, clinical and laboratory characteristics of study cohort

Parameters	All patients (n=157)	No-MACCEs (n=116)	MACCEs (n=41)	p-value
Age	66.9±8.7	66.4±8.3	68.2±9.5	0.263
Male, n (%)	114 (72.6)	83 (71.6)	31 (75.6)	0.616
BMI, kg/m^2	27.0±3.7	27.3±3.8	26.7±3.4	0.576
Hypertension, n (%)	107 (68.2)	81 (69.8)	26 (63.4)	0.449
Diabetes mellitus, n (%)	66 (42)	46 (39.7)	20 (48.8)	0.309
Hyperlipidemia, n (%)	96 (61.1)	68 (58.6)	28 (68.3)	0.275
Current smoker, n (%)	39 (24.8)	30 (25.9)	9 (22.0)	0.618
Family history, n (%)	54 (34.4)	41 (35.3)	13 (31.7)	0.673
PCI, n (%)	90 (57.3)	70 (60.3)	20 (48.8)	0.198
CABG, n (%)	51 (32.5)	33 (28.4)	18 (43.9)	0.069
Medical treatment, n (%)	19 (12.1)	16 (13.8)	3 (7.3)	0.274
Chronic renal failure, n (%)	33 (21)	24 (20.7)	9 (22)	0.865
COPD, n (%)	19 (12.1)	16 (13.8)	3 (7.3)	0.274
Atrial fibrillation, n (%)	37 (23.7)	29 (25.2)	8 (19.5)	0.401
LVEF, (%)	54.1±7.9	55.5±7.0	51.7±9.5	0.007
RAS bloker, n (%)	53 (33.8)	37 (31.9)	16 (39.0)	0.407
Statin usage, n (%)	57 (36.3)	45 (38.8)	12 (29.3)	0.276
Beta blocker, n (%)	56 (35.7)	40 (34.5)	16 (39.0)	0.602
CCB, n (%)	54 (34.4)	40 (34.5)	14 (34.1)	0.969
Laboratory parameters				
FBG, mg/dL, IQR	108.0 (95.0-148.0)	105.5 (94.0-140.3)	125 (97.5-159.5)	0.332
eGFR, mL/dk/1.73 m^2	79.4±24.3	80.3±22.2	77.0±29.6	0.469
CRP, mg/L, IQR	5.8 (2.6-11.4)	5.5 (2.3-9.9)	7.5 (3.3-24.9)	0.001
HDL-C, mg/dL	41.3±9.8	41.4±9.7	41.2±10.4	0.922
LDL-C, mg/dL	115.7±40.9	112.3±39.4	125.3±43.6	0.079
Triglyceride, mg/dL, IQR	141.0 (94.5-204.0)	142.0 (91.3-207.0)	137.0 (96.0-193.5)	0.617
Haemoglobin, g/dL	13.0±1.9	13.1±2.0	12.6±1.7	0.083
Platelet, 10^9/L	247.9±68.5	238.1±56.7	275.5±89.6	0.002
Neutrophil, 10^9/L, IQR	4.61 (3.80-6.23)	4.40 (3.80-5.78)	5.70 (4.23-7.97)	<0.001
Lymphocyte, 10^9/L, IQR	1.94 (1.48-2.40)	1.96 (1.56-2.40)	1.70 (1.30-2.23)	0.078
NLR, IQR	2.48 (1.98-3.52)	2.31 (1.90-3.0)	3.30 (2.39-4.63)	<0.001
PLR, IQR	124.8 (95.0-159.5)	117.0 (91.7-145.8)	152.0 (115.6-189.4)	<0.001
SII, IQR	595.3 (409.2-886.7)	534.0 (383.4-730.8)	925.3 (626.9-1182.5)	<0.001

Continuous variables were presented as means ± standard deviations if normally distributed and medians [interquartile ranges (IQRs)] if not normally distributed, while categorical variables were given as count and percentages. MACCEs: Major advers cardiovascular and cerebrovascular events, BMI: Body mass index; COPD: Chronic obstructive pulmonary disease, LVEF: Left ventricular ejection fraction, RAS: Renin anjiyotensin system, CCB, calcium channel blocker, FBG: Fasting blood glucose, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, SII: Systemic immune-inflammation index

In every multivariable model, LVEF, CRP, and carotid artery tortuosity were discovered to be independent predictors. Taking into account the inflammatory parameters other than CRP, high platelet count (HR= 1.005, p=0.010) in Model 1, high PLR (HR= 1.006, p=0.033) in Model 3, and elevated SII values (HR= 1.000, p=0.027) in Model 4, independently predicted the development of the MACCEs (Table 3a, b). The SII performed better and adequately than the other previously stated inflammatory indicators in our ROC curve analyses testing the predictive and discriminative potential of SII, PLR, platelet, and CRP in predicting the one-year MACCEs (AUC= 0.762, CI 95%: 0.673-0.850, p=0.001) (Figure 1). Systemic immunological inflammation index cut-off values of 615 and higher were also established, with a sensitivity and specificity of 81% and 63%, respectively. According to the established cut-off values (SII 615), the high-risk group had more adverse one-year outcomes, as seen by the Kaplan-Meier curves in Figure 2.

Table 2. Procedural parameters associated with development of the MACCEs

Parameters	All patients (n=157)	No-MACCEs (n=116)	MACCEs (n=41)	p-value
Symptomatic CAD, n (%)	124 (79.0)	87 (75.0)	37 (90.2)	0.039
Bilateral CAD, n (%)	33 (21.0)	23 (19.8)	10 (24.4)	0.538
Type 3 arcus aorta, n (%)	15 (9.6)	9 (7.8)	6 (14.6)	0.198
Tortuosity	28 (17.8)	15 (12.9)	12 (31.7)	0.007
Predilatation, n (%)	17 (10.8)	13 (11.2)	4 (9.8)	0.797
Postdilatation, n (%)	68 (43.3)	53 (45.7)	15 (36.6)	0.312
Distal EPD (filter), n (%)	100 (63.7)	73 (62.9)	27 (65.9)	0.738
Open cell stenting, n (%)	58 (36.9)	37 (31.9)	21 (51.2)	0.028
Closed cell stenting, n (%)	97 (61.8)	78 (67.2)	19 (46.3)	0.018
Access site complications, n (%)	8 (5.1)	4 (3.4)	4 (9.8)	0.114
CIN, n (%)	6 (3.8)	5 (4.3)	1 (2.4)	0.591
Restenosis, n (%)	3 (1.9)	3 (2.6)	0 (0)	0.298
Primary end-points				
Non-fatal stroke/TIA, n (%)	11 (7.0)	0 (0)	11 (26.8)	<0.001
Non-fatal MI, n (%)	5 (3.2)	0 (0)	5 (12.2)	<0.001
Death, n (%)	25 (15.9)	0 (0)	25 (61)	<0.001

Categorical variables were given as count and percentages. MACCEs: Major advers cardiovascular and cerebrovascular events, CAD: Carotid artery disease, EPD: Emboli protection device, CIN: Contrast-induced nephropathy, TIA: Transient ischemic attack, MI: Myocardial infarction

Table 3a. Without using inflammation-based ratings, univariate and multivariate Cox regression analysis revealed factors that were found to be independently linked with the MACCEs

Variables	Univariate HR (95% CI)	p	Model 1 Multivariate* HR (95% CI)	p
LVEF	0.962 (0.931-0.995)	0.023	0.948 (0.917-0.980)	0.002
CRP	1.006 (1.002-1.010)	0.007	1.008 (1.003-1.014)	0.004
Symptom	2.462 (0.877-6.906)	0.087	-	-
Tortuosity	2.139 (1.108-4.129)	0.023	2.462 (1.248-4.860)	0.009
OCS	1.792 (0.972-3.306)	0.062	-	-
Platelet	1.006 (1.002-1.009)	0.001	1.005 (1.001-1.010)	0.010
Nutrophil	1.143 (1.061-1.231)	<0.001	1.054 (0.963-1.154)	0.252
Lymphocyte	0.642 (0.384-1.073)	0.091	-	-
NLR	1.258 (1.132-1.398)	<0.001	-	-
PLR	1.008 (1.004-1.013)	<0.001	-	-
SII	1.001 (1.000-1.001)	<0.001	-	-

*The variables with a p-value of less than 0.05 in the univariate analysis were incorporated into the multivariate cox regression analysis by using Enter method. CRP: C-reactive protein, HR: Hazard ratio, CI: Confidence interval, MACCEs: Major advers cardiovascular and cerebrovascular events, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, SII: Systemic immune-inflammation index, LVEF: Left ventricular ejection fraction, OCS: Open cell stent

Table 3b. Factors that were found to be independently associated with the MACCEs in multivariate cox regression analyses models including inflammation based scores

Variables	Model 2 Multivariate* HR (95% CI)	p	Model 3 Multivariate * HR (95% CI)	p	Model 4 Multivariate* HR (95% CI)	p
LVEF	0.963 (0.931-0.996)	0.028	0.961 (0.930-0.993)	0.018	0.960 (0.930-0.991)	0.011
CRP	1.008 (1.003-1.013)	0.003	1.009 (1.004-1.014)	<0.001	1.007 (1.002-1.013)	0.009
Tortuosity	2.182 (1.078-4.419)	0.030	2.097 (1.039-4.233)	0.039	2.204 (1.102-4.405)	0.025
NLR	1.013 (0.983-1.260)	0.091	-	-	-	-
PLR	-	-	1.006 (1.000-1.011)	0.033	-	-
SII	-	-	-	-	1.000 (1.000-1.001)	0.027

*The variables with a p-value of less than 0.05 in the univariate analysis were incorporated into the multivariate cox regression analysis by using Enter method. CRP: C-reactive protein, HR: Hazard ratio, CI: Confidence interval, MACCEs: Major advers cardiovascular and cerebrovascular events, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, SII: Systemic immune-inflammation index, LVEF: Left ventricular ejection fraction

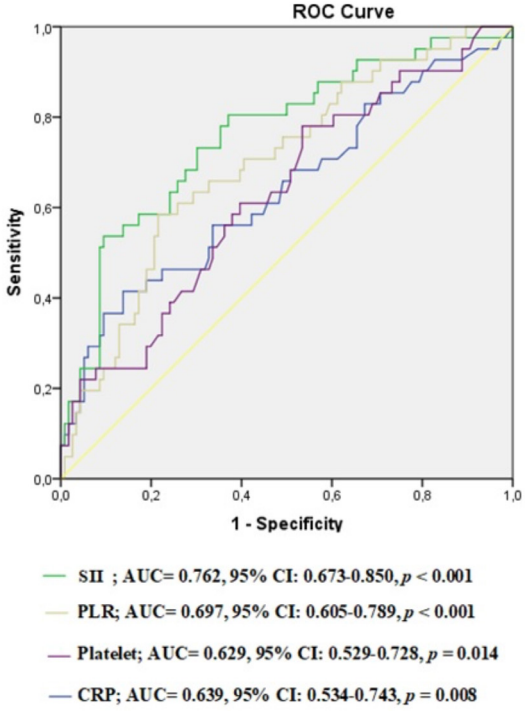

Figure 1. Predictive performance of SII, PLR, platelet and CRP in determining the one-yer MACCEs
SII: Systemic immune-inflammation index, PLR: Patelet-lymphocyte ratio, CRP: C-reactive protein, AUC: Area under the curve, CI: Confidence interval, ROC: Receiver operating characteristic curve

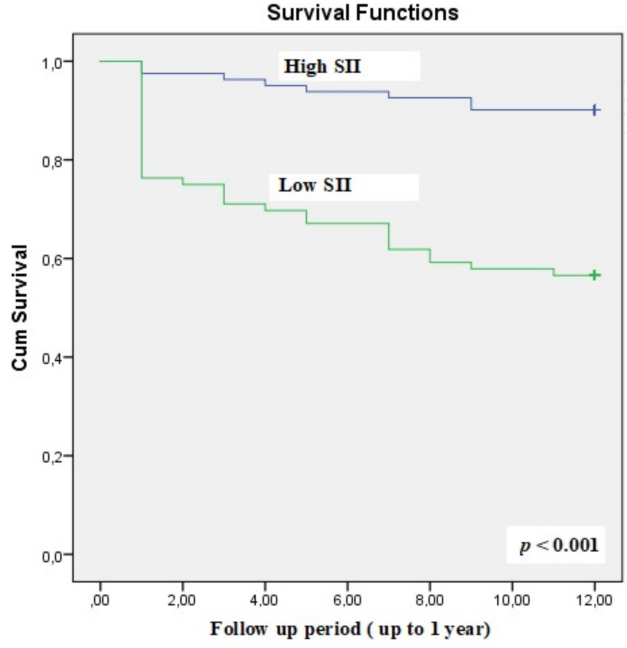

Figure 2. The Kaplan-Meier curve exhibited that patients with a high SII value (≥615) had a poor prognosis compared to those with a low SII value (<615)
SII: Systemic immune-inflammation index

Discussion

We believe that this is the first study in the literature to demonstrate a link between the SII index and one-year MACCEs in patients with established CAD who underwent CAS. The main findings of this study include: (i) Individuals who suffered MACCEs had higher baseline SII index values; (ii) LVEF, carotid artery tortuosity, CRP, platelet counts, PLR and SII independently predicted the development of MACCEs but not neutrophil, lymphocyte and NLR; (iii) predictive performance of SII for one-year MACCEs was better and adequate than platelet, PLR and CRP; and (iv) patients with baseline SII ≥615 points are at high risk for MACCEs at the end of 1 year after the index procedure.

Carotid artery stenosis or atherosclerotic plaque causes 20-30% of all ischemic strokes. The pathophysiology of CAD and carotid artery stenosis is mostly attributed to atherosclerosis, which is seen to be a chronic inflammatory disease. From the onset of the disease to the appearance of clinical consequences, inflammation is central to the progression of atherosclerosis (13). The immune response

and inflammatory reactions in the vascular endothelium layer involve all immune system cells, including neutrophil and lymphocyte cells. Because neutrophils produce cytokines, chemokines, and proteases that contribute to endothelial dysfunction, they can directly influence the development of oxidative stress. The primary immune system cells, on the other hand, are lymphocytes. In particular, it has been demonstrated that T lymphocytes control the inflammatory response to prevent endothelium damage and subsequently the atherosclerotic process. Due to its part in platelet activation and thrombus formation, it also represents a significant stage in the development of atherosclerosis. For neutrophil adherence and activation in the early stages of atherosclerosis, activated platelets are necessary. Platelets can also release some chemo-attractants, pro-inflammatory cytokines, and platelet-derived growth factors that facilitate endothelial dysfunction. These mechanisms cascade worsen the process of inflammation and atherosclerosis in the vessel wall (14).

Various inflammatory indicators seen in standard blood tests are associated with the presence and prognosis of cardiovascular disease in the past. According to published research, atherosclerotic vascular disease and poor cardiovascular outcomes are linked to increased neutrophil counts, higher platelet counts, and low lymphocyte counts (15,16). Numerous studies have demonstrated the predictive significance of NLR and PLR for poorer outcomes in individuals with cardiovascular and cerebrovascular disorders (15-19). It has been proposed that PLR, which reflects hemostasis and inflammation, is more useful than platelet and lymphocyte count alone in the prediction of atherosclerotic vascular load (20,21). Additionally, it has been hypothesized that it is a risk factor for some cardiovascular conditions, including CAD, heart failure, and calcific aortic stenosis, as well as a predictor of unfavorable cardiovascular outcomes (21). In a study, Varım et al. (22) showed that PLR is connected to having critical stenosis in at least one carotid artery. Also reported by İdil Soylu et al. (23) was a link between the PLR and the degree of carotid artery stenosis. Increased PLR was also been proposed in their study as an independent determinant of stroke. Additionally, Tek et al. (19) observed that PLR continued to predict all-cause mortality even after controlling for related risk variables, regardless of the degree of carotid artery stenosis. Platelet-to-lymphocyte ratio was demonstrated to be an independent predictor of postoperative stroke in another study by Deşer et al. (24) in patients following CEA surgery. Platelet-to-lymphocyte ratio was positively connected with the degree of carotid artery stenosis. Neutrophil-to-lymphocyte ratio can be utilized as an independent prognostic predictor to assess the occurrence of restenosis in patients undergoing CAS, however, PLR was not discovered to be a prognostic marker (25). Pereira-Neves et al. (26), in contrast to Bao et al. (25), showed that both NLR and PLR may predict subclinical atherosclerosis, the advancement of atherosclerosis in carotid artery disease, the likelihood for carotid stenosis to become symptomatic, as well as morbidity after CEA and CAS. As far as we are aware, PLR was predictive for a bad 1-year outcome in our trial, which was the first time patients with established CAD had CAS. Neutrophil-to-lymphocyte ratio was not. This finding may be related to plaque characteristics. Neutrophils are the most predominant cells in the acute phase of the inflammatory process. Neutrophil-to-lymphocyte ratio has also been proposed as a marker that simultaneously demonstrates the damaging consequences of neutrophil increase as a marker of acute inflammation and as a marker of physiological stress (27). So much so that Ionita et al. (28) reported that rupture-prone atherosclerotic plaques have more increased macrophage counts and higher neutrophil counts compared with stable plaques. Furthermore, it was discovered that elevated NLR was linked to an increased risk of non-calcified carotid artery plaque rupture (29). Additionally, neutrophils are directly linked to distal embolization in individuals with symptomatic carotid artery stenosis who are receiving CAS (30). Considering the available information, in our cohort, one-fifth of the cases were asymptomatic, and the absence of acute inflammatory reaction in the plaques of these patients may have affected the predictive performance of NLR.

Hu et al. (31) originally identified the SII, a new inflammatory marker based on circulating immune-inflammatory cells such as platelets, neutrophils, and lymphocytes, in patients with hepatocellular carcinoma and found that it was related to a poor prognosis. In comparison to NLR or PLR alone, it has been observed that this inflammatory-based score may accurately reflect the balance of the host's immunological and systemic inflammatory state (32,33). Compared to NLR and PLR, it was also been suggested to be a more valuable marker in predicting the severity of disease and prognosis in various clinical scenarios such as malignancies, autoimmune diseases, pulmonary embolism, and, even in coronavirus disease-2019 infection (33-37). Systemic immunological inflammation index has also been linked to worse outcomes in some cardiovascular illnesses, including CAD, chronic heart failure, valvular heart disease, hypertension, and carotid artery disease (4,14,38-50). Higher SII was independently linked to a higher risk of future cardiac death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure in research by Yang et al. (38) in patients with CAD. According to Gölen and Okuyan (41), the SII

is a marker for the presence of a problematic carotid artery and is linked to death and a bad prognosis. In addition, among asymptomatic individuals with 50% or greater carotid artery stenosis, a high SII score was substantially linked to the emergence of symptoms in another investigation (42). In the study by Keskin et al. (4) in patients undergoing CAS, SII was found to have good discriminative performance and was independently linked with in-hospital and long-term clinical outcomes. Based on the discovery of prevalent cerebrovascular, peripheral, or CAD, polyvascular disease (coexisting disease in 2 arterial beds) was established. Addition, polyvascular disease raises the chance of significant unfavorable cardiovascular events, which are a combination of myocardial infarction, ischemic stroke, and cardiovascular death (43,44). Strong correlations between polyvascular disease and traditional cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes mellitus, and cigarette use, point to the same pathogenesis. Few studies have compared the cardiovascular risk factor profiles of peripheral artery disease with carotid artery disease, though, and the results are conflicting (43-45). Additionally, mounting research has shown that inflammation is a key factor in the promotion of atherosclerosis, destabilizing atherosclerotic plaque and raising the risk of stroke (46). So that patients with polyvascular disease have greater levels of circulating inflammatory markers, such as high-sensitivity CRP and interleukin-6 (43). Increased CRP levels were related to the severity and development of atherosclerotic disease in several arterial areas in the Rotterdam trial (47). In line with results from the literature, CRP was a standalone predictor of MACCEs in our polyvascular research population. For treating carotid artery stenosis, CAS is now regarded as an alternative to carotid endarterectomy, particularly in individuals with high surgical risk. Previous studies have revealed several prognostic variables for CAS, including age, diabetes mellitus, and lesion features (ulceration and contralateral stenosis). Besides, several complications are associated with CAS procedures that still pose challenges and are associated with poor outcomes, such as thromboembolic events, cerebral hyperperfusion syndrome, intracranial hemorrhage, and restenosis (48). To maintain favorable outcomes, identifying prognostic factors is essential for optimizing treatment indications and periprocedural management. Considering available data, considering the importance of inflammation in atherosclerotic diseases, the identification of new inflammatory risk factors beyond traditional risk factors may provide additional risk stratification in patients with CAD undergoing CAS.

Study Limitations

It is important to note that the current has some restrictions. First off, this study was retrospectively planned with a small sample size and depended on experience from a single center. One hundred-fifty seven participants were recruited in the study, and 195 patient records were evaluated between April 2015 and January 2020. Because of unobserved variables, there may be selection bias, and some patients were removed because of missing data. In addition, the parameters examined can be influenced by hospital and study location characteristics. Second, given that the study only involved one institution, some findings might have been underpowered. Third, no clear explanation of the distinction between the use of stents and filters has been provided, leaving the choice of the stent and the usage of filters up to the operators. Fourth, blood samples were collected before the CAS procedure. The relationship between dynamic changes in SII and prognosis without serial measurements of CAS patients remains unclear. Fifth, we did not assess plaque stability or infarct size in the study population. Finally, to support our findings, larger, prospective, multicenter, and randomized controlled investigations are required.

Conclusion

Inflammatory parameters such as SII, PLR, platelet, and CRP are independently associated with one-year MACCEs in patients with a known diagnosis of CAD undergoing CAS. Furthermore, SII had better and sufficient discrimination power than the aforementioned other inflammatory parameters in predicting MACCEs. Systemic immunological inflammation index obtained by cheaper and easily accessible blood parameters may be a promising indicator to identify high-risk patients after CAS.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (date: 28.09.2022, approval no: 175-2022).

Informed Consent: The retrospective nature of our investigation, written informed consent from participants could not be acquired.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.I.B., Design: H.I.B., Data Collection or Processing: M.K., H.O., A.R.T., Analysis or Interpretation: M.K., A.G., Literature Search: Z.A., A.R.T., A.Y.K., S.C., Writing: H.I.B., M.K., A.R.T.

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