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The Value of Atherogenic Index of Plasma in Estimating Coronary Artery Calcium Scores

Plazma Aterojenik İndeksinin Koroner Arter Kalsiyum Skorlarını Tahmin Etmedeki Değeri

Ahmet Lütfü Sertdemir[1], Ahmet Taha Şahin[1], Nergiz Aydın[1], Mustafa Duran[3], Abdullah İçli[1], Cengiz Kadıyoran[2], Pınar Diydem Yılmaz[2]

[1]Necmettin Erbakan University Faculty of Medicine, Department of Cardiology, Konya, Turkey
[2]Necmettin Erbakan University Faculty of Medicine, Department of Radiology, Konya, Turkey
[3]Konya City Hospital, Clinic of Cardiology, Konya, Turkey

Abstract

Objective: Coronary calcium load is a strong indicator of the presence and severity of atherosclerotic plaques in the coronary arteries. The atherogenic index of plasma (AIP) has been established for the evaluation of plasma atherogenicity and is strongly associated with an increased cardiovascular risk. Herein, we aimed to explore the compatibility of the risk groups determined by the coronary artery calcium (CAC) score and the risk groups predicted by the AIP.

Materials and Methods: The records of 173 patients who underwent cardiac computed tomography for suspected coronary artery disease between January 2019 and January 2022 were analyzed. Patients were divided into five groups based on calculated CAC cut-off values that have been commonly used in the literature.

Results: Regarding, calculated AIP levels, patients with severe CAC had significantly higher levels of AIP compared to other groups ($p<0.001$). To determine the AIP cut-off value to predict severe CAC, the receiver operating characteristic curve was drawn and the best cut-off value was determined as 0.60 by using the Youden index, (area under the curve: 0.774, 95% confidence interval: 0.685-0.863, $p<0.001$). Above this threshold, CAC could be detected with a sensitivity of 75.8% and a specificity of 67.1%.

Conclusion: This study demonstrated that the AIP is an independent predictor of coronary calcification.

Keywords: Atherogenic index of plasma, coronary artery calcium score, computed tomography

Öz

Amaç: Koroner arter kalsiyum (KAK) yükü, koroner arterlerdeki aterosklerotik plakların varlığının ve ciddiyetinin güçlü bir göstergesidir. Plazmanın aterojenik indeksi (AIP), plazma aterojenitesinin değerlendirilmesi için oluşturulmuştur ve artmış kardiyovasküler risk ile güçlü bir şekilde ilişkilidir. Burada KAK skoruna göre belirlenen risk grupları ile AIP tarafından tahmin edilen risk gruplarının uyumluluğunu araştırmayı amaçladık.

Gereç ve Yöntemler: Ocak 2019 ile Ocak 2022 tarihleri arasında koroner arter hastalığı şüphesi nedeniyle kardiyak BT çekilen 173 hastanın kayıtları incelendi. Hastalar literatürde yaygın olarak kullanılan hesaplanan KAK kesim değerlerine göre beş gruba ayrıldı.

Bulgular: Hesaplanan AIP düzeylerine bakıldığında şiddetli KAK hastalarında diğer gruplarla karşılaştırıldığında anlamlı düzeyde daha yüksek AIP düzeyleri mevcuttu ($p<0,001$). Şiddetli KAK'yi öngörmek için AIP kesim değerini belirlemek amacıyla alıcı işletim karakteristiği eğrisi çizildi ve Youden indeksi kullanılarak en iyi kesim değeri 0,60 olarak belirlendi, (eğrinin altında kalan alan: 0,774, %95 güven aralığı: 0,685-0,863, $p<0,001$). Bu eşiğin üzerinde KAK %75,8 duyarlılık ve %67,1 özgüllükle tespit edilebildi.

Sonuç: Bu çalışma AIP'nin koroner kalsifikasyonun bağımsız bir belirleyicisi olduğunu gösterdi.

Anahtar Kelimeler: Plazmanın aterojenik indeksi, koroner arter kalsiyum skoru, bilgisayarlı tomografi

Address for Correspondence/Yazışma Adresi: Ahmet Taha Şahin MD, Necmettin Erbakan University Faculty of Medicine, Department of Cardiology, Konya, Turkey
Phone: +90 534 577 77 30 **E-mail:** tahasahin94@gmail.com
ORCID ID: orcid.org/0000-0002-2928-1059

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Introduction

Calcium load strongly indicates of the presence and severity of atherosclerotic plaque in the coronary arteries (1-3). Previous reports have shown that calcium load not only provides prognostic information for describing patients at high risk of future cardiovascular events but also acts as a predictor of mortality over and above conventional cardiovascular risk factors (4-6). In this context, computed tomography (CT), a non-invasive tool for assessing the extent of coronary calcification, strongly predicts future cardiovascular events based on calculated coronary artery calcium (CAC) scores (7,8). However, CT is not suitable for detecting early calcifications, including microcalcifications and fragmented calcifications (9).

The atherogenic index of plasma (AIP) has been established to assess plasma atherogenicity and is explosively associated with the increased cardiovascular threat (10-12). It has been reported that this index is more effective than other atherogenic biomarkers or individual lipoprotein indices in distinguishing the high-risk population (13,14). On the other hand, no related research has investigated the contribution of AIP to the CAC score in determining the risk of coronary artery disease and its impact on the treatment decision, especially in cases where no consensus can be reached on the clinical approach. Because of these reasons, this study aimed to assess the harmoniousness of the risk groups determined by the CAC score and those predicted by the AIP.

Materials and Methods

Study Population

The study protocol was approved by the Clinical Research Ethics Committee of Necmettin Erbakan University Faculty of Medicine (decision no: 2022/3883, date: 01.07.2022). The study individuals were retrospectively identified from the medical archives of patients who underwent coronary CT for suspected coronary artery disease between January 2019 and January 2022. Demographic and clinical factors of the study individuals and the indication for cardiac CT imaging were analyzed retrospectively. Exclusion criteria were active infection, presence of malignancy, history of chronic inflammatory disease, liver failure, chronic renal disease (serum creatinine level ≥1.5 mg/dL), and documented coronary artery disease. Acute coronary syndrome patients were also excluded from the study. One hundred seventy-three study patients were enrolled. Informed consent form was taken from all study patients, and the study was approved by the committee following the ethical guidelines of the 1975 Declaration of Helsinki.

CAC Assessment

CAC imaging with high temporal resolution was performed via a 64-slice multi-detector CT scanner (Siemens Medical Solutions, Forchheim, Germany). Consecutive slices were acquired during a single breath hold from the tracheal bifurcation to the level of the diaphragm. According to this method, a lesion was defined as ≥3 consecutive pixels with a peak attenuation of at least 130 Hounsfield units (HU) and an area of ≥1 mm^2 (15). With its peak HU, each area of calcified plaque was measured for the left coronary and right coronary vessels and pooled to calculate the total CAC score using software (Syngo Multimodality Workplace Siemens, Siemens, Germany). Total CAC scores were defined as none (0), minimal (1-10), mild (11-100), moderate (101-400), or severe (≥400) based on cut-off values commonly used in the literature (15). All CAC scores were calculated by two radiologists who blinded to clinical data. Study participants were divided into five categories with similar numbers of patients based on their calculated total CAC score. The AIP was calculated with the formula AIP= log [triglyceride (TG)/ high-density lipoprotein (HDL-C)] (16).

Statistical Analysis

Continuous data are presented as mean ± standard deviation if normally distributed, or as median (25^{th}-75^{th} percentiles), if not normally distributed. Continuous variables were compared using Student's t-test or the Mann-Whitney U test. Categorical variables are expressed as numbers and percentages and were analyzed using the χ^2 test or Fisher's exact test. A multivariate Cox regression analysis was used to identify the risk factors for the estimation of CAC scores; hazard ratios and 95% confidence intervals (CIs) were calculated. All statistical analyses were conducted using SPSS software version 24.0 for Windows (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant during the study. The area under the receiver operating characteristic (ROC) curves (AUCs) was used to assess the predictive value of the AIP for the presence of severe coronary calcification. The Youden index was also used to determine the best cut-off value for the AIP to predict severe coronary calcification.

Results

From January 2019 to January 2022, of the 867 patients screened, a total of 173 patients met all selection criteria and were ultimately included in the study. The baseline demographic, electrocardiographic, echocardiographic, and laboratory characteristics of the patients are given in Table 1. There were no significant differences in electrocardiographic and echocardiographic characteristics between all groups. Regarding baseline laboratory values, all groups had similar laboratory characteristics ($p>0.05$). However, plasma neutrophil count, blood urea nitrogen (BUN), serum total cholesterol, serum TGs, and serum HbA1c were significantly higher in patients with severe CAC compared to other groups ($p<0.05$). Serum HDL levels were also significantly lower in patients with severe CAC compared to other groups ($p<0.05$). In terms of calculated AIP levels, patients with severe CAC had significantly higher AIP levels compared to other study groups ($p<0.001$).

To identify the prognostic indicators of severe CAC, several variables were included in the univariate Cox regression analysis. After removing the variables that did not affect the presence of severe CAC in the univariate analysis, multivariate Cox regression analysis was performed, which identified serum BUN level, serum HbA1c level, and AIP as independent predictors of severe CAC (Table 2). According to our data, AIP was the best predictor of CAC among the aforementioned parameters (p<0.001). To determine the AIP cut-off value for predicting severe CAC, the ROC curve was plotted and the best cut-off value was determined to be 0.60 with the Youden index (AUC: 0.774, 95% CI: 0.685-0.863,

Table 1. The demography, electrocardiography, echocardiography, and laboratory parameters of the patients according to the CAC scores

Parameters	CAC score: 0 (n=32)	CAC score: 1-10 (n=35)	CAC score: 11-100 (n=38)	CAC score: 101-400 (n=35)	CAC score ≥400 (n=33)	p-value
Age (years)	54.5 (39-78)	57 (32-80)	56 (33-81)	54 (36-88)	59 (39-81)	0.700
Sex: Male, n (%)	22 (68.8)	25 (71.4)	25 (65.8)	26 (74.3)	26 (78.8)	0.786
Smoking, n (%)	14 (43.8)	15 (42.9)	17 (44.7)	20 (57.1)	20 (60.6)	0.430
Electrocardiography parameters						
Heart rate (min)	76 (55-90)	76 (60-102)	77 (55-96)	77 (56-98)	82 (61-96)	0.263
PR interval (ms)	145 (120-200)	146 (120-176)	153 (110-180)	160 (110-200)	152 (110-190)	0.618
QRS duration (ms)	96 (80-110)	90 (80-110)	92 (80-128)	93 (80-120)	96 (80-127)	0.577
QTc interval (ms)	391 (350-442)	400 (335-455)	396 (340-450)	398 (328-446)	400 (340-465)	0.972
Echocardiography parameters						
LVEF (%)	62.0±4.9	61.2±5.4	60.4±6.2	59.9±6.2	60.3±6.6	0.599
LVEDD (mm)	4.5±0.3	4.6±0.3	4.6±0.4	4.7±0.4	4.6±0.3	0.972
LVESD (mm)	2.8±0.2	2.9±0.3	2.9±0.3	2.9±0.3	2.8±0.3	0.979
Laboratory parameters						
WBC (x10^3/μL)	7.3 (4.1-15.4)	7.4 (4.8-12.0)	7.7 (4.5-15.5)	7.7 (5.2-18.3)	8.6 (4.4-13.9)	0.076*
Neutrophils (x10^3/μL)	4.2 (1.8-12.3)	4.1 (1.7-8.8)	4.3 (2.1-12.3)	4.2 (2.9-16.1)	4.9 (2.9-10.4)	0.029*
Lymphocytes (x10^3/μL)	2.1 (1.1-3.8)	2.2 (1.2-4.3)	2.3 (1.5-3.7)	2.5 (0.9-4.0)	2.6 (0.3-3.6)	0.486
Hemoglobin (g/dL)	14.1 (11.3-16.9)	14.4 (11.1-17.0)	15.2 (10.5-17.4)	15.0 (11.5-17.5)	14.8 (11.4-16.8)	0.095
Platelets (x10^3/μL)	221 (132-408)	254 (179-379)	251 (133-424)	273 (127-436)	275 (129-393)	0.404
Creatinine (mg/dL)	0.82 (0.59-1.14)	0.86 (0.56-1.23)	0.90 (0.52-1.12)	0.94 (0.51-1.20)	0.92 (0.62-1.20)	0.070
GFR (mL/min)	87 (61-120)	92 (60-121)	91 (68-125)	90 (61-132)	88 (64-131)	0.512
BUN (mg/dL)	28 (17-44)	25 (12-48)	28 (16-42)	28 (21-47)	32 (21-49)	0.013*
HbA1c (%)	5.5 (4.6-7.7)	5.8 (4.8-6.6)	6.0 (4.7-9.5)	6.0 (4.7-9.4)	6.1 (4.7-9.7)	0.001*
ALT (IU/mL)	21 (8-44)	21 (7-45)	20 (9-45)	23 (9-44)	24 (11-48)	0.889
Total cholesterol (mg/dL)	169 (123-238)	200 (95-271)	205 (70-250)	211 (99-302)	197 (133-325)	0.002*
LDL (mg/dL)	101 (43-167)	118 (36-182)	122 (21-175)	124 (28-212)	109 (61-218)	0.070
HDL (mg/dL)	50 (31-80)	46 (34-86)	42 (25-66)	40 (25-70)	38 (27-61)	<0.001*
Triglycerides (mg/dL)	89 (53-188)	126 (55-329)	174 (91-309)	212 (94-392)	231 (75-646)	<0.001*
AIP	0.26 (0.02-0.75)	0.38 (0.07-0.74)	0.57 (0.21-0.98)	0.75 (0.30-1.10)	0.81 (0.23-1.50)	<0.001*

CAC: Coronary artery calcium, PR: Prevalence ratio, LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end diastolic distance, LVESD: Left ventricular end-systolic dimension, WBC: White blood cell, GFR: Glomerular filtration rate, BUN: Blood urea nitrogen, ALT: Alanine transferase, LDL: Low-density protein, HDL: High-density lipoprotein, AIP: Atherogenic index of plasma

Table 2. Regression analyses for the prediction of CAC score

Parameters	Univariate			Multivariate		
	B±SE	95% CI	p-value	B ± SE	95% CI	p-value
WBC (x10³/μL)	0.118±0.046	0.026-0.209	0.012*	-0.039±0.101	(-0.238)-0.160	0.701
Neutrophils (x10³/μL)	0.114±0.052	0.012-0.216	0.029*	0.037±0.043	(-0.048)-0.122	0.393
Hemoglobin (g/dL)	0.106±0.064	(-0.020)-0.231	0.098	-	-	-
Creatinine (mg/dL)	1.720±0.635	0.466-2.974	0.007*	0.338±0.510	(-0.670)-1.346	0.509
BUN (mg/dL)	0.036±0.014	0.009-0.062	0.009*	0.027±0.010	0.007-0.047	0.010*
HbA1c (%)	0.471±0.098	0.277-0.664	<0.001*	0.272±0.085	0.105-0.439	0.002*
Total cholesterol (mg/dL)	0.007±0.002	0.002-0.012	0.004*	-0.004±0.004	(-0.012)-0.004	0.316
LDL (mg/dL)	0.006±0.003	0.000-0.012	0.037*	0.003±0.002	(-0.002)-0.007	0.239
HDL (mg/dL)	-0.054±0.009	(-0.071)-(-0.037)	<0.001*	0.004±0.012	(-0.020)-0.029	0.738
Triglycerides (mg/dL)	0.008±0.001	0.006-0.010	<0.001*	0.000±0.002	(-0.004)-0.004	0.816
AIP	3.273±0.283	2.715-3.830	<0.001*	3.061±0.289	2.490-3.632	<0.001*

CAC: Coronary artery calcium, CI: Confidence interval, WBC: White blood cell, BUN: Blood urea nitrogen, LDL: Low-density protein, HDL: High-density lipoprotein, AIP: Atherogenic index of plasma

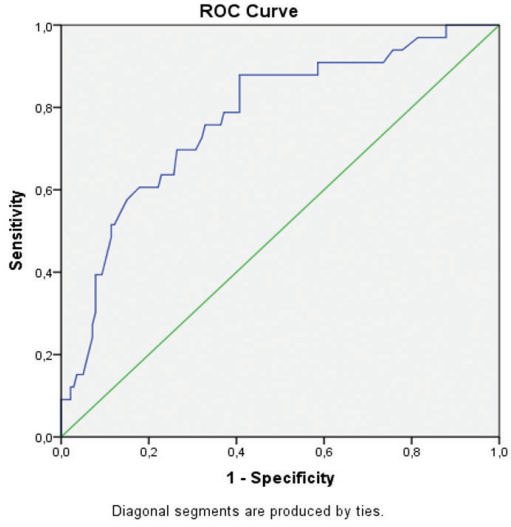

Figure 1. The ROC curve of AIP for predicting CAC score ≥400
AIP ≥0.60 sensitivity 75.8%, specificity 67.1%
AUC: 0.774 (95% CI: 0.685-0.863), p<0.001
ROC: Receiver operating characteristics, AIP: Atherogenic index of plasma, CAC: Coronary artery calcium, AUC: Areas under the curve, CI: Confidence interval

p<0.001; Figure 1). Above this threshold, CAC was detected with a sensitivity 75.8% and a specificity 67.1%.

Discussion

The key finding of this study is that AIP is may be a useful and valuable indicator of the extent of coronary calcification in patients with uncertain and suspected coronary artery disease. As we know in the literature, this is the first study to demonstrate the strong relationship between AIP and the severity of coronary calcification in patients with suspected coronary artery disease.

Primary prevention of CVD includes low-risk strategies such as behavioral and lifestyle management, as well as treatment modalities for optimal control of comorbidities (1). Furthermore, the identification of individuals who would benefit from cardiovascular treatment could place an enormous burden on the healthcare system, and it remains a challenge for physicians to assess the appropriate patients with the most appropriate diagnostic approach to classify cardiovascular risk. Therefore, various risk stratification tools have been developed to identify study patients who are not only at high risk for future cardiovascular events but also prefer invasive and non-invasive cardiovascular treatment. In this context, CAC imaging has been developed as a quantitative measure of coronary atherosclerotic burden and a predictor of future cardiovascular events in patients with uncertain and suspected coronary artery disease (17,18). Based on the available data, when applied to selected individuals, this diagnostic approach has a high discriminatory ability for the degree of coronary artery disease and may prevent further examination of coronary artery disease. In addition, this imaging modality is useful in assessing myocardial scar and the size of the ventricles and ascending aorta (19). However, the predictive value of CAC estimation for detecting coronary plaque instability remains controversial (9). Furthermore, lower CAC values are not sufficient to exclude an increased risk of future cardiovascular events, especially in individuals with modifiable cardiovascular risk factors such as diabetes mellitus, smoking, or a family history of premature cardiovascular death (20). Therefore, the American Heart

Association guidelines for cholesterol screening do not recommend the diagnostic use of CAC imaging in people with these risk factors (21). Therefore, novel non-invasive diagnostic tests are urgently needed to determine the pre-test probability of uncertain coronary artery disease and to accurately stratify people with uncertain coronary artery disease.

In our study, we used the most appropriate atherosclerotic index to examine the presence and degree of coronary artery disease in patients undergoing cardiac CT for suspected coronary artery disease. In addition, to observe the relationship between CAC score and AIP, we divided patients into subgroups according to their current CAC score. According to our data, when patients were divided into subgroups with similar numbers, significantly higher AIP levels were found in patients with high CAC scores.

As there is a direct link between altered lipid metabolism and the onset and development of coronary heart disease, the logarithm of the molar ratio of TG to HDL-C is consistent with an elevated risk of coronary heart disease (22,23). Furthermore, this relationship has been confirmed by several studies in different atherosclerotic conditions such as obesity, hypertension, DM, insulin resistance, and metabolic syndrome (24-25). Therefore, AIP stands out as a potential biomarker for research into the presence and severity of coronary artery disease. However, any other studies have not investigated the association between AIP and an increased risk of coronary heart disease, especially in people without a known history of coronary heart disease. In our study, we used a well-known CT imaging parameter to confirm the presence of atherosclerosis and observed a significant correlation between AIP and the calculated total CAC score. According to our study, the higher the CAC score, the higher the AIP value. After adjustment for variables affecting the presence and degree of coronary artery disease, multivariate regression analysis determined that AIP was still an independent risk factor for severe CAC. Based on these results, we suggest that high AIP can be considered a quantitative measure of coronary atherosclerotic burden and an indicator of future cardiovascular scenes in patients with uncertain coronary artery disease.

There are some limitations of our study. First, it is a retrospective, single-center study with a limited number of patients. Second, due to the lack of continuous measurement of blood tests in this study, AIP levels were measured at a single point in time, and the fluctuation of AIP levels was not taken into account. Follow-up monitoring could be provide extra predictive value. Thirdly, we did not compare AIP measurements with other hematological and biochemical markers.

Conclusion

The current study revealed that the AIP is an independent predictor of coronary calcification. This index is a simple, inexpensive, and non-invasive prognostic tool that can be used for cardiovascular risk stratification.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Necmettin Erbakan University Faculty of Medicine (decision no: 2022/3883, date: 01.07.2022).

Informed Consent: Informed consent form was taken from all study patients, and the study was approved by the committee following the ethical guidelines of the 1975 Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.L.S., A.İ., C.K., Concept: A.L.S., Design: A.T.Ş., Data Collection or Processing: A.T.Ş., C.K., P.D.Y., Analysis or Interpretation: N.A., A.İ., Literature Search: M.D., A.İ., Writing: A.L.S.

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