

Interplay Between Lipid-Derived Atherogenic Indices and Coronary Artery Calcium Score in Cardiovascular Risk Assessment

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ABSTRACT

Objective: To evaluate the association between lipid-derived atherogenic indices (atherogenic index of plasma (AIP), Castelli Risk Index-I (CRI-I), Castelli Risk Index-II (CRI-II), Atherogenic coefficient (AC), non-HDL-C) and coronary artery calcium score (CACS), and to compare the diagnostic ability of these indices for early diagnosis of coronary artery disease.

Methodology: This cross-sectional analytical study took place at departments of Cardiology, Pathology, and Cardiovascular Imaging at Punjab Institute of Cardiology, Lahore, from 2-05-2025 to 28-01-2026. 188 individuals presenting with chest pain were recruited through consecutive sampling. Blood samples were drawn for fasting lipid profile and HbA1c. AIP, CRI-I, CRI-II, AC and non-HDL-C were then calculated using standard formulae. CACS was determined using the Agatston scoring method on coronary CT angiography. Statistical analysis included Pearson's correlation, one-way ANOVA, and ROC curve analysis. The optimal cut-off value was identified using Youden's index.

Results: All the indices showed statistically significant correlation with CACS ($p < 0.05$). AIP showed the strongest positive association ($r = +0.278$, $p < 0.001$), followed by CRI-I ($r = +0.245$, $p = 0.001$) and AC ($r = +0.245$, $p = 0.001$). One-way ANOVA revealed that all indices differed significantly among all four classes of CACS ($p < 0.05$). AIP showed the highest discriminatory ability through ROC analysis (AUC=0.709; 95% CI: 0.636–0.782). The optimal cut-off value of AIP for predicting CAD was >0.27 . This threshold yielded a sensitivity of 50.5% and a specificity of 84.6% with an overall diagnostic accuracy of 69%.

Conclusion: AIP, CRI-I, CRI-II, AC and non-HDL-C showed significant positive correlation with CACS. AIP showed the highest diagnostic performance and an AIP cut-off value >0.27 may help in identifying individuals at increased risk of CAD.

Keywords: Atherogenic Indices, Coronary artery disease, Lipid Profile.

Authors' Contribution:

^{1,2}Conception; Literature research; manuscript design and drafting; ^{3,4}Critical analysis and manuscript review; ^{5,6,7}Data analysis; Manuscript Editing.

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Introduction

Coronary artery disease (CAD) is a condition in which atherosclerotic plaque builds up in coronary artery leading to narrowing and obstruction of lumen of

vessel, resulting in reduced blood flow which ultimately increases the risk of angina, myocardial infarction, heart failure and sudden death of individuals.^{1,2} CAD remains one of the leading causes

of morbidity and mortality worldwide. According to a study done in 2019, reported that coronary artery disease leads to approximately 18.6 million deaths per year.³ Although the prevention and management of the disease has progressed significantly, identifying individuals at risk at an early stage of CAD remains challenging. CAD is emerging as a major public health concern in developing countries like Pakistan.⁴ High prevalence of many modifiable risk factors such as diabetes mellitus, hypertension, smoking, and obesity have contributed to increased incident of Coronary artery disease especially in younger population in low and middle income countries.⁵ Atherosclerosis, the pathological process of CAD, is a progressive change characterized by lipid deposition, endothelial dysfunction, chronic inflammation and plaque formation within the arterial wall.

Conventional lipid profile parameters such as triglycerides (TG), total cholesterol (TC), highly density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) are used for CAD assessment.⁶ However, these markers do not fully represent the complex balance between atherogenic and anti-atherogenic lipoproteins. Therefore, many lipids derived atherogenic indices have gained significant attention as they are considered potentially more comprehensive indicators of cardiovascular risk. These lipid-derived indices include atherogenic index of plasma (AIP), Castelli Risk index-I (CRI-I), Castelli Risk index II (CRI-II), Atherogenic co-efficient (AC), non-HDL-C and comprise two or more lipid fractions in one measure. AIP is calculated as $\log_{10} (TG/HDL-C)$ and is considered as the surrogate marker of plasma atherogenicity.⁷ Similarly, Castelli risk indices and atherogenic co-efficient provide insights regarding the balance between atherogenic and protective lipoproteins, while non-HDL-C reflects total burden of atherogenic cholesterol particles that contribute to atherosclerosis.

On the other hand, besides biochemical markers, there are many imaging-based techniques that are

directly used for assessment of subclinical atherosclerosis. Coronary artery calcium score (CACS) is basically the quantification of calcified plaques and is measured by Agatston method on cardiac computerized tomography.⁸ CACS is also considered as established marker of cardiovascular event risk stratification. Since CACS is a cardiac imaging technique, it is not routinely available in many healthcare settings in low- and middle-income countries, this technique also exposes individuals to ionizing radiation.⁹

Although both CACS and lipid derived indices are independently related to CVD risk assessment, the relationship between CACS and lipid-derived atherogenic indices remain an area of interest. Also, limited dataset is available providing diagnostic accuracy of these lipid-derived indices using CACS as standard particularly related to Pakistani or South Asian population. The limitations of CT-defined CACS highlight the need for the development of simple, routinely available and easily accessible marker that may provide an economical and accessible tool for early cardiovascular risk assessment and may guide selection of individuals to benefit from CT angiography. Therefore, this study aims to evaluate the association between five lipid derived atherogenic indices (AIP, CRI-I, CRI-II, AC and non-HDL-C), which represents different aspects of atherogenicity with CACS in individuals presenting with retrosternal chest pain. This study will also assess the diagnostic performance of the indices in predicting early onset of coronary artery disease for Cardiovascular risk stratification or preventive interventions.

Methodology

This cross-sectional analytical study was conducted at the Departments of Cardiology, Pathology and Cardiovascular Imaging, Punjab Institute of Cardiology, Lahore from 2nd June 2025 to 28th January 2026. Our study population comprised individuals attending the outpatient department

with retrosternal chest pain undergoing cardiovascular evaluation. The inclusion criteria of study population included individuals ≥ 18 years of age, no history of chronic kidney disease, no significant ECG changes, not on corticosteroid therapy. Individuals on lipid-lowering therapy, with previously placed coronary artery stents, with a history of coronary artery bypass grafts, or having history of valvular heart disease were excluded from the study.

The sample size was calculated using OpenEpi sample size calculator for estimating a single population proportion. Based on the expected prevalence of 17% from a previously published article, assuming a finite population of 1,014 individuals, the minimum required sample size of 179 was estimated using a 95% confidence level, and a 5% margin of error, but it was increased to 188 individuals in order to compensate for missing or incomplete data¹. A total of 188 individuals were recruited using consecutive sampling technique and after obtaining informed consent from these individuals, 5 mL of the blood sample was drawn after an overnight fasting and these individuals underwent CT angiography.

Drawn blood samples were tested for parameters of lipid profile and glycated hemoglobin HbA1c. Parameters of lipid profile including serum triglycerides (TG), serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using standardized enzymatic colorimetric methods on a fully automated Siemens Atellica CH analyzer. HbA1c was tested through high performance liquid chromatography technique using BioRad D10 Haemoglobin system. Five lipid profiles derived atherogenic indices were calculated and these indices include Atherogenic index of plasma (AIP), Castelli risk index I (CRI-I), Castelli risk index II (CRI-II), Atherogenic co-efficient (AC), and non-high-density lipoprotein cholesterol (non-HDL-C).

These indices were calculated using following formulae;

$AIP = \log_{10} (TG/HDL-C)$, (TG and HDL-C expressed in mmol/L)

$CRI-I = TC/HDL-C$

$CRI-II = LDL-C/HDL-C$

$AC = (TC - HDL-C) / HDL-C$

$Non-HDL-C = TC - HDL-C$

CT angiography of individuals was performed using 640-slice Toshiba Aquilion ONE™ multidetector CT scanner. ECG-synchronized image acquisition was done using iodinated contrast material and coronary artery calcium score (CACS) was measured using Agatston method. Based on the Agatston calcium score, participants were categorized into four groups: Group 1 (CACS = 0); Group 2 (CACS 1-99); Group 3 (CACS 100-399); Group 4 (CACS >400).

All the data was recorded using Social Packages for the Social Sciences (SPSS) version 23.0. Categorical variables for e.g., number of males and females, number of hypertensive individuals, number of diabetic individuals, number of smokers in each group were recorded as frequencies (n) and percentages (%). Continuous variables e.g., age of individual in each group was recorded as mean $\pm$ SD. After assessing the normality of data using the Shapiro-Wilk test, the correlation analysis between CACS and AIP, CRI-I, CRI-II, AC and non-HDL-C was performed using Pearson's correlation. The differences in AIP, CRI-I, CRI-II, AC and non-HDL-C among the four classes of CACS was noted using one-way analysis of variance (ANOVA). In order to compare the discriminatory ability of AIP, CRI-I, CRI-II, AC and non-HDL-C for identification of coronary artery calcium (CACS >0), receiver operating characteristics (ROC) curve analysis was performed. The area under the ROC (AUC) for each marker was calculated to compare its predictive performance for initiation of coronary artery disease. The optimal cut-off for the markers showing AUC > 0.7 were identified using Youden's index, the specificity, sensitivity, negative predictive value (NPV) and positive predictive value (PPV) of the proposed cut-

off values was also determined, the *p*-value <0.05 was considered statistically significant.

The study was conducted after obtaining ethical approval from the Ethical Review Committee of Punjab Institute of Cardiology, Lahore. (ERC letter # RTPGME-Research-340-A, dated 19th May, 2025).

Results

The demographic details of individuals including age, smoking history, hypertension history, diabetic status (HbA1C >5.7%), were noted. The demographic detail of our study population is enlisted in table 1. AC and non HDL-C was tested using Pearson's correlation. The correlation analysis demonstrated that CACS showed positive and statistically significant association with all indices but AIP showed the strongest positive correlation of all the indices ($r=+0.278$, $p <0.001$). The value of correlation coefficient (*r*) and *p*-values of all the indices with CACS is represented in table 2.

One-way ANOVA was performed to compare the mean values of lipid profile parameters (TG, TC, HDL-C, LDL-C) and lipid-derived atherogenic indices (AIP, CRI-I, CRI-II, AC and non-HDL-C) among four CACS group. The results of one-way ANOVA revealed that mean TG, TC, AIP, CRI-I, CRI-II, AC and non-HDL-C differed significantly among all CACS groups $p <0.05$. However, HDL-C and LDL-C did not differ with increasing CACS status. The results of all these parameters are noted in form of mean $\pm$ SD in table 3. Normality assessment of the collected data was performed using the Shapiro-Wilk test which demonstrated variables were normally distributed $p >0.05$. The correlation of CACS with AIP, CRI-I, CRI-II, ROC curve analysis revealed that all lipid derived indices AIP, CRI-I, CRI-II, AC and non-HDL-C demonstrated significant discriminatory ability of the individuals with coronary artery calcification than those without calcification ($p <0.001$). Atherogenic index of plasma displayed the highest discriminatory ability with an AUC of 0.709 (95% CI: 0.636-0.782) followed by CRI-I (AUC=0.676), AC

(AUC=0.676), CRI-II (AUC=0.676) and non-HDL-C (AUC=0.662). AUC, S.E and 95% CI of all these indices in differentiating individuals with calcification are enlisted in table 4.

	Group 1	Group 2	Group 3	Group 4
Number of individuals	91	53	31	13
Number of males	56 (61.5%)	39 (73.5%)	20 (64.5%)	11 (84.6%)
Number of females	35 (38.5%)	14 (26.5%)	11 (35.5%)	2 (15.4%)
Number of smokers	11 (12.1%)	7 (13.2%)	4 (13%)	2 (15.4%)
Number of diabetic individuals	15 (16.4%)	26 (49%)	21 (67.7%)	7 (53.8%)
Number of hypertensive individuals	35 (38.5%)	21 (39.6%)	24 (77.4%)	10 (76.9%)
Age (years)	40.0 $\pm$ 13.4	53.1 $\pm$ 9.05	58.0 $\pm$ 8.6	62.9 $\pm$ 7.04

	Pearson's r	<i>p</i> -value
Atherogenic Index of Plasma	+0.278	<0.001
Castelli Risk Index I	+0.245	0.001
Castelli Risk Index II	+0.219	0.003
Atherogenic Co-efficient	+0.245	0.001
Non HDL-C	+0.144	0.049

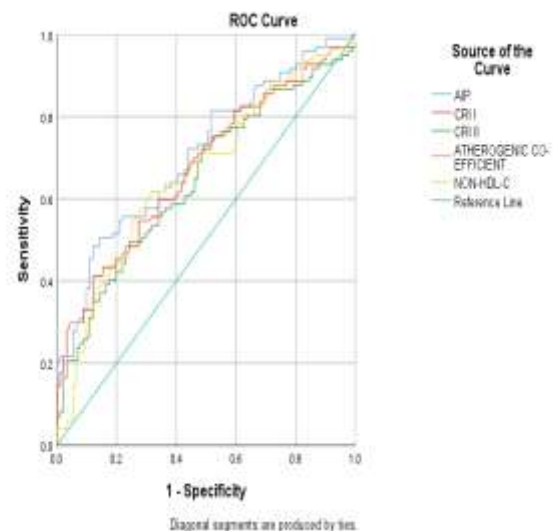


Figure 1: ROC for AIP, CRI-I, CRI-II, AC and non-HDL-C in differentiating individuals with coronary artery calcification from those without calcification.

Table III: Results of One-Way ANOVA showing various parameters in CACS classes						
Parameter	Group 1 n=91 Mean±SD	Group 2 n=53 Mean±SD	Group 3 n=31 Mean±SD	Group 4 n=13 Mean±SD	F-value	p-value
Triglycerides	125.24±50.17	177.28±94.58	278.10±167.25	211.62±65.68	12.08	<0.001
Total Cholesterol	177.69±38.09	192.70±38.30	202.35±56.63	200.92±47.76	3.59	0.015
HDL-C	42.57±8.48	40.02±8.42	40.61±11.30	35.54±10.99	2.64	0.51
LDL-C	117.52±35.16	131.49±38.03	124.32±54.97	146.46±44.89	2.71	0.47
HbA _{1c}	5.39±0.74	6.01±0.99	7.06±2.08	6.61±1.65	12.08	<0.001
CACS	0±0	28.49±24.61	225.32±90.68	874.85±532.86	162.73	<0.001
Atherogenic Index of Plasma	0.08±0.22	0.24±0.61	0.35±0.04	0.41±0.21	12.08	<0.001
Castelli Risk Index I	4.28±1.05	5.01±1.4	5.30±2.06	5.87±1.28	8.71	<0.001
Castelli Risk Index II	2.83±0.94	3.43±1.25	3.10±1.18	4.29±1.32	8.28	<0.001
Atherogenic Co-efficient	3.28±1.05	4.01±1.40	4.30±2.06	4.87±1.28	8.71	<0.001
Non HDL-C	135.12±36.73	152.68±38.52	161.74±55.13	165.38±40.64	5.08	0.002

Table IV: AUC, S.E, 95% CI for AIP, CRI-I, CRI-II, AC and non-HDL-C in differentiating individuals with coronary artery calcification from those without calcification.				
	AUC	S.E	95%CI	p-value
AIP	0.709	0.37	0.636-0.782	<0.001
CRI I	0.676	0.39	0.600-0.752	<0.001
CRI II	0.648	0.40	0.570-0.726	<0.001
Atherogenic Co-efficient	0.676	0.39	0.600-0.752	<0.001
Non-HDL-C	0.662	0.40	0.584-0.740	<0.001

Discussion

This study evaluated the association between five lipid-derived atherogenic indices namely atherogenic index of plasma (AIP), Castelli Risk Index-I (CRI-I), Castelli Risk Index-II (CRI-II), atherogenic coefficient (AC), and non-HDL-C, with coronary artery calcium score (CACS) in patients presenting with retrosternal chest pain. This study also investigated the diagnostic ability of these markers in early detection of coronary artery disease. Overall, all five indices demonstrated significant positive associations with CACS, while AIP showed the strongest correlation and the highest

discriminatory performance among the evaluated markers. These findings suggest that lipid-derived indices, particularly AIP, may provide additional information for cardiovascular risk stratification when interpreted alongside established clinical risk factors.

CACS is a well-established marker of subclinical atherosclerosis as it quantifies the burden of calcified plaque in coronary artery.¹¹ Individuals in our study were grouped on the basis of their CACS. The demographic findings demonstrated a progressive increase in age across the CACS categories. The mean age increased from 40.0±13.4 years in individuals with CACS=0 to 62.9±7.04 years among those with CACS >400. A higher prevalence of diabetes mellitus and hypertension was also observed in groups with greater coronary calcium burden. These findings are consistent with the known fact that advancing age, diabetes mellitus and hypertension are known contributors of coronary artery disease which contribute to formation and progression of atherosclerotic plaque through specific pathophysiological mechanisms.¹² Diabetes mellitus accelerates endothelial dysfunction while hypertension

promotes arterial remodeling.¹³ Our findings are consistent with a Pakistani study, which reported that increasing age, diabetes mellitus, and hypertension were significantly associated with higher coronary artery calcium scores.¹⁴ These findings support the observed progressive increase in coronary calcium burden across CACS categories in our study and highlight the contribution of conventional cardiovascular risk factors to coronary atherosclerotic burden in the Pakistani population. In present study, a significant positive correlation was observed between all lipid derived atherogenic indices and CACS. This observation suggests the explanation that AIP, CRI-I, CRI-II, AC and non-HDL-C increased with increasing coronary artery calcification. AIP showed the strongest correlation with CACS ($r=+0.278$, $p < 0.001$) followed by CRI-I ($r=+0.245$, $p=0.001$), AC ($r=+0.245$, $p=0.001$), CRI-II ($r=+0.219$, $p=0.003$), and non-HDL-C ($r=+0.144$, $p=0.049$). Though the correlation coefficients of these indices were modest, their consistent positive direction indicates that a more atherogenic lipid profile was associated with greater coronary calcium burden. The highest association of AIP is attributed because it incorporates TG and HDL in single calculation, reflecting the predominance of small dense lipoprotein particles that are highly atherogenic particles and promote endothelial dysfunction and coronary arteries calcification.¹⁵ Our findings are consistent with a large Pakistani study of 7,351 individuals from the National Diabetes Survey of Pakistan, which demonstrated a significant association of AIP with cardiovascular risk factors, particularly diabetes and male sex. Similarly, our study found higher AIP values with increasing CACS, supporting the potential role of AIP as an accessible marker of cardiovascular risk in the Pakistani population.¹⁶ CRI-I represents the ratio of total cholesterol to anti-atherogenic cholesterol (HDL-C). High levels of total cholesterol are associated with greater risk of cardiovascular disease as there are many studies that consistently report that total cholesterol remains a major risk of ischemic heart

disease.¹⁷ Similarly, AC represents the ratio of atherogenic lipoproteins to high-dense lipoproteins. High values of AC reflect overall burden of atherogenic lipoproteins that lead to plaque calcification in coronary arteries.¹⁸

The results of one-way ANOVA also indicated that these indices worsened with increasing CACS category. Significant differences across CACS categories were observed in AIP, CRI-I, CRI-II, AC and non-HDL-C. In particular, AIP increased from 0.08 ± 0.22 in the CACS=0 group to 0.41 ± 0.21 in the CACS >400 group. Similarly, CRI-I, CRI-II, AC and non-HDL-C generally demonstrated higher values with increasing CACS categories. These findings indicate that worsening of the overall atherogenic lipid profile accompanied increasing coronary calcium burden. Interestingly, HDL-C and LDL-C individually did not demonstrate statistically significant differences among CACS categories. This observation may suggest that composite lipid-derived indices can capture the interaction between different lipid fractions more effectively than individual lipid parameters.

ROC curve analysis showed that all the lipid-derived indices had a significant discriminatory ability in differentiating individuals with coronary artery calcification from those individuals without coronary artery calcification. AIP showed the highest AUC of 0.709 (95% CI: 0.636-0.782), $p < 0.001$, which showed that AIP demonstrated better risk stratification as compared to other indices. This result supports that AIP can be used as a screening marker for risk stratification in populations with high cardiovascular risk or in healthcare settings with limited facilities.¹⁹ A cut-off value of >0.27 for AIP was found to be associated with presence of coronary artery calcification. This cut-off value demonstrated sensitivity of 50.5%, specificity of 84.6% with an overall diagnostic accuracy of 69%. A similar study conducted revealed that the threshold value of >0.49 for AIP was associated with the severity of coronary lesion.²⁰ The moderate sensitivity of AIP suggests that many individuals have AIP greater than

0.27 but no coronary artery lesion. Therefore, AIP can be used as a rule-in biomarker instead of rule-out biomarker for early prediction of CAD.

The findings of this study have important clinical implication particularly in resource limited healthcare settings. As lipid-derived indices can easily be calculated without any additional cost, making them economical and accessible marker of risk stratification for CAD. Incorporating AIP into routine clinical assessment may help identify individuals who may require further imaging-based investigations such as coronary CT-angiography.

Conclusion

Lipid-derived atherogenic indices may provide better prediction of coronary artery disease as they integrate two or more fractions of lipid profile parameters. Coronary artery calcium score is the well-established marker of coronary artery atherosclerosis. AIP, CRI-I, CRI-II, AC and non-HDL-C showed significant positive correlation with CACS. Among all the lipid-derived indices in our study, AIP showed the better diagnostic ability and may be useful in risk stratification for CAD. An AIP cut-off value of >0.27 is associated with the possibility of coronary artery calcification.

Limitation: Certain limitations of our study included cross-sectional study design, single centered study, and reliance on CACS for coronary atherosclerotic burden. CACS only captures calcified lesions and may miss other lesions such as non-calcified and mixed lesions.

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