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Original Article / Özgün Araştırma

Systemic Immuno-Inflammation Index May Predict the Burden of Coronary Artery Disease

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Abstract

Background: Atherosclerosis has a significant place in the pathophysiology of coronary artery disease. In clinical practice, complete blood count is considered as a routine laboratory technique that can be easily applied. Systemic immune inflammatory index (SII), which can be easily calculated with this laboratory method, can be used to evaluate the balance of inflammation, considering the multifaceted effects of atherosclerosis.

Aim: In our investigation, we purposed to determine the relationship between the intensity of inflammation, which we calculated with whole blood using this biomarker in 166 patients, and the intensity of coronary artery disease, which was evaluated with coronary angiography.

Method: 166 patients who underwent coronary angiography because of acute coronary syndrome were included in our investigation. SYNTAX scores of the patients were calculated using the application on the website (http://www.SYNTAXcore.com.) SYNTAX scores are divided into 3 groups: 0-22, low; 23-32, medium; 33 and above, high. In our study, we divided the SYNTAX score into two groups: 0-22 was defined as low, 23 and above as medium-high. We examined the relationship between the SII and the low and medium-high groups.

Findings: In patients consulting with acute coronary syndrome, a statistically significant positive result was found between the coronary artery disease assessed with Systemic immune inflammatory index (SII) and SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) score. (p=0.022)

Conclusion: SII calculation is a practical method and can provide the clinicians with important clues about the prevalence of acute coronary syndrome in terms of treatment management; however, more in-depth, well-designed studies are required for SII.

Keywords: Acute Coronary Syndrome, Systemic immune inflammatory index (SII), SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) score

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Sistemik İmmün İnflamasyon İndeksi Koroner Arter Hastalığının Yükünü Tahmin Edebilir

Öz

Arkaplan: Koroner arter hastalığının patofizyolojisinde ateroskleroz önemli bir yer almaktadır. Aterosklerozun çok yönlü etkileri göz önüne alındığında tam kan sayımıyla kolayca hesaplanabilen sistemik immün inflamatuar indeks (SII) inflamasyon dengesini tanımlamak için kullanılabilmektedir.

Amaç: Biz çalışmamızda 166 hastada değerlendirilen bu biyobelirteç ile inflamasyon şiddetinin,koroner anjiografi ile değerlendirilen koroner arter hastalığı şiddeti ile ilişkisini incelemeyi amaçladık.

Yöntem: Çalışmamıza Akut koroner sendrom nedeni ile koroner anjiografisi yapılan 166 hasta dahil edildi. Hastaların SYNTAX skoru web sitesindeki uygulama üzerinden hesaplandı. (http://www.SYNTAXcore.com.) SYNTAX puanı 3 gruba ayrılmaktadır: 0-22, düşük; 23-32, orta; 33 ve üzeri, yüksek. Biz çalışmamızda SYNTAX puanını iki gruba ayırarak inceledik: 0-22 düşük, 23 ve üzeri orta-yüksek olarak tanımladık. SII ile düşük ve orta-yüksek grup arasındaki ilişkiyi inceledik.

Bulgular: Akut koroner sendrom ile başvuran hastalarda sistemik immun inflamatuar indeks (SII) ile SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) skoru ile değerlendirilen koroner arter hastalığı yaygınlığı arasında istatiksel olarak anlamlı sonuç tespit edildi.(p=0,022)

Sonuç: SII klinik olarak pratik bir yöntem olup akut koroner sendrom yaygınlığı ile ilgili biz klinisyenlere tedavi yaklaşımı açısından önemli ipuçları verebilir, ve bulduğumuz sonucun hasta tedavi yaklaşımına katkı sağlayacağı inancındayız. Yine de SII için daha derinlemesine ve iyi düzenlenmiş araştırmalara gereksinme duyulmaktadır.

Anahtar kelimeler:Akut Koroner Sendrom; Sistemik immün inflamatuar indeks (SII), SYNTAX (TAXUS ve Kalp Cerrahisi ile PCI Arasındaki İlişki) skoru.

INTRODUCTION

Atherosclerotic coronary artery disease (ACD) is one of the most important causes of death[1]. Atherosclerosis plays a fundamental part in the pathophysiology of coronary artery disease. In this pathophysiology, lipid disorders, endothelial damage, inflammation and immune dysfunction is important part in the progression of coronary artery disease[2]. Vulnerable plaque can easily rupture and turn into a thrombus plaque[3]. Inflammation has an important role in the formation of vulnerable plaque and plaque rupture[4]. The existence of inflammatory cells, such as T cells, macrophages, monocytes, and dendritic cells are the primary cells in the formation of atherosclerotic formation[5]. Besides these, cytokines, immune cells and other biomedical markers is important part in the advancement and severity of the inflammatory response. An rise up in white blood cells and its subtypes, such as eosinophils, lymphocytes and monocytes has been found out to be closely associated with cardiovascular side effects[6].

In addition, the parameters for the Syntax score evaluated in our study are as follows; number of patient vessels, calcification, segment, tortuosity, presence of thrombus, lesion length, right or left dominance, aorto-osteal lesion, bifurcation, trification, diffuse disease, total occlusion and stenosis of more than 50% in 1.5 mm coronary vessels[7]. The other parameter assessed in our study, systemic immune inflammatory index (SII), was defined as a new comprehensive inflammatory biomarker defined by Hu et al. in 2014 and is calculated using neutrophil, lymphocyte and platelet counts[8]. SII was found to be associated with poor prognosis for coronary artery disease[9]. There are also studies indicating that it is associated with atherosclerotic burden and is relevant with 3-vessel disease[10].

SII is a marker of coronary artery disease and the correlation between the severity of inflammation and the extent of coronary artery disease has been demonstrated in some past studies[11]. In our study, we tried to test this relationship and examine it to contribute to the literature.

METHOD

All of 256 patients who were admitted to our hospital due to acute coronary syndrome (ACS) between January 1, 2023 and December 31, 2023 were retrospectively screened for blood parameters from the external center they consulted to before their hospital admission via the E-nabiz health information system of the Ministry of Health of the Republic of Turkey and the values after their admission to our hospital via the hospital information system. The blood parameters requested during the patients' hospitalization, as well as routine nursing observation evaluations made during their hospitalization process and patient files were examined. Systemic inflammatory index (SII) was described as (neutrophil count) × (platelet count)/(lymphocyte count). The SII calculation was evaluated by considering the blood parameters taken at an external center before their admission to our hospital. Body mass index was defined according to WHO (World Health Organization) criteria[12]. Hypertension was defined as defined in the 2021 European Society of Hypertension Practice Guidelines[13]. The 2019 ESC Diabetes, pre-diabetes and cardiovascular disease criteria were used to described type 2 diabetes[14]. Accordance with the 2019 ESC/EAS Guidelines, dyslipidemia was determined in patients whose lipid profile did not meet the theraphy targets according to their risk levels for the treatment of dyslipidemia[15]. Patients diagnosed with ACS in accordance with the European Society of Cardiology guidelines were included[16]. Patients who underwent coronary angiography using the radial and femoral arteries were examined. Patients who underwent coronary artery revascularization were evaluated in accordance with the recommendations specified in the 2021 ACC/AHA/SCAI Guidelines. The SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) scores of patients who underwent coronary angiography with ACS were evaluated by two independent researchers by monitoring their coronary angiography. The SYNTAX question was calculated using the application on the website (http://www.SYNTAXcore.com.) SYNTAX score is divided into 3 groups: 0-22, low; 23-32, medium; 33 and above, high. In our study, we examined the SYNTAX score by dividing it into 2 groups as low between 0-22 and medium-high between 23 and above (Figure 1).

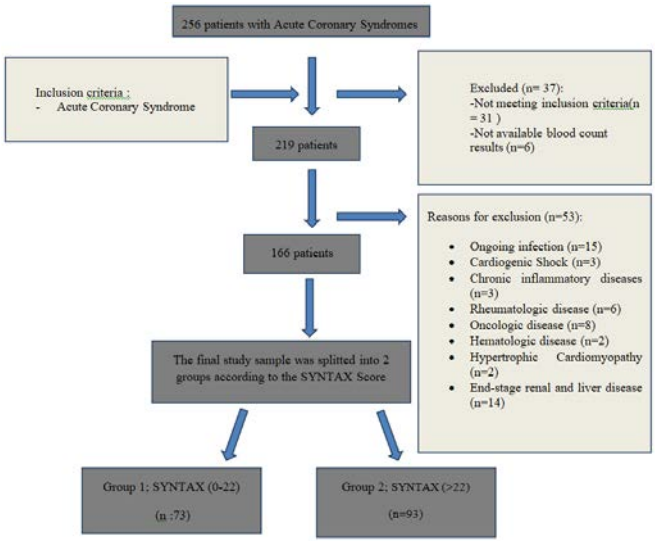

Figure 1. Work group flow chart

Again, the laboratory data of the patients were scanned retrospectively. Cardiogenic shock, serious active and chronic infection, active bleeding, autoimmune diseases, pregnancy, aortic dissection, hypertrophic cardiomyopathy, endocarditis, percarditis, major surgery, oncology patients receiving active treatment, end-stage renal failure were excluded from the study. Beside, patients with chronic diseases such as DM (diabetes mellitus), COPD (chronic obstructive pulmonary disease) that are considered to be at risk for coronary

artery disease were not excluded from the investigation. Our investigation was affirmed by the local ethics committee in accordance with the Helsinki Declaration (ethics committee date: 7/5/2024 number: 2024/5-3).

Statistical Analysis

Data were analyzed using SPSS version 25.0 for Windows (IBM Corp., Armonk, NY, USA). Subjective methods and objective methods, Lilliefors and Shapiro-Wilk tests, were used to assess the normal distribution of continuous variables. Continuous variables were expressed as mean±standard deviation (SD) or median (interquartile range), and categorical variables were expressed as percentages. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Specificity and sensitivity values were calculated using the receiver-operator characteristic (ROC) curve to estimate the SII cut-off value. $p<0.05$ was considered statistically significant.

RESULTS

Clinical and demographic and findings of the investigation groups are given in Table 1. The ages of patients with SYNTAX scores >22 were significantly different between the groups compared to patients with SYNTAX scores between 0-22 (p=0.000). Again, diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HPL) and smoking were observed to be statistically importantly higher in patients with SYNTAX scores above >22 (p=0.002,0p=0.000,p =0.000,p=0.013). 11% of patients with SYNTAX scores between 0-22 and 60% of patients with SYNTAX scores >22 consisted of patients who had previously had a myocardial infarction and received stent placement (p=0.000). Again, 7.5% of patients with a SYNTAX score of >22 had previously undergone bypass surgery (p=0.007). It was observed that the effective radiation dose and the amount of contrast material used were elevated in patients with a SYNTAX score of >22 (p=0.008, p=0.048).

Table I: Demographic data and Clinical Findings

		SYNTAX (0-22) (n=73)	SYNTAX (>22) (n=93)	*p* value
Gender (Female/Male), n(%)		19(%26)/54(%74)	31(%33,3)/62(%66,7)	0,307
Age, (years)		56,96(±12,4)	66,03(±8,5)	**0,000**
BMI, (kg/m2)(IQR)		25,6(20,5-34,3)	25,3(20,8-33,3)	0,614
HR (minute) (IQR)		75,3(50-125)	75,8(49-106)	0,872
EF, %(IQR)		52,05(30-60)	49,25(25-65)	0,066
DM, n(%)		13(%17,8)	37(%39,8)	**0,001**
HT, n(%)		33(%45,2)	74(%79,6)	**0,000**
HPL, n(%)		29(%39,7)	69(%74,2)	**0,000**
SMOKING, n(%)		31(%42,5)	71(%76,3)	**0,000**
COPD, n(%)		2(%2,7)	7(%7,5)	0,148
Previous PCI, n%		19(%26)	60(%64,5)	**0,000**
Previous CABGO, n%		0(%0)	7(%7,5)	**0,007**
Hospitalization day, IQR		3,14(1-8)	3,19(1-6)	0,724
KİLLİP 1/2/3/4		71/1/1/0	90/0/2/1	0,546
Access Radial/Femoral		68/5	83/10	0,387
Angio Duration,min (IQR)		29,1(8-95)	33,9(10-120)	0,065
Radiation (Dose-area product)(Gy cm2) (IQR)		10476,0(193,2-86003)	14748,5(1300-88088)	0,045
Radiation (Effective Dose) (mSv) (IQR)		1845,1(182-6100)	2345,1(180-6035)	**0,008**
Contrast Volume(ml) (IQR)		155,4(35-450)	182,3(15-400)	**0,048**
Myocardial infarction type	STEMI, n(%)	24(%32,9)	49(%67,1)	0,404
	NSTEMI, n(%)	25(%26,9)	68(%73,1)	

BMI: Body mass index ;HR : Heart Rate ; SBP : Systolic blood pressure ,DBP : Diastolic blood pressure , EF:Ejection Fraction , DM :Diabetes Mellitus, HT: Hypertension,HPL :Hyperlipidemia, COPD :Chronic Obstrictive Lung Disease , PCI :Percutaneous coronary intervention, CABGO :Coronary artery bypass graft operation, STEMI:ST-Elevation Myocardial Infarction ;Non-STEMI :Non- ST-Elevation Myocardial Infarcti

Laboratory details of the study groups are given in Table 2. Among the groups, the application creatine, CRP, and urea values of patients with SYNTAX scores >22 were significantly higher than those of patients with SYNTAX scores between 0-22 (p=0.018, p=0.044, p=0.004). Curve analysis was performed for the systemic immune inflammatory index. When the cut-off was taken as 743.52, the sensitivity was determined as 57% and the specificity as 42%, and the SII index response was observed to be higher in patients with SYNTAX scores >22 than in patients with SYNTAX scores between 0-22 (AUC: 0.603, 95% CI: 0.517-0.690, p=0.022) (Table 3, Figure 2).

Table II: Labaratory findings

	SYNTAX (0-22) (n=73)	SYNTAX (>22) (n=93)	*p* value
WBC(x10^3/uL)	10,2(±3,2)	10,5(±2,9)	0,515
Creatinine, (mg/dL)	0,88(±0,23)	0,98(±0,32)	**0,018**
Sodium (mEq/L)	137,3(±3)	137,5(±3)	0,597
Potassium(mEq/L)	4,04(±0,5)	4,1(±0,5)	0,105
CRP(mg/dL) (IQR)	0,74(0,03-6,4)	1,2(0,03-11,9)	**0,044**
Urea (mg/dl)(IQR)	34,3(1,5-76)	41,1(20-139)	**0,004**
Total cholesterol (mg/dl)	172,5(±47,3)	181,8(±50,1)	0,225
HDL cholesterol (mg/dl)	38,6(±11,2)	40,8(±9,1)	0,177
LDL cholesterol (mg/dl)	101,3(±38,2)	106,2(±40,3)	0,489
Triglyceride(mg/dl)	159,2(±134,3)	173,6(±132,4)	0,429
TSH(gr/L)	2,5(±7,8)	1,8(±3,0)	0,624
HBA1C (IQR)	6,3(5,2-11,5)	7,0(4,4-12,6)	**0,004**
Albumin (gr/L)	4,0(±0,45)	4,0(±0,39)	0,237
Hgb (g/dL)	14,4(±1,68)	14,2(±1,65)	0,518
MCV(fL)	87,9(±4,1)	89,4(±5,7)	0,059
RDW(%)	12,2(±1,7)	12,1(±1,1)	0,468
Plt (10^9/L)	240,7(±72,0)	240,1(±62,5)	0,957
Mpv (fL)	8,18(±1,44)	8,13(±1,43)	0,832
Neutrophils	6,9(±2,9)	9,1(±11,0)	0,093
Lymphocytes	2,2(±1,0)	1,9(±0,89)	**0,014**
Monocytes	0,66(±0,23)	0,72(±0,3)	0,156
ALT(U/L)	25,8(±27,8)	22,5(±18,4)	0,363
AST(U/L)	63,8(±145,1)	51,1(±83,0)	0,478
Total Bilirubin(umol/L)	0,55(±0,41)	0,56(0,38)	0,838
Üric Acid (mg/ dL)(IQR)	5,2(2,9-8)	5,4(2,3-10,4)	0,402

WBC: White Blood Cell, CRP= C-Reactive Protein, HDL =High Density Lipoproteine, LDL =Low Density Lipoproteine, TSH = Thyroid Stimulating Hormone , HbA1c: Hemoglobin A1c, Hgb= Hemoglobin, MCV =Mean Corpuscular Volüm,RDW = Red Cell Distribution,MPV= Mean Platelet Volüme , Plt= Platelet ,ALT =Alanine Aminotransferase, AST =Aspartate Aminotransferase,

Table III: Roc Curve Analysis

Risk Factor	AUC(%95)	Cutt off	P Value	Sensitivity (%)	Spesifity (%)
SII	0,603(0,517-0,690)	743,52	0,022	0,57	0,42

SII :Systemic immune ınflamatory ındex

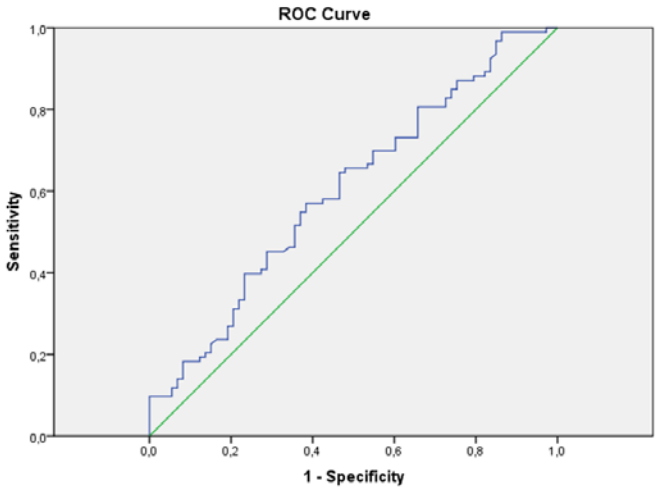

Figure 2: Roc Curve Analysis

DISCUSSION

In our study, it was found that the SII response was higher as the SYNTAX score increased. (Table 3) Many studies have found that SII has a significant prognostic predictive ability. SII has been used to predict the prognosis of cancer, intracerebral hemorrhage, and coronary artery disease[2,17,18]. We also tried to put forward that SII can be used to predict the prognosis of coronary artery disease.

Atherosclerosis is the primary cause of coronary artery disease. Inflammation-endothelial dysfunction stimulates the development of atherosclerosis. Increased inflammatory markers increase the risk of cardiovascular disease, but the main mechanisms are not clarified yet[7]. Many observational investigations have monitored that inflammation plays an momentous role in the growth and progression of coronary artery disease. Increased neutrophil and decreased lymphocyte numbers induce oxidative stress, leading to damage to the vascular wall[19]. Neutrophils interact with platelets, leading to important complications such as thrombosis and atherosclerosis. are associated with biological processes. After lymphocyte apoptosis, the atherosclerotic lipid core ruptures and stimulates thrombus formation[19]. Inflammation is caused the ischemic-reperfusion injury in the heart tissue in ACS; therefore, the advantage of dropping the residual inflammatory risk with diverse theraphy are extensively studied[20].

Current data have not identified a significant relationship between instability of the atherosclerotic lesion and systemic inflammation, but it is suggested that many immune cells and proinflammatory cytokines contribute to this effect[19]. Leukocytes and their subtypes (lymphocytes, monocytes and neutrophils) are assessed by total blood cell count, which has been shown to be a cost-effective and accessible way to assess the inflammatory process involved in atherosclerosis pathophysiology and to modify the risk of ACS and stroke[21]. In addition, high WBC is an independent biomarker of mortality in MI patients[22]. Monocytes initiate and promote the development of atherosclerosis by removing reactive oxygen species (ROS), proinflammatory cytokines, and proteolytic enzymes[23]. They adhere to the endothelium and diversify into macrophages and then into foam cells that uptake lipids and activate the release of cytokines and ROS[24]. Monocyte count has been identified as a predictor of CVD mortality in long- and short-term look out, independent of other classical risk factors. Neutrophils aggravate the vascular atherosclerotic process by inducing myocardial apoptosis[22,23]. In addition, high neutrophil counts are positively associated with the risk of plaque unstabilization[23] and are elevated.

There is a risk of thrombosis in the microcirculatory circulation. However, lymphocytes may prevent progression of atherosclerosis. A decreased lymphocyte count is associated with a poor prognosis in patients with ACS and is also associated with an increased incidence of MACE and heart failure [25]. Platelets have a dual effect on plaque formation: their adhesion to the vascular wall

causes atherosclerosis and, by activation, they promote inflammation and thrombosis[25].

SII parameters are calculated using neutrophil, lymphocyte and platelet counts, which are used in clinical practice. SII has also been demonstrated to be link with cardiovascular disease mortality[10,26]. Inflammation is a significant part in its development and has been indicated to be an important marker in the risk assessment and prediction of major adverse events. The use of SII is attractive as a simple, accessible and practical method. A high SYNTAX score has been shown to be linked with adverse cardiovascular outcomes in many previous studies[6]. In our investigation, we invented that a high SYNTAX score was associated with a high SII response (Table 3).

LIMITATION

In addition to the strengths of the study highlighted earlier, there are some limitations to our study. Our study was designed as a single-center, retrospective, and cross-sectional study. Our relatively small sample size suggests that larger-scale studies are needed for this patient population. The results of this study cannot be generalized. Our study was conducted on white people and did not have data relevant to education level, marital status, and socioeconomic characteristics

CONCLUSION

In summary, the results of our study contribute to the growing evidence supporting the use of SII as a biomarker predicting the extent of coronary artery disease in clinical practice. SII is also relevant with the seriousness of coronary artery disease. Future prospective investigations are required to determine the causal relationship in the use of SII, its use in the prevention of ACS, and clinical applications.

Ethics Committee Approval: Our investigation was affirmed by the local ethics committee in accordance with the Helsinki Declaration (ethics committee date: 7/5/2024 number: 2024/5-3).

Conflict of Interest: The authors declared no conflicts of interest.

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

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