Commentary

Association of systemic immune-inflammation index (SII) with presence of isolated coronary artery ectasia

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Abstract

Introduction: The systemic immune-inflammation index (SII) has been developed based on the calculation of N×P/L (N, P and L represent neutrophil count, platelet count and lymphocyte count, respectively), and it is widely used as a marker of inflammation and an indicator of cardiovascular outcomes in patients with coronary artery disease. We examined a possible association between SII and the presence of isolated coronary artery ectasia (CAE).

Material and methods: In this retrospective case-control study, a total of 4400 patients who underwent elective coronary angiography between June 2015 and July 2020 were retrospectively screened. Following the application of exclusion criteria, our study population consisted of 139 CAE patients and 141 age- and gender-matched subjects who proved to have normal coronary angiograms.

Results: The median value of SII was found to be statistically significantly higher in patients with CAE ($p < 0.01$). SII level ≥ 809 measured on admission had 48% sensitivity and 82% specificity in predicting isolated CAE in ROC curve analysis. In this ROC analysis, the predictive powers of neutrophil-to-lymphocyte ratio (NLR) and SII in determining the presence of ectasia were compared, and the predictive power of SII was significantly stronger than N/L ratio ($p = 0.003$). In the multivariate analysis, hyperlipidaemia (OR = 1.978, 95% CI: 1.168–3.349, $p = 0.01$), smoking (OR = 1.86, 95% CI: 1.090–3.127, $p = 0.023$) N/L ratio (OR = 1.192, 95% CI: (1.114–1.997, $p = 0.07$) and SII (OR = 1.002, 95% CI: 1.001–1.003, $p < 0.01$) were independent predictors of the presence of isolated CAE.

Conclusions: SII is a readily available clinical laboratory value that is associated with the presence of isolated CAE. Our findings may indicate a common pathophysiological mechanism between CAE and coronary artery disease.

Key words: systemic immune inflammation index (SII), inflammation, coronary artery ectasia.

Introduction

The term ectasia was first used by Bjork [1]. Markis *et al.* [2] performed the first prospective evaluation of incidence of coronary artery aneurysm. Coronary ectasia is defined as localised or diffuse dilatation of the coronary artery ≥ 1.5 times the adjacent normal vessel segment [3].

Although the underlying mechanisms are not fully understood, coronary artery ectasia (CAE) is considered to be an original form of vascular remodelling in response to atherosclerosis. However, it is not clear why some patients develop CAE while most do not. In previous histopatho-

logical studies, elastin, collagen, and extracellular matrix damage and inflammatory cell accumulation have been reported in ectatic arteries [4–6].

In recent years, there has been increasing interest in describing a simple inflammatory marker in order to facilitate early recognition of patients who may have an increasing risk for future cardiovascular disease. Recently, the systemic immune inflammation index (SII) has been developed based on the calculation of N×P/L (N, P and L represent neutrophil count, platelet count and lymphocyte count, respectively) to consider patients' inflammatory and immune status simultaneously. High SII has been reported to be associated with poor outcomes in cancer patients [7].

As inflammation plays a significant role in the development of CAE, we hypothesized that there may be a relation between SII and CAE. Hence, in the present study, we aimed to evaluate the potential utility of SII in predicting CAE.

Material and methods

Study population

In this retrospective case-control study, a total of 4400 patients who underwent elective coronary angiography between June 2015 and July 2020 were retrospectively screened. After evaluation regarding exclusion criteria, 139 (3.1%) patients were found to have an isolated CAE. Exclusion criteria were as follows: I) evidence of acute or chronic infection, II) systemic inflammatory or autoimmune disease, III) a history of any liver disease (with liver function parameters more than three times the upper normal limit), IV) any clinically significant endocrine, hematologic, respiratory, or metabolic diseases, V) malignancy. VI) acute coronary syndrome.

The control group consisted of 141 angiographically normal coronary artery patients who matched this group in terms of age, gender, and body mass index. Baseline demographic characteristics and related clinical information were retrieved from the hospital's electronic database. Our local ethics committee approved the study protocol in accordance with the principle of the Declaration of Helsinki. Informed consent was waived because this study had a retrospective design.

Laboratory analysis

In our hospital, blood samples are collected from the antecubital vein by an atraumatic puncture prior to the coronary angiography and sent to the laboratory for analysis within 1 hour after collection. Venous blood was collected in a tube containing K3 EDTA for measurement of haematological indices in all patients undergoing coronary angiography. Haematological indices were evaluated from CBC (complete blood count) analysis performed by a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland Inc. Mervue, Galway, Ireland).

SII

In all patients, blood samples were collected from the antecubital vein before coronary angiography. Complete blood cell counts, including platelet, neutrophil, and lymphocyte, were determined with an auto-analyser. The SII was calculated as total peripheral platelet count (P) × neutrophil-to-lymphocyte ratio (N/L) (SII = P × N/L ratio) [7].

Coronary angiography

In the current study, the patients who were diagnosed with typical angina or those with a suspected or positive finding in one of the non-invasive methods that is performed for detection of coronary ischemia underwent elective coronary angiography. Coronary angiography was performed via the femoral or radial artery according to Judkins's technique. All coronary angiograms were recorded into DICOM digital media with a rate of 25 frames/ms. All coronary angiograms were evaluated by two experienced interventional cardiologists who were blinded to the patient's clinical data.

Definitions

The CAE was defined as proposed in a previous study [8]. Hypertension was defined as a systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mm or higher or use of an antihypertensive medicine [9]. The presence of diabetes mellitus was defined as fasting blood glucose of ≥ 126 mg/dl or higher or current use of antidiabetic treatment or being on a diet [10].

Statistical analysis

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 percentages. The chi-squared (χ^2) test was used to compare categorical variables between the groups, while the Kolmogorov-Smirnov test was employed to assess whether the variables were normally distributed. Student's t-test or the Mann-Whitney U test was used to compare the continuous variables between the groups according to whether they were normally distributed or not. Variables found to be associated at a level of $p < 0.05$ according to the univariate analysis were included in the multivariate logistic regression

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Table I. Demographic distribution and laboratory findings of all patients

Variables	All population (n = 280)	Ectasia(–) (n = 141)	Ectasia(+) (n = 139)	P-value
Male gender, n (%)	119 (42.5)	60 (42.6)	59 (42.4)	0.986
Age	56.9 ±8.0	57.9 ±8.8	55.9 ±7.0	0.035
BMI	25.3 ±1.3	25.2 ±1.3	25.4 ±1.3	0.235
Hypertension, n (%)	158 (56.6)	78 (55.3)	80 (57.6)	0.706
Diabetes, n (%)	168 (60)	86 (61)	82(59)	0.733
Smoking, n (%)	106 (37.9)	44 (31.2)	62 (44.6)	0.021
Hyperlipidaemia, n (%)	114 (40.7)	43 (30.5)	71 (51.1)	< 0.001
Creatinine [mg/dl] median [IQR]	0.8 [0.8–1.0]	0.8 [0.9–1.1]	0.8 [0.8–0.9]	0.945
CRP [mg/dl] median [IQR]	0.9 [0.6–1.5]	0.9 [0.6–1.5]	1.1 [0.6–1.6]	0.507
Haemoglobin [g/dl]	13.8 ±2.4	13.9 ±2.1	13.6 ±2.7	0.174
Neutrophil, median [IQR]	2.47 [1.25–3.92]	1.27 [0.7–2.32]	3.76 [2.73–5.59]	< 0.001
Lymphocyte, median [IQR]	1.14 [0.55–1.49]	0.57 [0.31–1.0]	1.45 [1.2–1.88]	< 0.001
Platelet	300.3 ±55.2	282.5 ±39.3	318.9 ±63.5	< 0.001
NLR, median [IQR]	2.3 [1.9–3.1]	2.2 [1.9–2.5]	2.6 [2.1–3.3]	0.001
SII, median [IQR]	667 [553–893]	617 [513–772]	768[600–1132]	< 0.001

CRP – C-reactive protein, NLR – neutrophil/lymphocyte ratio, SII – systemic immune-inflammation index, BMI – body mass index.

analysis with the results reported as the odds ratios (OR) and 95% confidence intervals (CI). The ability of NLR and SII to determine the presence of coronary ectasia was analysed using the receiving operating characteristic (ROC) curve and area under the curve (AUC), accompanied by the 95% confidence interval. The optimal cut-off value was also calculated from the point of maximal sensitivity and specificity by using Youden's index. To compare the predictive performance of the CAR, CRP and albumin the test of DeLong *et al.* was also used. The threshold of statistical significance was established at $p < 0.05$. All statistical analyses were performed using the software SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). ROC curves of the models were compared using the MEDCALC software (Software bvba 13, Ostend, Belgium).

Results

The mean age of study population was 55.9 ±7.0 years and 59 (42.4%) patients were male.

Table II. Vascular involvement and extent of ectatic vessels

Distribution of ectasia:	
LAD	28 (19.8%)
CX	36 (25.5%)
RCA	83 (58.8%)
Number of ectatic vessels:	
One vessel	65 (46.1%)
Two vessels	45 (31.9%)
Three vessels	31 (21.9%)

RCA – right coronary artery, Cx – circumflex artery, LAD – left anterior descending artery.

The demographic and laboratory data of all patients are summarized in Table I. The prevalence of comorbidities, including hypertension, diabetes, and body-mass index (BMI) were not different between the groups. There were similarities in both groups between CRP and haemoglobin levels. Neutrophil, lymphocyte and platelet levels were significantly higher in the group with ectasia ($p < 0.001$).

Moreover, we found that isolated CAE most commonly affects the right coronary artery (58.8%), left anterior descending artery (19.8%), and circumflex artery (25.5%) (Table II). When we divided the study population into two groups according to the SII value, diabetes, hyperlipidaemia and the presence of isolated CAE were significantly more frequent in the high SII group ($p < 0.001$, $p = 0.04$, $p < 0.001$, respectively, Table III). Also we found that smoking was more common in the ectasia(+) group (31.2% vs. 44.6%, $p = 0.02$, Table I).

In the ROC curve analysis, SII value > 809 was identified as an effective cut-off point in the segregation of the presence or absence of isolated CAE (AUC = 0.674, 95% CI: 0.616–0.729, $p < 0.001$). SII value > 809 yielded sensitivity of 42%, specificity of 82%, N/L ratio for detecting the presence of coronary ectasia (AUC = 0.628, 95% CI: 0.562–0.684; $p < 0.001$). In this ROC analysis, the predictive powers of NLR and SII in determining the presence of ectasia were compared, and the predictive power of SII was statistically significantly stronger than NLR ($p = 0.003$) (Figure 1).

Variables found to be statistically significant in univariate analyses were included in the mul-

Table III. Baseline characteristics of patients with low and high SII

Variables	Low SII (n = 187)	High SII (n = 93)	P-value
Male gender, n (%)	88 (47.1)	31 (33.3)	0.029
Age	57.2 ±7.9	56.3 ±8.3	0.357
BMI	25.4 ±1.3	25.2 ±1.4	0.160
Hypertension, n (%)	111 (59.4)	47 (50.5)	0.161
Diabetes, n (%)	125 (66.8)	43 (46.2)	0.001
Smoking, n (%)	69 (36.9)	37 (39.8)	0.639
Hyperlipidaemia, n (%)	65 (34.8)	49 (52.7)	0.004
Creatinine [mg/dl] median [IQR]	0.8 [0.8–1.0]	0.8 [0.8–1.0]	0.434
CRP [mg/dl] median [IQR]	0.9 [0.6–1.5]	1.0 [0.8–1.6]	0.989
Haemoglobin [g/dl]	13.8 ±2.6	13.8 ±2.2	0.776
Neutrophil, median [IQR]	2.1 [0.8–2.72]	4.48 [3.36–6.75]	< 0.001
Lymphocyte, median [IQR]	1.06 [0.39–1.3]	1.4 [1.1–1.9]	< 0.001
Platelet	280.3 ±36.6	341.2 ±64.8	< 0.001
NLR, median [IQR]	2.1 [1.9–2.4]	3.4 [2.84–4.1]	< 0.001
SII, median [IQR]	599 [511–672]	1139 [896–1408]	< 0.001
CAE, n (%)	40 (28.3)	141 (71.6)	< 0.001

CRP – C-reactive protein, RCA – right coronary artery, Cx – circumflex artery, LAD – left anterior descending artery, NLR – neutrophil/lymphocyte ratio, SII – systemic immune-inflammation index.

tivariate logistic regression analysis (Table IV). In the multivariate analysis, hyperlipidaemia (OR = 1.978, 95% CI: 1.168–3.349, p = 0.01), smoking (OR = 1.86, 95% CI: 1.090–3.127, p = 0.023) N/L ratio (OR = 1.192, 95% CI: 1.114–1.997, p = 0.07) and SII (OR = 1.002, 95% CI: 1.002–1.003, p < 0.01) were independent predictors of the presence of isolated CAE.

Discussion

This is the first study evaluating the relationship between SII and the presence of isolated CAE. As a simple and easily obtained haematological parameter from complete blood count, SII may be used in predicting risk of CAE.

In previous publications, CAE was found in 1.5–5% of patients included in coronary angiographic studies [11]. In this study, we reported an incidence of isolated CAE of 3.1% among patients who underwent coronary angiography for the presence of chest pain or had objective signs of ischaemia.

Coronary atherosclerosis is present in almost 50% of patients with CAE, suggesting a common causative mechanism in the formation of both coronary artery disease (CAD) and CAE. Previously, inflammatory markers such as CRP, interleukin-6, and vascular adhesion molecules were investigated in patients with CAE [12]. A recent study by Li *et al.* showed that interleukin-6 and CRP were significantly higher in patients with CAE than in patients with normal coronary arteries [13]. In our study, there was no significant difference in CRP levels in low and high SII groups. The importance of NLR in cardiovascular disease has been
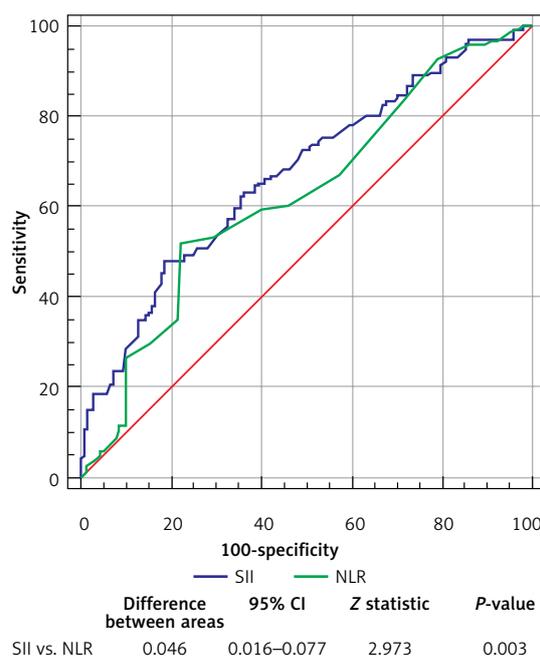

	Difference between areas	95% CI	Z statistic	P-value
SII vs. NLR	0.046	0.016–0.077	2.973	0.003

Figure 1. ROC curves of the SII (blue) and NLR (green) scores for detecting the presence of coronary ectasia

investigated in a few studies. Işık *et al.* found that a greater baseline NLR value was independently associated with the presence of isolated CAE [14]. Kundi *et al.* reported that high monocyte/HDL ratio (MHR) is an independent predictor of CAE and obstructive coronary artery disease [15].

The associations between CAE and inflammatory vasculitides such as Kawasaki disease, Takayasu arteritis, Behçet's disease, and connec-

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Table IV. Two different adjusted multivariate Cox proportional risk regression analysis models to determine the predictors of coronary ectasia

Variables	Model 1 Multivariate		Model 2 Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	0.971 (0.941–1.002)	0.067	0.972 (0.941–1.004)	0.067
Smoking	1.722 (1.030–2.880)	0.038	1.846 (1.090–3.127)	0.023
Hyperlipidaemia	2.348 (1.413–3.903)	0.001	1.978 (1.168–3.349)	0.011
NLR	1.492 (1.114–1.997)	0.007	–	–
SII	–	–	1.002 (1.001–1.003)	< 0.001

tive tissue diseases support the inflammatory origin of CAE [16]. Plasma E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 were significantly higher in patients with isolated CAE [17]. In a study, higher levels of inflammatory markers including tumour necrosis factor α and interleukin 6 (IL-6) were increased in patients with CAE [18]. Furthermore, Turhan *et al.* [19] found that CRP, an indicator of the systemic inflammatory response, was also significantly higher in patients with isolated CAE than in those with a normal coronary artery. Accumulation of inflammatory cells in the medial layer of coronary arteries was also reported in histopathological examinations of patients with CAE [20, 21]. In addition, the levels of cellular adhesion molecules CD 11b and CD 45 were higher in patients with CAE [22].

Chronic inflammation has been considered to have major roles in several important diseases. Zhong *et al.* [7] first reported on the use of the SII in hepatocellular carcinoma, and the index had significant associations with prognostic clinical outcomes, including vascular invasion, tumour size and early recurrence. More and more clinical observation studies indicate that SII is a powerful tool for predicting survival outcomes in multiple solid cancers [23, 24]. Recently, Seo *et al.* [25] reported for the first time the predictive value of SII in patients with chronic heart failure. The current study further extended the importance of SII to cardiovascular disease. We found that the rate of development of ectasia is higher in smokers compared to non-smokers. Cigarettes accelerate atherosclerosis together with insecticides, toxic substances, the direct effect of some trace elements and the metabolic and biochemical disorders it causes. Oxidative stress caused by smoking plays an important role in the development of atherosclerosis. Radical oxidative products due to oxidative stress increase the use of antioxidant enzymes and lead to their reduction. The relationship between the reduction of these enzymes and mitochondrial DNA damage in the vessel wall is thought to play an important role

in atherosclerosis and organ damage [26]. This physiopathological mechanism may explain the higher incidence of coronary ectasia in smokers.

Our results provided evidence that the inflammatory process caused by high SII levels may cause microvascular dysfunction in CAE patients. The SII is a simple and inexpensive marker of inflammation, and it can be calculated easily from complete blood count parameters. Elevated SII, which is a newly introduced inflammatory marker, may have predictive value for the prediction of CAE in daily clinical practice.

In conclusion, we observed that SII levels were higher in CAE patients than in healthy subjects. Our findings may indicate a common pathophysiological mechanism between CAE and coronary artery disease. Since there are common pathophysiological mechanisms between coronary ectasia and coronary artery disease, there is no specific treatment for coronary ectasia. There is no evidence that the treatment of coronary ectasia can reduce SII. Long-term prospective studies are needed. Finally, our findings warrant further studies to describe a clear role of this marker.

This study had some limitations. First, our study had a retrospective design. Second, we were not able to evaluate the plaque burden because patients without evidence of luminal narrowing shown by angiography may also have a plaque burden in the wall of the coronary vessels. Third, use of a spot laboratory value rather than values at a time interval may be another limitation because the development of CAE is a chronic condition. Finally, we did not evaluate other well-known inflammatory markers such as fibrinogen in the study.

Conflict of interest

The authors declare no conflict interest.

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