

Examining the relationship between the atherogenic index of plasma and coronary plaque burden: insights from a retrospective intravascular ultrasound analysis

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ABSTRACT

Aims: In the context of coronary artery disease development, inflammation and lipid metabolism play significant roles. This study explores the link between the Atherogenic Index of Plasma (AIP) and plaque burden in intravascular ultrasound (IVUS) examined patients.

Methods: A retrospective analysis included seventy-six consecutive IVUS patients from June 2020 to May 2023. AIP, calculated as the log of plasma triglyceride divided by high-density lipoprotein cholesterol, measured atherogenicity. Plaque burden, a percentage, was determined by dividing the total plaque area by the total vessel area. Multivariate regression and Spearman's correlation analyzed the relationship between AIP and high plaque burden.

Results: The median age was 59 years, with 72.4% males. Univariate analysis identified age, diabetes mellitus (DM), smoking, and AIP as plaque burden predictors. Multivariate analysis showed AIP (OR=1.53, 95% CI:1.12-2.02, p=0.021) and DM independently predicted high plaque burden (OR=1.03, 95% CI:1.01-1.45, p=0.044). Spearman's correlation indicated a positive correlation between AIP and high plaque burden (rho: 0.682, p<0.05).

Conclusion: This study suggests AIP, a surrogate marker of atherosclerosis, may predict plaque burden in IVUS-examined patients.

Keywords: Atherogenic index of plasma, coronary plaque burden, intravascular ultrasound

INTRODUCTION

Coronary artery disease (CAD) manifests as a clinical outcome of atherosclerotic plaque formation, whether obstructive or non-obstructive, within the epicardial arteries.¹⁻³ In the complex process of atherogenesis, which is the main cause of CAD, basic risk factors such as inflammation, abnormal glucose metabolism and dyslipidemia contribute to the development of CAD.^{4,5} The Atherogenic Index of Plasma (AIP) serves as a comprehensive metric, capturing the delicate balance between atherogenic and anti-atherogenic factors.⁶ Previous studies have explored the connection between AIP, CAD and coronary plaque burden, revealing an association between elevated AIP levels, an increased risk of CAD, and a higher prevalence of coronary plaques.⁷⁻⁹ Elevated AIP levels indicate an imbalance in lipid metabolism, characterized by heightened atherogenic lipids like low-density lipoprotein (LDL) cholesterol and diminished levels of anti-atherogenic lipids, including high-density lipoprotein (HDL) cholesterol.¹⁰ This underscores the link between an unfavourable lipid

profile, reflected by an increased atherogenic index, and the progression of atherosclerosis.¹¹

Atherosclerosis, marked by the accumulation of fatty deposits within arteries, underscores the importance of assessing plaque burden to evaluate disease severity and its impact on vascular health.¹² Intravascular ultrasound (IVUS) serves as a sophisticated imaging modality, providing high-precision visualization and measurement of atherosclerosis and plaque burden.¹³ Unlike conventional angiography's two-dimensional depiction of blood vessels, IVUS uses a catheter equipped with an ultrasound probe to generate real-time cross-sectional images of vessel walls. This capability not only facilitates the evaluation of plaque size but also enables the characterization of atherosclerotic plaques, aiding in precise disease assessment and guiding tailored treatment strategies. IVUS plays a pivotal role in interventional cardiology, offering detailed insights into plaque features and informing therapeutic decisions, including the optimal placement of stents or other interventions to optimize vascular health.^{14,15}

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Despite existing research exploring the relationship between AIP and atherosclerosis, a distinct research gap exists concerning the utilization of IVUS, a modality celebrated for its heightened accuracy in assessing plaque burden. This study aims to bridge this gap by investigating the association between IVUS-measured plaque burden and the AIP. Our findings aspire to illuminate the predictive capacity of the AIP in the context of IVUS-measured plaque burden, providing valuable contributions to the understanding of vascular health and atherosclerotic conditions.

METHODS

Ethics

The study adhered to the ethical principles outlined in the Declaration of Helsinki, and Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee approved the study protocol on 13.12.2023 (Decision Number: 665). The retrospective nature of the study obviated the need for written informed consent.

This retrospective observational study enrolled 76 consecutive patients presenting to our outpatient clinic with stable angina pectoris and/or angina-equivalent symptoms, who subsequently underwent IVUS following conventional angiography between June 2020 and May 2023. IVUS examinations were conducted based on the following criteria: (i) presence of angiographically indeterminate left main CAD: This criterion is applied to cases demonstrating a 50% to 70% diameter narrowing of the left main coronary artery on angiography. (ii) IVUS guidance for coronary stent placement, especially in left main coronary artery stenting cases: IVUS was employed as a guiding tool both before and after coronary stent placement, with a particular focus on cases involving LMCA stenting.¹⁶ Individuals who fulfilled any of the following criteria were not included in the study: those with endocrine disorders, individuals who had taken antihyperlipidemic medication in the last six months, those experiencing ongoing infections, individuals with current malignancies, advanced liver disease, or end-stage renal disease. Demographic, laboratory, and clinical data for the final analysis were subsequently retrieved from our institution's electronic medical record system for the remaining 76 individuals.

Coronary Angiography and IVUS

During coronary angiography and IVUS procedures, either radial or femoral access was employed for vascular entry. Following the administration of 300 mcg of perlinganite and 60/kg IU of unfractionated heparin to prevent thrombotic complications, imaging was initiated. IVUS images were subsequently analyzed by two independent reviewers. Plaque burden, denoted as a percentage, was calculated by dividing the total plaque

area by the total vessel area. Individuals exhibiting a plaque burden surpassing 70% were categorized as having a high plaque burden, while those with a plaque burden below 70% were classified as having a low plaque burden. The study cohort consisted of a final group of 76 subjects, all of whom underwent IVUS using either a commercially available 40-MHz rotational transducer (OptiCross/Boston Scientific/Costa -Rica). The IVUS pullbacks were executed automatically. The images, acquired at a rate of 30 frames per second in digital format, adhered to DICOM standards and were stored in the picture archiving and communication system for subsequent analysis and reference.

Definitions and Risk Factors

Baseline laboratory parameters, including complete blood count using the Beckman Coulter LH 750 instrument in Fullerton, California, USA, and lipid profile analyzed with the Cobas C7001 system from Roche Diagnostics in Rotkreuz, Switzerland, were meticulously documented for each patient before the procedure. Renal function was assessed using the validated Modification of Diet in Renal Disease Study formula.¹⁷ Hypertension (HT) was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or use of antihypertensive medication.¹⁸ Diabetes mellitus (DM) was identified based on fasting glucose levels ≥ 126 mg/dl, postprandial levels ≥ 200 mg/dl, or antidiabetic therapy. Dyslipidemia was confirmed with patterns such as total cholesterol ≥ 240 mg/dl, LDL ≥ 130 mg/dl, HDL <40 mg/dl (men) or <50 mg/dl (women), and triglycerides ≥ 150 mg/dl.¹⁹ Body mass index (BMI) was calculated as the ratio of weight in kilograms to the square of height in meters (kg/m^2). Smoking status was determined by considering a participant a current smoker if they were consistently smoking or had smoked in the 1 month leading up to the study. The AIP was computed using the formula $\log(\text{plasma TG}/\text{HDL})$,²⁰ providing a valuable metric for assessing the atherogenic risk profile of the participants.

Statistical Analysis

The data were summarized as median [interquartile range (IQR)] for continuous variables and as percentages (n) for categorical variables. The normality of the distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Participants were stratified into two groups based on plaque burden. Non-normally distributed continuous variables were compared using the Mann–Whitney U-test, while the Pearson Chi-square test was employed to compare the frequency of categorical variables between these groups.

Parameters demonstrating significant differences between the groups were included in both univariate and multivariate regression analyses. Subsequently,

the predictive performance of serum AIP was assessed through receiver operating characteristics curve (ROC) analysis. Spearman analysis was conducted to explore the correlation between plaque burden and AIP. A significance level of $p < 0.05$ was applied to all analyses, and a confidence interval of 95% was considered. Statistical Package for the Social Sciences (SPSS version 22.0, SPSS Inc., Chicago, IL, USA) was utilized for these statistical assessments.

RESULTS

Baseline Characteristics

The total study population included 76 participants with a median age of 59 years (IQR:55-68) years, 55 (72.4%) of whom were male. The median age in the high plaque burden group was older than in the low plaque burden group [62 (55-69) vs 56.5 (52-61), $p = 0.041$]. Similarly, the high plaque burden group exhibited a statistically higher incidence of DM ($p = 0.011$) and smoking

($p < 0.031$). Male gender, family history of CAD, and BMI were, on the other hand, comparable between the groups. In addition, the high plaque burden group had higher TG and low HDL levels ($p < 0.05$, for all). **Table 1** presents a comprehensive overview of the demographic, clinical, and laboratory characteristics of the study population categorized by plaque burden.

Independent Predictors of Plaque Burden

Univariate analysis showed that age, smoking, DM and AIP were significantly associated with plaque burden (age: OR 1.03, 95% CI 1.01-1.05, $p = 0.049$; smoking: OR 1.05, 95% CI 1.02-1.25, $p = 0.031$; DM: OR 1.34, 95% CI 1.05-1.52, $p = 0.029$; AIP: OR 1.71, 95% CI 1.41-2.5, $p < 0.001$) (**Table 2**). The AIP (OR:1.53, 95% CI 1.12-2.02, $p = 0.021$) and DM (OR=1.03, 95% CI:1.01-1.45, $p = 0.044$) continued to be an independent predictor of plaque burden even after several risk factors, including important clinical variables in the univariate model, were included in the multivariate model for adjustment (**Table 2**).

Table 1. Baseline characteristics of the study population

Variables	Plaque Burden			p-value*
	Overall (n= 76)	Low (n=21)	High (n=55)	
Demographic features and risk factors				
Age; median, (IQR)	59 (55-68)	56.5 (52-61)	62 (55-69)	0.041
Male; n (%)	55 (72.4%)	10 (55.6)	45 (77.6)	0.068
DM; n (%)	45 (59.2)	6 (33.3)	39 (67.2)	0.011
HT; n (%)	52 (68.4)	12 (66.7)	40 (69.0)	0.855
HL; n (%)	56 (73.7)	13 (72.2)	43 (74.1)	0.872
Smoking; n (%)	38 (50.0)	5 (27.8)	33 (56.9)	0.031
Family history of CAD; n (%)	25 (32.9)	3 (16.7)	22 (37.9)	0.093
BMI	23.6(22.7-24.6)	23.7(22.5-24.4)	23.7(23.0-24.3)	0.315
Angiographic results, n (%)				
Laboratory findings				
Total cholesterol, mmol/L; median [IQR]	4.33 (3.50-5.53)	4.14 (3.05-5.30)	4.33 (3.68-5.59)	0.337
Triglyceride, mmol/L; median [IQR]	1.54 (1.07-2.14)	1.07(0.85-1.46)	1.71 (1.32-2.23)	<0.001
HDL-C, mmol/L; median [IQR]	1.03 (0.82-1.26)	1.19(0.97-1.35)	0.99(0.80-1.21)	0.034
LDL-C, mmol/L; median [IQR]	2.59 (1.70-3.47)	2.61 (1.58-3.45)	2.59 (1.91-3.47)	0.574
Creatinine, mg/dl; median [IQR]	0.85 (0.74-1.04)	0.87 (0.71-0.98)	0.85 (0.7-1.04)	0.990
e-GFR, ml/min/1.73 m ² ; Median [IQR]	91 (72-99)	95 (71-99)	91 (71-99)	0.660
Glucose, mg/dl; median [IQR]	106 (90-151)	108 (96-122)	125 (114-157)	0.174
WBC,10 ³ /dl; median [IQR]	8.4 (7.2-10.5)	7.2 (6.2-9.4)	8.6 (7.2-10.8)	0.108
Haemoglobin, g/dl; median [IQR]	13.3 (12.0-14.6)	13.6 (12.4-14.5)	13.5 (11.9-14.5)	0.341
Platelet count,10 ³ /dl; median [IQR]	254 (204-300)	263 (220-296)	253 (205-309)	0.660
Lymphocyte, cells/μl, median [IQR]	2.0 (1.5-2.5)	2.0 (1.6-2.9)	2.1 (1.4-2.5)	0.696
Neutrophils, cells/μl; median [IQR]	4.9 (4.1-7.4)	5.2 (4.6-7.6)	4.8 (3.9-7.3)	0.396
CRP, mg/l; median [IQR]	3.95 (1.35-7.9)	4.9 (3.9-6.1)	7.6 (5.5-9.3)	0.305
Albumin, g/dl; median [IQR]	4.0 (3.7-4.3)	2.7 (0.75-8.0)	4.1 (2.0-8.1)	0.681
Medications prescribed at discharge, n (%)				
Antiplatelets, n (%)	58 (76.3)	16 (76.1)	48 (76.3)	0.901
B-blockers, n (%)	37 (48.6)	10 (47.6)	27 (49.0)	0.801
ACEIs or ARBs	22 (28.9)	6 (28.5)	16 (29.0)	0.755
OAD, n (%)	25 (32.8)	5 (23.8)	20 (36.3)	0.091

Values are presented as numbers (n) and percentages (%), mean±standard deviation, or median (interquartile range 25th-75th percentiles). For continuous data, the p-value was calculated using the Mann-Whitney U-test, and for categorical variables, the Chi-Square test or Fisher's exact test, as appropriate.
* $p < 0.05$ was considered statistical significance. Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CRP, C-reactive protein;DM,diabetes mellitus;e-GFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; HL, hyperlipidemia; IQR, interquartile range, LDL-C, low-density lipoprotein cholesterol; OAD, oral antidiabetic drug; WBC, white blood cell.

Table 2. Univariate and multivariate regression analysis for predicting plaque burden

Variable	Univariate Analysis			Multivariate Analysis		
	OR	CI(95%)	p value*	OR	CI (95%)	p value*
Age	1.03	1.01-1.05	0.049	0.98	0.96-1.00	0.280
Smoking	1.05	1.02-1.25	0.031	1.01	0.99-1.05	0.080
DM	1.34	1.05-1.52	0.029	1.03	1.01-1.45	0.044
TG/HDL	1.75	1.41-2.5	<0.001	1.53	1.12-2.02	0.021

*p<0.05 was considered statistical significance. Abbreviations: DM, diabetes mellitus; e-GFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; TG, Triglyceride.

Diagnostic Performance of AIP for Plaque Burden

ROC analysis was conducted to assess the predictive capability of AIP levels in estimating a high plaque burden. The results of the ROC analyses indicated that AIP exhibited a reasonable ability to predict a high plaque burden (AUC:0.897, p<0.001), as illustrated in **Figure 1**. The determined cut-off value for AIP was 0.25, providing a sensitivity of 78.8% and specificity of 83.7%.

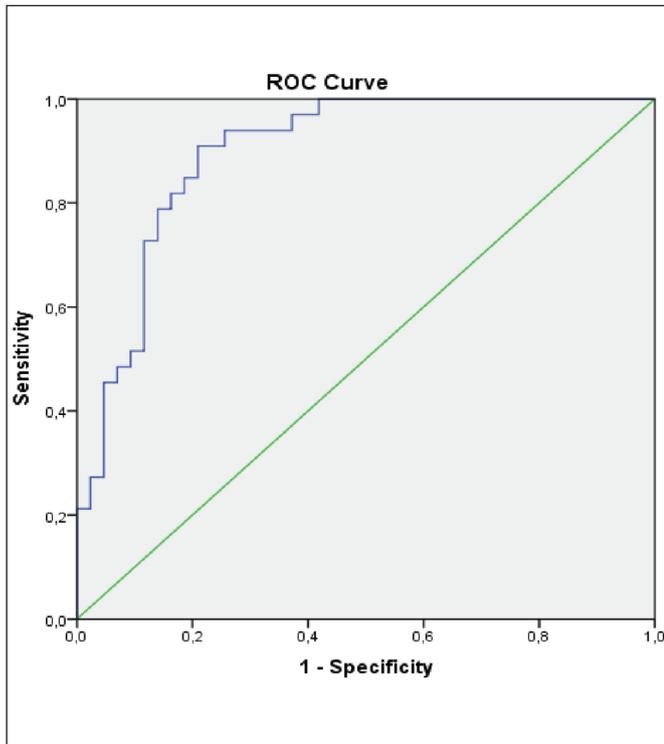


Figure 1. Receiver operating characteristics (ROC) curve analysis

Additionally, Spearman’s analysis demonstrated a positive correlation between AIP and plaque burden (rho=0.682, p<0.001), as depicted in **Figure 2**. These findings suggest that AIP levels may serve as a valuable predictor for identifying individuals with a high plaque burden.

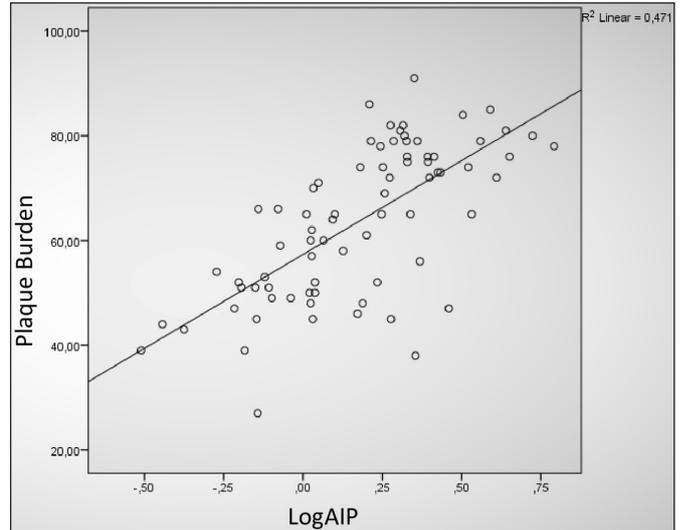


Figure 2. Spearman’s correlation analysis

DISCUSSION

Our study revealed a robust positive correlation between AIP and plaque burden as detected by IVUS. These findings provide valuable insights into the intricate interplay among lipid metabolism, inflammation, and atherogenesis, particularly within the context of CAD.

Lipid accumulation in the arterial intima is the initial phase of the progression of atherosclerosis.² The relationship between LDL-C, HDL-C, total cholesterol, TG levels, and intimal lipid deposition is well demonstrated.^{1,2,4} Moreover, small dense LDL (Sd-LDL) particles, resulting from the conversion of triglycerides, are more susceptible to oxidation, promoting the formation of foam cells. Oxidized apoprotein B and LDL-C are recognized as highly atherogenic.^{21,22} Furthermore, Sd-LDL particles exacerbate atherosclerosis by activating oxygen radicals, promoting lipid peroxidation, and expressing adhesion molecules in endothelial cells, all of which are associated with endothelial dysfunction.^{1,22} Contrary, HDL-C comprises antioxidant properties by transporting peripheral cholesterol to the liver and containing some antioxidant enzymes.¹ AIP is a new prognostic index associated with plasma TG and HDL-C levels.²³ AIP levels rise in response to elevated TG and/or decreased HDL levels.^{10,21} An increase in AIP suggests a decrease in the diameter of LDL particles and a rise in sd-LDL levels.^{4,21,24} AIP has also been shown to accurately reflect sd-LDL levels.^{21,22} All current approaches for detecting sd-LDL are costly, have limitations, and are difficult to scale in clinical settings. AIP, on the other hand, is simple to calculate. Based on these findings, there is growing evidence that AIP might be a significant predictor of atherosclerosis and cardiovascular diseases.^{6,7,24}

Our study has revealed a significant correlation between an elevated AIP and arterial plaque burden. Notably, this heightened risk of plaque burden persisted even after adjusting for traditional cardiovascular risk factors. Our findings align with prior research that has established a robust connection between the AIP index and atherosclerosis.^{7,9,10} The incorporation of the AIP index into routine clinical diagnostic models holds promise for enhancing the precision of identifying atherosclerosis and plaque burden.

To the best of our knowledge, our study is the first to investigate plaque burden in patients diagnosed with CAD using the AIP in conjunction with IVUS. IVUS, offering a more comprehensive evaluation that goes beyond mere stenosis detection, provides superior insights into plaque structure, vulnerability, and burden compared to conventional angiography.²⁵ Despite technological advancements, IVUS has become pivotal in guiding invasive treatments for CAD through anatomical assessments. However, concerns persist about its widespread use, primarily due to potential invasive complications and associated costs. As emphasized in our study, a cost-effective, and reliable approach may involve integrating AIP indices with clinical findings. This combination could serve as a significant parameter for predicting atherosclerosis and plaque burden, providing a valuable tool for risk assessment and management in clinical practice.

Limitations

The findings of our study have several limitations. Firstly, inherent limitations are associated with the retrospective observational nature of the study. Secondly, the sample size may be considered insufficient, necessitating a larger cohort for more robust statistical analyses. Thirdly, in instances where IVUS image quality is suboptimal, accurately assessing plaque boundaries may pose challenges, potentially leading to measurement inaccuracies. Fourth, as automatic measurements are not feasible and rely on operator experience, the potential for bias exists. To mitigate all these limitations, our study was conducted by experienced operators who captured optimal images, revealing a strong relationship between AIP and plaque burden.

CONCLUSION

This investigation presents compelling evidence suggesting that the AIP, recognized as a surrogate marker for atherosclerosis, could function as a valuable predictive tool in evaluating plaque burden among patients undergoing IVUS examinations.

These results enhance our comprehension of the interconnection between lipid metabolism, inflammation, and the development of atherosclerosis, offering potential assistance in the evaluation of risks and the management of the associated diseases.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date:13.12.2023, Decision No: 665).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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