

Utility of Atherogenic Index of Plasma in Predicting Plaque Burden in Patients with Chest Pain and Intermediate Pretest Probability of Coronary Artery Disease

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Abstract

Objective: We aimed to explore the utility of atherogenic index of plasma (AIP) on plaque burden detected by coronary computed tomography angiography (CCTA) in patients with chest pain and intermediate probability of coronary artery disease (CAD).

Methods: AIP was calculated as the logarithmically transformed ratio of the serum triglycerides to HDL-cholesterol in 167 patients with chest pain (age 46.5 ± 11.8 yrs; 104 were men) and correlated with segment stenosis score (SSS), SIS and total plaque score (TPS), studied with CCTA, and compared with other lipid ratios.

Results: Obstructive CAD lesions were detected in 45.5% of patients with intermediate pretest probability of CAD. CCTA documented CAD was detected in 61.7% subjects with AIP value >0.24 , while CAD was detected in 26.5% patients with AIP value <0.24 . AIP was 0.49 ± 0.12 in patients with CAD versus 0.14 ± 0.03 ; $p < 0.001$ in those without CAD. The total coronary artery calcium score (CACs) was significantly higher in patients with AIP >0.24 than in patients with AIP <0.24 ($p < 0.001$). AIP was correlated with SSS, SIS, TPS, and CACS ($p < 0.001$). Moreover, it seems to be the strongest ratio than other lipid ratios. AIP was the strongest predictor of plaque burden. ROC analysis demonstrated that AIP >0.29 was the optimal cut-off value in predicting CAD, with AUC=0.78, $p < 0.001$, and it was the strongest discriminator index compared with other lipid indices.

Conclusion: AIP was significantly correlated with plaque burden and extent of CAD in patients with intermediate pretest probability of CAD who presented with chest pain and it could help in risk stratification.

Keywords: Atherogenic index; Coronary; Plaque burden; Angiography

Introduction

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in both developing and developed countries. Dyslipidemia is one of the major risk factors for coronary artery disease. Lower high-density lipoprotein cholesterol (HDL-C), higher low-density lipoprotein cholesterol (LDL-C), and elevated triglycerides (TG) may contribute to the progression of atherosclerosis [1,2].

A growing body of evidence shows that the use of conventional lipid profile indices might be inaccurate in evaluation of cardiovascular (CV) risk [3-5].

A considerable proportion of subjects with CV atherosclerosis have levels of both total cholesterol and LDL-C within the accepted reference values [6,7]. Furthermore, reduction of LDL-C to the recommended levels, about 50% many, still at high risk to develop CV atherosclerotic diseases [8].

The comprehensive lipid indexes, such as non-HDL-C, TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, was believed to be superior to single lipid parameters in predicting cardiovascular outcomes [9,10]. Dobiášová et al. [11] defined AIP as the logarithmically transformed ratio of TG to HDL-C, which reflects the presence of atherogenic small

LDL and small HDL particles, and could be calculated simply. Moreover, they reported that, AIP has higher value in predicting coronary artery (CAD) in patients with higher risk for CAD.

Coronary computed tomography angiography (CCTA) is a noninvasive modality with high specificity and negative predictive value; it can detect coronary artery stenosis with a good image quality [12,13].

The prediction of plaque burden in patients with intermediate pretest probability for CAD is not clearly studied. We hypothesized that AIP, might be superior to other lipid ratios in predicting CAD in subjects presented with chest pain and supposed to have intermediate pretest probability for CAD. Therefore, we aimed to investigate the association between AIP and plaque burden utilizing CCTA, compared with other lipid ratios, in such patients.

Subject and Methods

We prospectively screened in a cross-sectional study, 250 consecutive patients presented with acute chest pain and referred to CCTA for exclusion of CAD. Subjects supposed to have intermediate pretest probability of CAD included men with atypical pain who were >30 -years-old, and for women with atypical pain who were >50 -years-old. CAD risk factors assessment for all individuals included: (i) Diabetes mellitus; (ii) Hypercholesterolemia; (iii) Hypertension; (iv)

Obesity; (v) Positive family history; and (vi) Smoking. Clinical examination was performed including blood pressure and pulse pressure evaluation. The pretest probability of CAD was determined by age, sex and the nature of chest pain during initial presentation, and classified as low (<10%), intermediate (10%-90%) and high (>90%) [14]. Exclusion criteria were acute myocardial infarction, documented CAD, and/or previous coronary revascularization, severe coronary artery calcification, valvular heart disease, atrial fibrillation, chronic liver disease asthma and those with allergy to contrast material.

After strict application of inclusion criteria for supposed intermediate probability of CAD, 167 of the presented population were deemed to have intermediate probability of CAD constituted the main cohort of the study. They were categorized according to the level of AIP into two groups: the first included patients with a low AIP (<0.24) and the second included those with a high AIP (≥ 0.24), based the previous classification of AIP value by Hartopo et al. [15]. A written consent was obtained from all participates and all procedures of the study was performed according to the 1964 Helsinki declaration.

Laboratory analysis

Blood samples for plasma lipid measurement were taken using fasting blood sample. The following parameters were analyzed; fasting blood sugar (FBS), serum total cholesterol and triglyceride were determined by enzymatic estimation, while high density lipoprotein cholesterol was determined by enzymatic estimation after precipitation using commercially available kits on spectrophotometer [16]. Low density lipoprotein cholesterol and very low-density lipoprotein were determined using the Friedewald's formula as follows: $VLDL=TG/5$, $LDL-C=(TC)-(VLDL+HDL)$. ApoB and apoA-1 were measured using an immuno-turbidimetric method (Tina-quant; Roche Diagnostics) calibrated against the World Health Organization/International Federation of Clinical Chemistry reference standard SP3-07.

The AIP was determined by calculation based on formula= $\log_{10}$ of $[TG: HDL]$ [17]. All other included biomarkers were analyzed by standard hematological and biochemical tests.

Coronary CCTA evaluation

Heart rates were optimized to obtain a rate <60 bpm using oral 5 mg Bisoprolol, unless treatment with β -blocker was contraindicated. Imaging was performed for all patients using a 64-slice CT scanner. All CT examinations were performed during breath holding in inspiration, of approximately 10-20 sec.

CCTA was carried out with a 64-slice MDCT scanner (LightSpeed VCT; GE Medical Systems, Milwaukee, WI) to obtain CAC and MDCT Image acquisition as follows: collimation 64×0.625 mm, tube rotation 0.35 sec and electrocardiogram-modulated tube current 110-550 mA at 120 kV. Non-ionic contrast material was injected at $5-6.5$ ml sec^{-1} . Aggressive dose modulation was utilized for all appropriate patients, with the maximal tube current centered at 75% of the R-R interval.

Calcium score was calculated as previously described in Agatston scoring method [18]. The score of individual lesion was calculated by multiplying the lesion area by the density factor obtained from the maximal HU in that specific area. The sum of each score of all lesions detected along entire coronary artery tree obtained was obtained and was considered as total calcium score.

Measurement of plaque burden

We analyzed only coronary artery segments with diameters >2 mm. Morphologically, plaques were defined as structures $>1 \text{ mm}^2$ within and/or adjacent to the vessel lumen, that were clearly distinguished from the lumen and adjacent pericardial fat tissue. Each coronary segment was assigned one coronary plaque regardless of the number of lesions in that specific segment. The amount of stenosis in all coronary segments was visually assessed according to the Society of Cardiovascular Computed Tomography guidelines and was reported as no obstruction, luminal obstruction <25% (mild CAD), luminal obstruction 25%-50% (moderate), luminal obstruction 50%-70% (moderately severe) and luminal obstruction >70% (severe) for each segment. Plaque characteristics were described as calcified plaque (>130 HU), non-calcified plaque (<130 HU) and mixed plaque for each segment. A detailed analysis of the extent and severity of the CAD were performed using previously validated scores. We used the segment involvement score (SIS), which is calculated with the sum of the number of segments with CAD, ranging from 0 to 17 [19] and the segment severity score (SSS). Regarding the diameter stenosis, normal or no stenosis was assigned a score of 0, non-obstructive CAD was assigned a score of 1, 50%-70% stenosis was assigned 2, whilst, a stenosis more than 70% was assigned 3. Lastly, the score is the sum of each individual score, ranging from 0 to 51 [20].

Statistical analysis

SPSS 18.0 (Chicago, IL, USA) was utilized for statistical analysis. Continuous variables were presented as mean $\pm$ standard deviation (SD), and categorical variables were expressed as percentages. Spearman's correlation methods were used for assessing the relationship between Lipid ratios and SSS, SIS and TPS. Multivariable logistic regression analysis was performed to assess independent association between obstructive CAD and the studied lipid ratios. To assess cut-off values of lipid ratios in predicting obstructive CAD on CCTA, receiver-operating characteristic (ROC) curve analysis was used.

Results

The baseline data of the 167 subjects (46.5 ± 11.8), presented with chest pain and had intermediate pretest probability of CAD are represented in (Table 1). The CACS was 275 ± 214 . CCTA evidence of any plaque was detected in 86 (51.5%) subjects of the study population. Calcified/or mixed plaques were detected in 59 patients, while non-calcified plaques were detected in 27 subjects.

Variable	n=167
Age	46.5 ± 11.8
Male (%)	109 (65.3%)
Body mass index (kg/m ²)	26.2 ± 3.7
Waist circumference (cm)	97.5 ± 11.2
Smoking (%)	91 (54.5%)
Family history of premature CAD	83 (49.7%)
Hypertension (%)	101 (60.5%)
Dyslipidemia	91 (54.53%)

Diabetes mellitus	95 (56.9%)
Systolic blood pressure (mmHg)	159 ± 12
Diastolic blood pressure (mmHg)	85 ± 11
Total cholesterol (mg/dL)	189 ± 39
LDL-C (mg/dL)	113 ± 33
HDL-C (mg/dL)	49 ± 13
TG (mg/dL)	95 ± 65
Hs-CRP (mg/L)	2.4 ± 0.9
CCTA	
Coronary calcium score	275 ± 214
Non-obstructive coronary artery disease	91 (54.5%)
Obstructive coronary artery disease	76 (45.5%)
Calcified plaque or Mixed plaque	59 (35.4%)
Non-calcified plaque	27 (16.2%)
Segment stenosis score	7.3 ± 4.9
Segment involvement score	5.2 ± 2.4
Number of stenosed vessels	
One-vessel disease	41
Two vessel disease	27
Multivessel disease	8

Table 1: Characteristics of all studied subjects; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; TG: Total glycosides; Hs-CRP: High sensitive C-reactive protein.

Our results showed that 118/167 (70.7%) of the study subjects had AIP >0.24, while the remaining subjects had AIP <0.24. Table 2 represents a comparison between patients with AIP >0.24 versus those with AIP <0.24. We found that men, hypertension, diabetes mellitus and systolic blood pressure were more prevalent in those with AIP >0.24 ($p < 0.05$, all). More so, the prevalence of CCTA documented obstructive CAD was 61.9% (73/118), among subjects with AIP >0.24, while it was only 6.1% (3/49), among patients with AIP <0.24. Furthermore, the median CACS was significantly higher in patients with AIP >0.24 compared with those with AIP <0.24 ($P < 0.001$). Additionally, SSS, SIS and TPS were significantly higher in subjects with AIP >0.24 compared with those with AIP <0.24.

Variable	Group with AIP >0.24 (118)	Group with AIP <0.24 (49)	P value
Age	46.5 ± 6.9	45.1 ± 5.8	0.17
Male (%)	84 (71.2%)	25 (52%)	<0.05
Body mass index (kg/m ²)	26.2 ± 3.1	23.1 ± 3.2	0.09
Waist circumference (cm)	99.8 ± 9.1	94.5 ± 7.3	<0.05
Smoking (%)	85 (72%)	31 (63.3%)	0.09

Hypertension (%)	73 (61.8%)	28 (57.1%)	0.15
Diabetes mellitus	78 (66.1%)	17 (34.7%)	<0.05
Systolic blood pressure (mmHg)	145.8 ± 13.5	135.8 ± 11.5	<0.05
Diastolic blood pressure (mmHg)	85.9 ± 7.5	78.2 ± 7.1	0.08
Median CACS	395.0 (53-745)	83 (0-379)	<0.001
Any plaque	73 (61.7%)	13 (26.5%)	<0.001
Calcified/Mixed plaque	46 (39.9%)	13 (26.5%)	<0.05
Non-calcified plaque	27 (22.9%)	0	0.00
Total plaque score	7.5 ± 3.9	0.8 ± 0.5	<0.001
Segment stenosis score	7.3 ± 4.5	0.5 ± 0.9	<0.001
Segment involvement score	5.2 ± 2.4	1.2 ± 1.1	<0.001
Number of stenosed vessels			
One-vessel disease	38	3	<0.001
Two vessel disease	27	0	0.000
Multivessel disease	8	0	0.000

Table 2: Coronary computed tomography angiography and coronary artery calcium (CAC) characteristics of subjects with AIP >0.24 versus subjects with AIP <0.24.

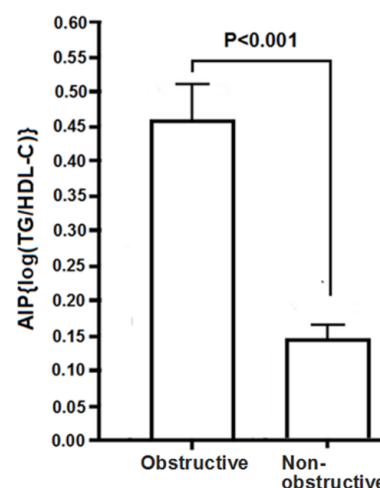


Figure 1: Comparison of atherogenic index of plasma between with versus coronary artery disease based on CCTA results. The AIP was significantly higher in patients with CAD ($p < 0.001$).

Compared with the patients without obstructive CAD, those with obstructive CAD, had significant increases in all lipid indices, including TC/HDL-C ($P < 0.05$), TG/HDL-C ($p < 0.01$), LDL-C/HDL-C ($p < 0.05$), apoB/apoA-1 ($p < 0.005$) and AIP ($p < 0.001$) (Figure 1). Moreover, men, systolic blood pressure, hypertensive subjects, diabetes mellitus, ApoB (g/L) and hs-CRP were significantly higher (Table 3).

Variable	Group with CAD (76=45.5%)	Group without CAD (91=54.5%)	P value
Age	46.7 ± 6.6	44.3 ± 6.2	0.093
Male (%)	59 (78%)	50 (54.9%)	<0.05
Body mass index (kg/m ²)	25.9 ± 3.3	23.5 ± 2.9	0.351
Waist circumference (cm)	97.5 ± 12.0	95.3 ± 9.8	0.269
Smoking (%)	34%	23%	0.162
Family history of premature CHD (%)	31.5%	28.2%	0.315
Systolic blood pressure (mmHg)	147.5 ± 16.5	131.5 ± 13.7	<0.05
Diastolic blood pressure (mmHg)	87.4 ± 7.8	76.5 ± 7.3	0.053
Hypertension (%)	60 (59.4%)	41 (40.6%)	<0.05
Diabetes mellitus	53 (69.7%)	42 (46.2%)	<0.05
Total cholesterol (mg/dL)	195.2 ± 31.8	172.4 ± 26.2	0.538
LDL-C (mg/dL)	115.4 ± 25.9	109.3 ± 21.5	0.731
HDL-C (mg/dL)	41.5 ± 7.2	54.2 ± 7.7	<0.05
TG (mg/dL)	98.2 ± 63.8	87.1 ± 45.4	<0.01
ApoA (g/L)	1.4 ± 0.4	1.4 ± 0.3	0.055
ApoB (g/L)	1.3 ± 0.3	1.0 ± 0.2	<0.03
Fasting glucose (mg/dL)	123.5 ± 22.1	109.8 ± 16.2	0.217
hs-CRP (median) (mg/L)	4.1 ± 1.3	1.3 ± 0.08	<0.05
LDL-C/HDL-C	2.6 ± 0.8	2.1 ± 0.8	<0.05
TG/HDL-C	2.3 ± 1.3	1.6 ± 1.0	<0.01
TC/HDL-C	4.6 ± 1.2	3.2 ± 1.1	<0.05
ApoB/apoA	0.93 ± 0.2	0.72 ± 0.2	<0.005
AIP	0.49 ± 0.12	0.14 ± 0.03	<0.001

Table 3: Baseline characteristics of patients with versus without obstructive coronary artery disease; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; TG: Total glycosides; Hs-CRP: High sensitive C-reactive protein; AIP: Atherogenic index of plasma.

Notably, AIP was 0.32 ± 0.06 in patient with one obstructive CAD (n=38), 0.45 ± 0.07 in those with two (n=27), 0.52 ± 0.03 in those with multi-vessel disease (n=8) (Figure 2).

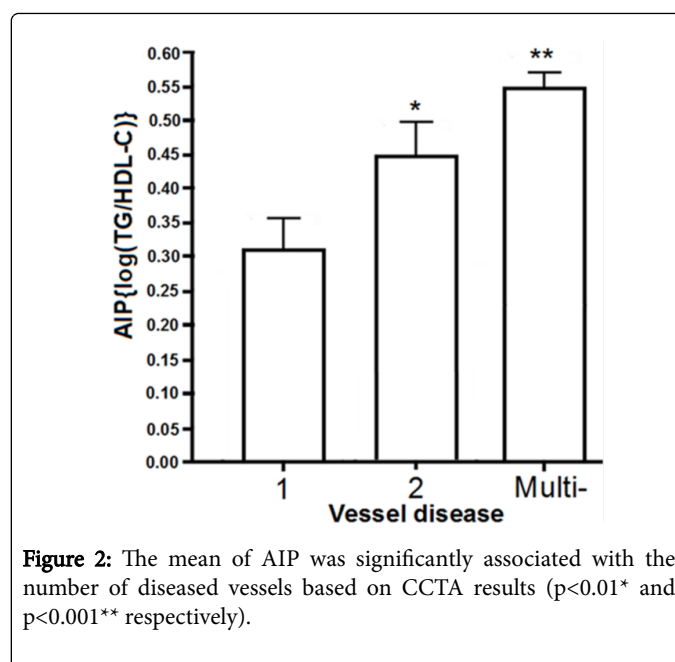


Figure 2: The mean of AIP was significantly associated with the number of diseased vessels based on CCTA results ($p<0.01^*$ and $p<0.001^{**}$ respectively).

Correlation between the lipid ratios and plaque burden

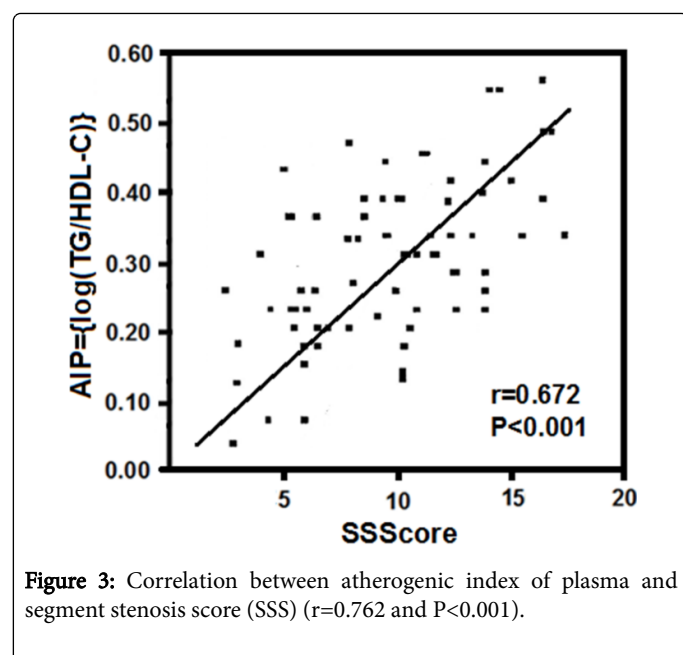
We analyzed the association between lipid ratios and plaque burden among the study cohort. When comparing all lipid ratios in terms of their power of correlation with high plaque burden, AIP index was stronger than any other ratio (Table 4). Figure 3 shows that, AIP was strongly correlated with SSS core ($r=0.672$; $p<0.001$).

	SSS		SIS		TPS	
	r	P	r	P	r	P
AIP	0.762	<0.001	0.539	<0.001	0.562	<0.001
ApoB/apoA-1	0.535	<0.01	0.513	<0.001	0.481	<0.03
LDL-C/HDL-C	0.138	0.071	0.155	0.063	0.193	0.059
TG/HDL-C	0.291	<0.05	0.211	<0.05	0.258	<0.05
TC/HDL-C	0.215	<0.05	0.195	<0.05	0.275	<0.05

Table 4: Correlation of lipid ratios with plaque burden in patients with coronary artery disease; SSS: Segmental stenosis score; SIS: Segment involvement score; TPS: Total plaque score.

AIP as a predictor of plaque burden on CCTA

Logistic regression analysis showed that, AIP has a significantly higher risk for plaque burden (odds ratio=4.26; 95% CI: 2.99-6.11; $p<0.001$), than any other studied variable. Whereas, with multivariate regression analysis, AIP emerged as the most powerful variable, in predicting the plaque burden (odds ratio=5.36; 3.28-7.89; $p<0.001$) (Table 5).



Variable	Univariate regression			Multivariate regression		
	OR		P value	OR		P value
Age	1.013	0.982-1.006	0.104	---		---
Men	1.951	1.529-2.382	<0.05	1.135	1.001-1.302	>0.05
BMI	0.952	0.748-1.164	0.3119	---		---
Systolic BP	1.625	1.142-2.153	<0.05	0.941	0.695-1.166	0.21
Diastolic BP	0.972	0.785-1.145	0.153	---		
Hypertension	1.813	1.295-2.452	<0.03	1.253	0.802-1.745	0.09
Diabetes	1.935	1.414-2.425	<0.03			0.06
hs-CRP	1.915	1.219-2.711	<0.05	0.892	0.725-1.085	0.35
LDL-C/HDL-C	1.836	1.355-2.329	0.293	---		
TG/HDL-C	1.962	1.436-2.528	<0.05	1.029	0.692-1.351	0.08
TC/HDL-C	1.735	1.288-2.195	<0.05	---		0.19
ApoB/apoA	2.385	1.562-3.295	<0.005	2.921	1.562-3.295	<0.005
AIP	5.361	3.218-7.893	<0.001	4.263	2.992-6.131	<0.001

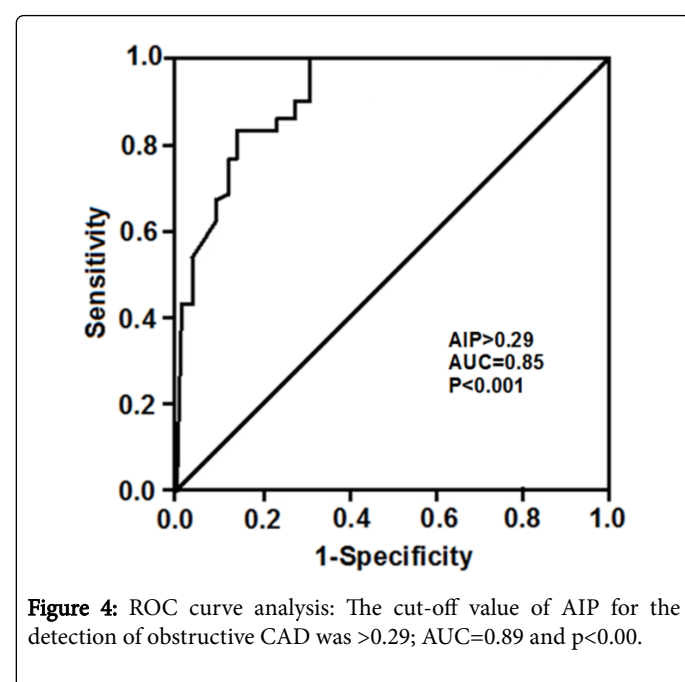
Table 5: Univariate and multivariate logistic regression analysis to determine the independent predictor for plaque burden.

ROC curve analysis demonstrated that, optimal cut-off value of AIP for the detection of obstructive CAD was >0.29 (sensitivity of 85% and

specificity of 79%, area under curve 0.78%) (Figure 4). Furthermore, the area under the curve (AUC), also indicated that AIP index had the strongest discriminatory power than other studied lipid ratios including, LDL-C/HDL-C, TC/HDL-C, TG/HDL-C, apoB/apoA-1 (AUC was 0.86, 0.61, 0.59, 0.64, and 0.74 respectively, and p was <0.001, <0.03, 0.05, 0.03, and 0.003 respectively) for detection of obstructive CAD (Table 6).

Lipid ratio	AUC	95% CI	P-value
LDL-C/HDL-C	0.61	0.55-0.68	0.03
TC/HDL-C	0.59	0.53-0.64	0.05
TG/HDL-C	0.64	0.56-0.71	0.03
ApoB/apoA	0.74	0.64-0.83	0.01
AIP	0.85	0.74-0.95	0.001

Table 6: Comparison of AUC among lipid ratios for predicting plaque burden among patients with intermediate risk for coronary artery disease.



Discussion

The current study, clearly demonstrated that, atherogenic index of plasma was an independent predictor of plaque burden in patients presented with chest pain and had deemed to have intermediate probability for CAD. We found that, 70.7% of patients with chest pain and intermediate pretest probability of CAD had $AIP>0.24$. Additionally, 61.9% of patients with $AIP>0.24$, had CCTA evidence of CAD, whilst only 26.5% of patients with $AIP<0.24$ had CAD. Interestingly, we found that, $AIP>0.29$ was the optimal cut-off value could predict the plaque burden in patients with pretest intermediate probability of CAD. Our index cut-off point is higher than that of Dobiášová et al. [11], a finding that may be related to different ethnic populations [21].

Clearly, higher values of TC, LDL-C, and TG and lowered levels of HDL-C, constitute the characteristics of atherogenic lipid profile, which is an important risk factor for cardiovascular diseases. Yet, the conventional lipid risk profile evaluation in assessing CAD may not always have adequate diagnostic accuracy [22,23].

In the current study, despite levels of LDL-C were comparable in the patient with and without CAD group AIP, which is a marker of LDL particular size, was found to be higher in the patient with CAD than in those with CAD. Meanwhile, although levels of total cholesterol and LDL-C were comparable among both groups; a significant positive correlation was found between AIP and segmental stenosis score [SSS]; segment involvement score [SIS]; and total plaque score [TPS], indicating that size of the particles rather than levels of LDL-C is important in increase. More so, our findings revealed that AIP was the strongest predictor associated with CAD with an unadjusted OR of 5.361 (95% CI: 3.218-7.893, $P < 0.001$). Meanwhile, AIP was the most powerful predictor for CAD (OR=4.263, 2.992-6.131; $P < 0.001$).

There is a considerable variation in AIP values in different ethnic populations, even in the same ethnic population, AIP also varied greatly [21]. In a study carried out by Cai et al. [24] the mean AIP level was 0.15 ± 0.34 (-1.7 to 1.55) in the overall population; and they reported that, this level was higher than that in a 40-year-old Slovak population (0.064 ± 0.310 in males and -0.150 ± 0.306 in females). In another study [25] conducted in a middle-aged Chinese population, the mean value of AIP was 0.092 ± 0.325 in the general population; this value was lower than the results of Cai et al.

Interestingly, we observed that AIP was the strongest discriminator for prediction plaque burden in subjects with intermediate pretest probability for CAD, compared to other lipid ratios. Notably we found that the AIP was the most powerful index, compared with all other ratios, including TC/HDL-C, TG/HDL-C, LDL-C/HDL-C, and apoB/apoA-1 ratio.

Khazaal [26] found that AIP had highest sensitivity and specificity when compared with the other three atherogenic indices (TC/HDL-C, HDL-C/LDL-C and LDL-C/HDL-C) in predicting cardiovascular risk in males. Nassau et al. [27] came to similar conclusion and reported that, a high AIP was clearly associated with a higher risk for CAD, compared with low AIP. Moreover, they found that atherogenic index of plasma was associated with the fractional esterification rate of HDL, and was inversely correlated with low density lipoprotein particle size.

All these arguments revealed that, AIP provides a good correction for the lack of normative distribution and reveals an association with smaller low-density lipoprotein particles, when compared to traditional pro-atherogenic lipid profile characterized by high total cholesterol, high triglycerides, high LDL and low high-density lipoprotein.

Limitation

First, the sample size of the studied population was relatively small. We depended upon CCTA for CAD exclusion including and invasive coronary angiography were not performed. Moreover we did not confirm plaque findings by standard methods like intravascular ultrasound, as it is not available. Adding to these limitations, this is a single-center study, so further multicenter studies are recommended.

Conclusion

We found that AIP value was significantly associated with plaque burden in patients with intermediate pretest probability for CAD compared with other lipid ratios. Moreover, our findings demonstrated that, AIP > 0.29 was the best cut-off value in predicting obstructive CAD in our cohort. Hence, the results revealed that, the AIP might confer as the better independent predictor for plaque burden. Being it is a simple index, AIP prevails a valuable parameter, which might be of great value in risk assessment of subjects with intermediate pretest probability of CAD.

Author Contribution

Ragab A. Mahfouz: Choice of the Idea; study design, sharing in the practical work and in writing the manuscript.

Mohammad Gouda: Sharing in the practical work and statistical analysis.

Islam Galal: Sharing in the practical work and in writing the manuscript.

Mohamed Salah: Sharing in the practical work and in writing the manuscript.

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