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ORIGINAL ARTICLE

# Atherogenic Combined Index: Validation of a Coronary Artery Disease Predictive Biomarker

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*Background/Aim.* The balance between atherogenic and antiatherogenic lipid particles significantly influences coronary artery disease (CAD), as an imbalance may contribute to the development and progression of atherosclerosis, which affects the risk and severity of CAD. This study aims to introduce and validate the atherogenic combined index (ACI) as a novel lipid biomarker that, comprehensively assesses the balance between atherogenic and antiatherogenic particles in the blood to effectively reflect the cumulative atherogenic effect and its association with the presence and severity of CAD.

*Material and Methods.* In this cross-sectional study, 1,830 patients diagnosed with CAD and a total of 650 patients without CAD were included in the study cohort for comprehensive analysis and comparison. Based on the tertiles of the SYNTAX score (SS), three subgroups of patients with CAD were identified. ACI and other atherogenic indices were compared to predict the presence and severity of CAD.

*Results.* The levels of ACI and other non-traditional lipid markers levels were higher in the CAD group compared to the non-CAD group ($p$ <0.05, for all). ACI showed a good linear association with the SYNTAX score ($r = 0.527$; $p$ <0.001). The multivariate logistic regression model showed that ACI was an independent predictor of the presence (OR: 1.602, 95% CI: 1.509–1.701, $p$ <0.001) and severity (OR: 1.296, 95% CI: 1.243–1.351, $p$ <0.001) of CAD after adjustment for various confounders.

*Conclusion.* The results suggest that ACI may serve as a promising and stronger tool for predicting the presence and severity of CAD. 

*Key Words:* Atherogenic combined index, Lipid biomarkers, Coronary artery disease, Non-traditional lipid profile.

## Introduction

Cardiovascular diseases (CVDs) remain a persistent global health challenge, with coronary artery disease (CAD) being a major contributor to morbidity and mortality (1). The World Heart Federation has recently acknowledged that prevention is the most effective way to combat CVD (2,3). In this context, low-cost, rapid, targeted, non-invasive, and predictive tools are required to identify individuals at high risk for CVD events. Molecular biomarkers have been effectively used as prognostic biomarkers for CVD in large-scale prospective investigations (4–6). However, the high cost of their analysis makes it difficult to use these molecular biomarkers in the general population in developing countries As a result, less expensive options are needed to identify high-risk groups. Many accessible tools have

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been developed as significant and practical biomarkers to predict CVD and atherosclerosis (7–9).

Atherosclerosis, a complex process involving lipid deposition on arterial walls, is a hallmark of CAD (10). The intricate balance between atherogenic and antiatherogenic lipoproteins significantly influences the development and progression of atherosclerosis (11). Traditional lipid profiles, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), have long served as crucial indicators of cardiovascular risk (12). The onset and progression of CAD have been widely investigated in relation to dyslipidemia, specifically elevated levels of TC, TG, LDL-C, and decreased HDL-C (13). Lipid-lowering therapy has traditionally focused on LDL-C reduction in clinical practice. However, even after LDL-C levels have reached recommended ranges, residual cardiovascular risk remains, and the limitations of conventional lipid indices necessitate a deeper exploration of novel biomarkers that provide a more refined understanding of atherogenic burden.

Composite lipoprotein ratios, such as the lipoprotein combined index (LCI = TC∗TG∗LDL-C/HDL-C), Castelli risk index-I (CRI-I = TC/HDL-C), Castelli risk index-II (CRI-II = LDL-C/HDL-C), atherogenic index (AI = non-HDL-C/HDL-C), and atherogenic index of plasma (AIP = log TG/HDL-C ratio), have recently become more predictive of CAD risk than traditional single lipid parameters (14–17,9). While previous investigations have explored markers such as the AI, the AIP, the CRI-I, the CRI-II, and the LCI, none has comprehensively captured the intricate dynamics of atherogenic and antiatherogenic elements in the blood. As a result, we postulated that using all conventionally measurable atherogenic lipid profiles as a composite in a single formulation, rather than a single lipid index, may provide a more comprehensive assessment of lipid status.

In this context, this study introduces the ACI as a novel lipid biomarker designed to address the shortcomings of existing non-traditional lipid indices in capturing the nuanced interplay between atherogenic and antiatherogenic particles. The ACI is obtained by a sophisticated logarithmic transformation of the ratio of traditionally measurable atherogenic lipoprotein particles to non-atherogenic lipid particles, expressed as (TG*non-HDL-C/HDL-C). This formulation aims to provide a more accurate representation of the cumulative atherogenic effect in the bloodstream. What distinguishes ACI from existing indices is its explicit consideration of critical atherogenic particles, including TG, very low-density lipoprotein (VLDL), and intermediate-density lipoprotein, which are often overlooked in current lipid markers. Previous studies have validated non-traditional lipid markers, including AI, AIP, CRI-I, CRI-II, and LCI, for CAD. However, there are shortcomings in these formulations, such as the incomplete representation of atherogenic particles like TG and VLDL, or the inclusion of HDL-C within total cholesterol, which complicate their accuracy in assessing atherogenic risk.

This detailed introduction underscores the imperative to refine lipid biomarkers improving our ability to perform predictive assessments of atherosclerotic risk. By positioning ACI as an innovative approach, this study aims to make a substantial contribution to the evolving field of lipid profiling. The investigation of the predictive value of ACI which incorporates distribution normalization after logarithmic transformation, represents a critical step toward improving the accuracy of lipid-based cardiovascular risk assessment. The results of this study promise to inform and reshape current paradigms in the assessment of the presence and severity of CAD.

## *Materials and Methods*

This multicenter, observational study was conducted at four centers to evaluate the relationship between non-traditional lipid parameters and CAD. A total of [Y] patients diagnosed with CAD were enrolled from these centers to ensure a diverse and representative sample. Inclusion criteria comprised adults aged 18–75 years with angiographically confirmed CAD, while exclusion criteria included patients with severe comorbidities or those receiving lipid-lowering therapy. Baseline clinical characteristics, including demographic information, medical history, and laboratory results, were collected. Echocardiographic evaluations were performed by two experienced cardiologists from the primary coordinating center to ensure consistency. The study was designed to provide a comprehensive analysis of the role of lipid profile in CAD beyond traditional markers, with data rigorously analyzed to draw meaningful conclusions.

### *Study Population*

This cross-sectional and observational study enrolled a total of 2,470 participants from January 2018–June 2023. The study included 1,830 consecutive patients who underwent coronary angiography due to non-ST elevation myocardial infarction (NSTEMI), forming the CAD group. Additionally, 640 consecutive subjects were recruited as a control group (non-CAD group), carefully matched for age and sex to the CAD group. These individuals were confirmed to be free of CAD by both invasive and non-invasive diagnostic tests. The study was conducted at four different medical centers to ensure a diverse and representative sample. Inclusion criteria comprised individuals aged 18–75 years diagnosed with CAD by angiography. Patients with significant comorbidities and those receiving lipid-lowering therapy were excluded to maintain co-

hort homogeneity. Comprehensive data collection included demographic characteristics, medical history, and laboratory results. The study aimed to comprehensively analyze the role of lipid parameters beyond traditional markers in CAD, using rigorous data analysis to draw meaningful conclusions.

According to current guideline recommendations, CAD was defined as ≥50% stenosis of at least one epicardial major coronary artery (i.e., >2 mm in diameter) as determined by coronary angiography (18). The European Heart Journal guidelines state that a combination of the following factors was used to diagnose NSTEMI: typical ischemic chest discomfort, a troponin-I level of >0.01ng/mL, changes in the 12-lead ECG without persistent ST-segment elevation but with ST-segment depression either permanent or temporal, ST-segment temporal elevation, inverted or flat T-wave, pseudo-normalization of the T-wave, or normal ECG (19). The following inclusion criteria were used in this study: individuals who were 18 years or older, and those with at least one major epicardial coronary artery with at least 50% diameter stenosis. Exclusion criteria included patients with a history of cholesterol-lowering medication for more than one month before admission, incomplete lipid profile data, moderate to severe hepatic or renal dysfunction, hematological disease, autoimmune disease, malignancy, acute or chronic inflammatory disease, prior coronary angioplasty or coronary artery bypass grafting, thyroid dysfunction, decompensated heart failure, or cardiomyopathy. The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki.

### *Data Collection and Laboratory Measurements*

Laboratory results, clinical and comorbid characteristics, and demographic information of the study subjects were taken from hospital patient databases. Data analysis was performed using laboratory measurements obtained from peripheral venous blood drawn from study participants after an overnight fast of at least eight hours. Levels of TG, TC, HDL-C, and LDL-C were determined by direct enzymatic colorimetry using a Roche Diagnostics Cobas 6000, c501 module (Roche, Mannheim, Germany) analyzer. The estimated glomerular filtration rate (e-GFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

### *Calculation of Non-traditional Lipid Profiles*

Non-HDL-C levels were calculated by subtracting HDL-C from TC (non-HDL-C = TC-HDL-C). The atherogenic index (AI), also known as the atherogenic coefficient, was obtained by dividing non-HDL-C by HDL-C (AI = non-HDL-C/HDL-C). The AIP is calculated by logarithmic transformation of the ratio of TG and HDL-C concentrations ($\log_{10}$ [TG/HDL-C]). CRI-I was obtained by dividing TC by HDL-C (CRI-I = TC/HDL-C), and CRI-II was obtained by dividing LDL-C by HDL-C (CRI-II = LDL-C /HDL-C). The LCI was obtained with the formula "LCI = TC*TG*LDL-C/HDL-C".

ACI, which we proposed as a new comprehensive atherogenic index, was obtained by the logarithmic transformation of the ratio of TG multiplied by non-HDL-C to HDL-C (ACI = $\log_{10}$ [TG*non-HDL-C/HDL-C]). Because of non-normal distributions, the analyses used log-transformed values of TG*non-HDL-C/HDL-C ratio.

### *Clinical Definitions and Measurements*

A previous diagnosis of hypertension or repeated office blood pressure measurements with a systolic blood pressure of at least 140 mmHg and/or a diastolic blood pressure of at least 90 mmHg were considered hypertension. A history of cholesterol-lowering medication usage or the presence of one of the following four lipid profile measures after at least eight hours of fasting was used to identify dyslipidemia: total cholesterol (TC) >200 mg/dL, LDL-C (low-density lipoprotein cholesterol) >130 mg/dL, HDL-C (high-density lipoprotein cholesterol) <40 mg/dL in men and <50 mg/dL in women, and TG >150 mg/dL are the four parameters considered (20). The criteria for diabetes mellitus were hemoglobin A1c ≥6.5%, anti-diabetic medication use, or fasting serum glucose ≥126 mg/dL. Body mass index (BMI) is calculated by dividing height ($m^2$) by weight (kg). Experienced cardiologists used echocardiography (Philips Epiq 7 device, Andover, MA, USA) to assess left ventricular ejection fraction (LVEF) using a modified Simpson method.

### *Coronary Angiographic Assessment and Analysis*

All coronary angiographic interventions were performed by experienced invasive cardiologists using the standard Judkins technique (Philips Allura Xper FD10 cardiovascular X-ray system) via radial or femoral access. The SYNTAX Score I (SS), which is used to determine the severity and extent of CAD, was assessed using an online calculator (https://syntaxscore.org/calculator/start.htm). All coronary lesions causing about 50% stenosis in arteries greater than 1.5 mm in diameter were included in the calculation of the SS. Based on the tertiles of their SS I, CAD patients were divided into three subgroups: mild group (0 ≤SS <9), moderate group (9 ≤SS <20), and severe group (≥20). Cardiologists were blinded to patient data during data collection. Angiographic images were evaluated by two experienced interventional cardiologists. In cases of disagreement, the opinion of a third interventional cardiologist was sought. For the SYNTAX score evaluation, the intra- and

inter-observer coefficient of variation were 2 and 3%, respectively.

## Statistical Analysis

Analyses were performed with SPSS 26.0 (SPSS Inc., Chicago, IL, USA) and MedCalc (trial version 12.7.8, Mariakerke, Belgium). The Kolmogorov-Smirnov test was used to test whether the distribution of continuous variables was normal. The Student's *t*-test or the Mann-Whitney *U* test was used to compare continuous variables, depending on their distribution. The Kruskal-Wallis test was used to make comparisons between multiple groups for variables that were not normally distributed, and the ANOVA test was used for variables that were normally distributed. The mild CAD group was taken as the reference group ($0 \leq SS < 9$). The median (interquartile range) or mean ± standard deviation (SD) was used to represent continuous data. The mean SD was used for normally distributed variables, and the median (interquartile range [IQR]) was used for non-normally distributed data. Categorical variables were presented as numbers (percentages), and comparisons were made using Fisher's exact test or the $\chi^2$ test, as needed. The correlation of lipid indexes with CAD severity (with SYNTAX score) was calculated by Pearson or Spearman coefficient analysis according to their distribution. Univariate and binary multivariate logistic regression analyses were performed to estimate the associations between atherogenic lipid indices (AI, AIP, CRI-I, CRI-II, LCI, and ACI) and the presence and severity of CAD. In logistic regression analysis, the goodness of fit of the multivariate model was assessed using the Hosmer-Lemeshow test. To avoid multicollinearity, traditional lipid profiles were not included in the regression models. Model 1 was unadjusted. Model 2 was adjusted for body mass index, diabetes mellitus, hypertension, dyslipidemia, and smoking. Based on model 2, model 3 was further adjusted for the status of laboratory results (fasting plasma glucose, creatinine, uric acid, albumin, C-reactive protein, estimated glomerular filtration rate, and white blood cell count). Based on model 3, model 4 was further adjusted for non-traditional lipid profiles (AI, AIP, LCI, CRI-I, and CRI-II). The ability of ACI and other lipid indices to predict and distinguish the presence and severity of CAD was compared by pairwise comparison using receiver operating characteristic (ROC) curve analysis. The Youden J index was used to evaluate the trade-off between sensitivity and specificity at different cut-off points and the one that optimizes both was selected. The best cut-off point was determined as the point on the ROC curve that yielded the highest Youden J index. The area under the curve (AUC) between the ACI and other lipid indices was compared by using Delong's test. A *p*-value less than 0.05 was considered statistically significant.

## Results

### *Overall Distribution Characteristics of the Study Population and ACI*

A total of 2,470 subjects were included in the study, of whom 1,830 had CAD and 640 did not. The mean age of the study population was 58.2 ± 12.5 years, and 1,700 (68.8%) were male. To normalize skewed data, stabilize variance, linearize relationships, facilitate interpretation of percentage changes, improve homoscedasticity in regression models, improve interpretability of multiplicative effects, and appropriately model variables with exponential growth models, the logarithmic transformation was applied to the lipid index formulated with the TG*non-HDL-C/LDL-C ratio (Figure 1).

### *Basic Clinical Characteristics of the CAD and Non-CAD Groups*

Basic demographic, clinical, and laboratory data of patients with and without CAD are summarized in Table 1. In the CAD group, BMI was higher, and the incidence of diabetes mellitus, hypertension, dyslipidemia, and smoking were significantly higher compared with the non-CAD group ($p < 0.001$, for all). While fasting plasma glucose (FPG), creatinine, uric acid, C-reactive protein (CRP), and white blood cells (WBC) were significantly higher in the CAD group than in the non-CAD group, albumin and estimated glomerular filtration rate (e-GFR) were significantly lower ($p < 0.05$, for all). Among traditional lipid profiles, TG ($p < 0.001$), TC ($p = 0.011$), LDL-C ($p = 0.024$), and non-HDL-C ($p < 0.001$) were significantly higher in the CAD group than in the non-CAD group, while HDL-C ($p < 0.001$) was lower. In addition, non-traditional lipid indices, AI (4.2 ± 1.5 vs. 3.0 ± 1.3, $p < 0.001$), AIP (0.77 ± 0.28 vs. 0.53 ± 0.32, $p < 0.001$), LCI (74 [44–119] vs. 65 [24–104], $p < 0.001$), CRI-I (4.7 ± 1.5 vs. 4.0 ± 1.3, $p < 0.001$), CRI-II (3.1 ± 1.0 vs. 2.5 ± 0.8, $p < 0.001$), and ACI (2.84 ± 0.34 vs. 2.41 ± 0.33, $p < 0.001$) values, were significantly higher in the CAD group than in the non-CAD group.

### Basic Clinical Characteristics of CAD Subgroups *(*mild, moderate, severe)

The basic demographic, clinical, and laboratory characteristics of the patients, who were divided into mild, moderate, and severe subgroups according to the severity of CAD, are shown in Table 2. Using the mild CAD group as a reference, the mean age ($p = 0.020$), male sex ($p = 0.003$), DM ($p = 0.022$), and smoking frequency ($p = 0.005$) were significantly higher in the severe CAD group. Laboratory results showed that uric acid ($p = 0.023$) and CRP ($p = 0.002$) levels were also significantly higher in the severe CAD group. Among the traditional lipid pro-

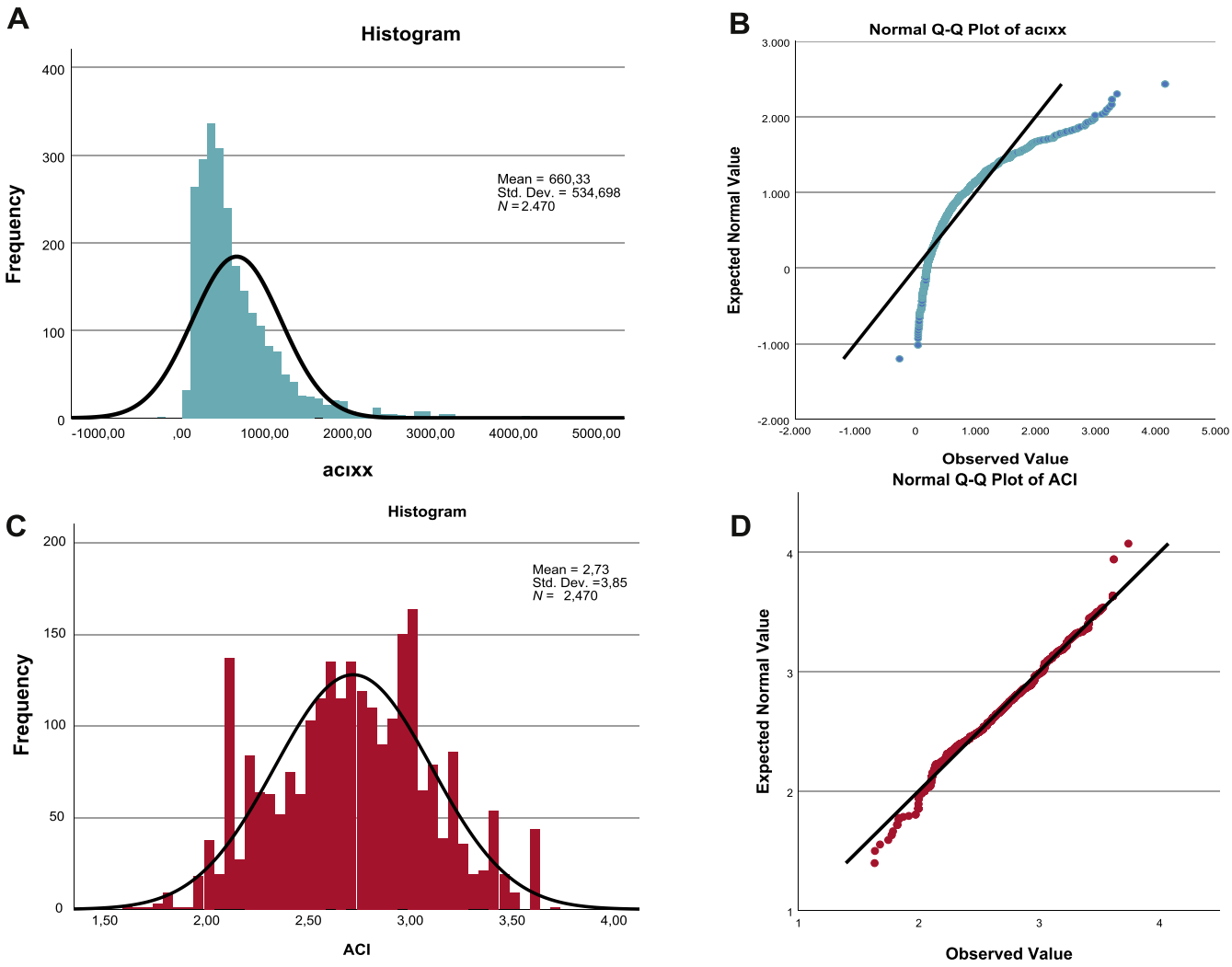


**Figure 1.** Histogram A, and normal *Q-Q* plot B, of the TG*non-HDL-C/HDL-C ratio show a positively skewed distribution. Histogram plot C, and normal *Q-Q* plot D, showing the normal distribution of ACI obtained after logarithmic transformation of TG*Non-HDL-C/HDL-C ratio. ACI, atherogenic combined index, TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

files, TG ($p$ <0.001), TC ($p$ <0.001), LDL-C ($p$ = 0.002), and non-HDL-C ($p$ <0.001) were significantly higher in the severe CAD group than in the mild CAD group, while HDL-C ($p$ <0.001) was lower. When non-traditional lipid profiles were compared between subgroups, the results showed that AI ($p$ <0.001), AIP ($p$ <0.001), LCI ($p$ <0.001), CRI-I ($p$ <0.001), CRI-II ($p$ <0.001), and ACI ($p$ <0.001) values were significantly higher in the severe CAD group than in the mild CAD group.

### *Correlation Between Lipid Indices and CAD Severity*

In correlation analysis, ACI ($r$ = 0.527, $p$ <0.001), AIP (0.374, $p$ <0.001), AI (0.305, $p$ <0.001), CRI-I (0.294, $p$ <0.001), CRI-II ($r$ = 0.112, $p$ <0.001) and LCI ($r$ = 0.291, $p$ <0.001) showed a positive correlation with CAD severity as measured by the SYNTAX score, and ACI showed a stronger correlation with CAD severity than other lipid indices (Figure 2).

### *Associations of Lipid Indices with the Presence and Severity of CAD*

In univariate logistic regression analysis (unadjusted-model-1), ACI was independently associated with the presence and severity of CAD when considered as a continuous variable (OR: 1.453, 95% CI: 1.404–1.504, $p$ <0.001; OR: 1.354, 95% CI: 1.303–1.407, $p$ <0.001; respectively) and as a categorical variable (OR: 12.324, 95% CI: 8.747–17.366, $p$ <0.001; OR: 16.452, 95% CI: 12.781–21.178, $p$ <0.001; respectively). Even after adjusting for potential confounding factors (model 4), there was still an independent relationship between the ACI and the presence and severity of CAD as a continuous variable (OR: 1.602, 95%

**Table 1.** Baseline demographic and clinical characteristics of the non-CAD and CAD groups

| Variables | Non-CAD group ($n$ = 640) | CAD group ($n$ = 1,830) | $p$ |
|---|---|---|---|
| Demographics and medical history | | | |
| Age, years | 57 ± 13 | 58 ± 12 | 0.123 |
| Sex, male, $n$ (%) | 425 (66.4) | 1275 (69.7) | 0.125 |
| BMI, kg/m$^2$ | 25.8 ± 3.2 | 26.6 ± 2.2 | <0.001 |
| Diabetes Mellitus, $n$ (%) | 125 (19.5) | 724 (39.6) | <0.001 |
| Hypertension, $n$ (%) | 164 (25.6) | 1038 (56.7) | <0.001 |
| Dyslipidemia, $n$ (%) | 160 (25.0) | 1324 (72.3) | <0.001 |
| Smoking, $n$ (%) | 151 (23.6) | 1128 (61.6) | <0.001 |
| Laboratory results | | | |
| FPG, (mg/dL) | 117 ± 33 | 125 ± 125 | <0.001 |
| Creatinine, (mg/dL) | 0.85 ± 0.23 | 0.88± 0.25 | 0.010 |
| Uric acid, (mg/dL) | 5.1 ± 1.4 | 5.2 ± 1.5 | 0.008 |
| Albumin, (mg/dL) | 4.2 ± 0.4 | 4.1 ± 0.5 | 0.020 |
| CRP, (mg/dL) | 0.40 (0.11–1.03) | 1.10 (0.33–1.93) | <0.001 |
| e-GFR, (mL/min) | 87 (69–97) | 92 (78–101) | <0.001 |
| WBC, (x1000/mm$^3$) | 7.9 ± 3.6 | 8.4 ± 3.7 | 0.001 |
| Hemoglobin, (mg/dL) | 14.0 ± 1.6 | 13.9 ± 1.8 | 0.393 |
| Traditional lipid profiles | | | |
| Triglycerides, (mg/dL) | 163 ± 88 | 179 ± 103 | <0.001 |
| TC, (mg/dL) | 160 ± 34 | 164 ± 38 | 0.011 |
| HDL-C, (mg/dL) | 41 ± 9.8 | 36 ± 10.0 | <0.001 |
| LDL-C, (mg/dL) | 106 ± 33 | 109 ± 36 | 0.024 |
| Non-HDL-C, mg/dL | 119 ± 34 | 128 ± 37 | <0.001 |
| Non-traditional lipid profiles | | | |
| AI | 3.0 ± 1.3 | 4.2 ± 1.5 | <0.001 |
| AIP | 0.53 ± 0.32 | 0.77 ± 0.28 | <0.001 |
| LCI (x10$^{-3}$) | 65 (23–104) | 74 (44–119) | <0.001 |
| CRI-I | 4.0 ± 1.3 | 4.7 ± 1.5 | <0.001 |
| CRI-II | 2.5 ± 0.8 | 3.1 ± 1.0 | <0.001 |
| ACI | 2.41 ± 0.33 | 2.84± 0.34 | <0.001 |

Values are mean ± SD; $n$ (%), or median (interquartile range) unless otherwise stated. BMI: body mass index; CAD: coronary artery disease; non-CAD. non-coronary artery disease; CRP: C- reactive protein; eGFR: estimated glomerular filtration rate; FPG: Fasting plasma glucose; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; WBC: White blood cells; ACI: atherogenic combined index; AI: atherogenic index; AIP: atherogenic index of plasma; CRI-I, Castelli risk index-I; CRI-II, Castelli risk index-II; LCI: lipoprotein combined index.

CI: 1.509–1.701, $p$ <0.001; OR: 1.296, 95% CI: 1.243–1.351, $p$ <0.001; respectively) and as a categorical variable (OR: 9.539, 95% CI: 6.988–13.021, $p$ <0.001; OR: 16.606, 95% CI: 12.435–22.175, $p$ <0.001; respectively) (Table 3).

### *Predictive Values of Lipid Indices in Detecting the Presence and Severity of CAD*

When ROC curve analysis was performed, the optimal cut-off value of ACI to predict the presence of CAD was >2.62 with 74% sensitivity and 73% specificity (AUC: 0.815, 95% CI: 0.795–0.834, $p$ <0.001). When lipid indices, AIP, AI, LCI, CRI-I, CRI-II, and ACI were compared pairwise by ROC analysis to predict the presence of CAD, ACI was superior to all other lipid indices in predicting the presence of CAD ($p$ <0.001, for all comparisons) (Figure 3). Moreover, the optimal cut-off value of ACI to predict CAD severity in ROC curve analysis was >2.95 with 81% sensitivity and 80% specificity (AUC: 0.815, 95 % CI: 0.795–0.834, $p$ <0.001). When lipid indices, AIP, AI, LCI, CRI-I, CRI-II, and ACI were compared pairwise with ROC analysis to predict the severity of CAD, ACI was superior to all other lipid indices in predicting CAD severity ($p$ <0.001, for all comparisons) (Figure 4).

## Discussion

As shown in Figure 1, the frequency distribution of the ACI obtained after the logarithmic transformation of the non-HDL-C*TG/HDL-C formulation was by the normal distribution. This study showed that all atherogenic lipid indices (AIP, AI, LCI, CRI-I, CRI-II, and ACI) were significantly higher in the CAD group than in the non-CAD group. In addition, all lipid indices showed a positive correlation with CAD severity and were identified as independent risk predictors for the presence and severity of CAD. However, ACI was shown to have a stronger positive correlation and predictive value for the presence and severity of CAD than other lipid indices (AIP, AI and LCI, CRI-I and CRI-II). These results suggest that ACI may be su-

**Table 2.** Baseline demographic and clinical characteristics of three subgroups for patients with CAD

| Variables | Mild,[a] ($n$ = 670) (0 ≤SS <9) | Moderate, ($n$ = 599) (9 ≤SS <20) | Severe, ($n$ = 561) (SS ≥20) | $p$ |
|---|---|---|---|---|
| Demographics and medical history | | | | |
| Age, years | 58.5 ± 12.6 | 58.3 ± 12.1 | 60.2± 12.5 | 0.020 |
| Sex, male, $n$ (%) | 452 (67.5) | 401 (66.9) | 422 (75.2) | 0.003 |
| BMI, kg/m$^2$ | 26.6 ± 2.1 | 26.6 ± 2.3 | 26.6 ± 2.3 | 0.177 |
| Diabetes Mellitus, $n$ (%) | 240 (35.8) | 240 (40.1) | 244 (43.5) | 0.022 |
| Hypertension, $n$ (%) | 396 (59.1) | 338 (56.4) | 304 (54.2) | 0.219 |
| Dyslipidemia, $n$ (%) | 467 (69.7) | 432 (72.1) | 417 (74.3) | 0.196 |
| Smoking, $n$ (%) | 388 (57.9) | 365 (60.9) | 375 (66.8) | 0.005 |
| Laboratory results | | | | |
| FPG, (mg/dL) | 125 ± 46 | 126 ± 48 | 131 ± 54 | 0.068 |
| Creatinine, (mg/dL) | 0.86 ± 0.21 | 0.89 ± 0.28 | 0.88 ± 0.27 | 0.198 |
| Uric acid, (mg/dL) | 5.2 ± 1.5 | 5.3 ± 1.5 | 5.4 ± 1.4 | 0.023 |
| Albumin, (mg/dL) | 4.13 ± 0.49 | 4.16 ± 0.50 | 4.10 ± 0.54 | 0.085 |
| CRP, (mg/dL) | 1.15 (1.04–1.25) | 1.37 (1.26–1.49) | 1.41 (1.29–1.53) | 0.002 |
| e-GFR, (mL/min) | 88 ± 18 | 87 ± 19 | 86 ± 17 | 0.331 |
| WBC, (x1000/mm$^3$) | 8.6 ± 3.6 | 8.3 ± 3.8 | 8.4 ± 3.7 | 0.280 |
| Hemoglobin, (mg/dL) | 13.9 ± 1.8 | 13.9 ± 1.9 | 13.9 ± 1.9 | 0.664 |
| Traditional lipid profiles | | | | |
| Triglycerides, (mg/dL) | 143 ± 99 | 181 ± 90 | 221 ± 105 | <0.001 |
| TC, (mg/dL) | 154 ± 36 | 170 ± 38 | 171 ± 37 | <0.001 |
| HDL-C, (mg/dL) | 39 ± 10 | 35 ± 9 | 34 ± 11 | <0.001 |
| LDL-C, (mg/dL) | 108 ± 36 | 112 ± 35 | 116 ± 37 | 0.002 |
| Non-HDL-C, mg/dL | 115 ± 34 | 135 ±34 | 135 ± 39 | <0.001 |
| Non-traditional lipid profiles | | | | |
| AI | 3.6 ± 1.3 | 4.3 ± 1.3 | 4.7 ± 1.7 | <0.001 |
| AIP | 0.66 ± 0.31 | 0.77 ± 0.22 | 0.91 ± 0.21 | <0.001 |
| LCI (x10$^{-3}$)[b] | 79 (73–84) | 102 (97–106) | 125 (120–131) | <0.001 |
| CRI-I | 4.1 ± 1.2 | 5.0 ± 1.4 | 5.1 ± 1.6 | <0.001 |
| CRI-II | 2.9 ± 0.9 | 3.2 ± 0.9 | 3.3 ±1.1 | <0.001 |
| ACI | 2.6 ± 0.3 | 2.8 ± 0.2 | 3.0 ± 0.2 | <0.001 |

CAD: coronary artery disease; FPG: fasting plasma glucose; CRP: C-reactive protein; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; AI: atherogenic index; AIP: atherogenic index of plasma; LCI: lipoprotein combined index; CRI-I: Castelli risk index-I; CRI-II: Castelli risk index-II; ACI: atherogenic combined index.

[a]Taken as a reference group;

[b]Multiplied by 10–3 for easy interpretation.

perior to other lipid indices in assessing the presence and severity of CAD.

CVDs, particularly CAD, remain a leading cause of morbidity and mortality worldwide. CAD represents a significant proportion of CVDs and imposes a large economic burden on the healthcare system (21). In this context, early and accurate identification of individuals at high risk for CAD, and effective management of the process are of great importance (22). Cost-effective (non-invasive, inexpensive, rapid, and specific) diagnostic tools are needed to early identify individuals at risk for developing CVD and take protective measures, especially in low- and middle-income countries (21–23).

Atherosclerosis, a chronic inflammatory process characterized by the accumulation of lipids in the arterial wall, is a major contributor to CAD. The intricate interplay between atherogenic and antiatherogenic lipoproteins plays a crucial role in shaping the atherosclerotic landscape. Traditionally, lipid profiles, including TC, HDL-C, LDL-C, and TG, have been central to risk assessment (24–26). However, the limitations of traditional lipid particles prompt the exploration of innovative lipid biomarkers that provide a more nuanced understanding of the atherogenic burden. Combining traditional lipid particles into different fractions may help improve cardiovascular risk prediction without increasing cost. Additionally, a single ratio of atherogenic and antiatherogenic lipid factors may provide information on risk factors that are difficult to measure with routine analysis and may better reflect metabolic and clinical interactions between lipid fractions (27). In this context, the validation of different lipid indices (AI, AIP, CRI-I, CRI-II, and LCI) for the development of CVD has been well established (5–9,14–17,28). However, none of these formulations (AI, AIP, LCI, CRI-I, and CRI-II), which are prepared by combining atherogenic and antiatherogenic particles in various ratios from the basic lipid profiles in the blood (TG, HDL-C, LDL-C, TC), completely cover all measurable atherogenic and antiatherogenic fractions. Thus, none of these non-traditional lipid profiles may reflect the atherogenic and antiatherogenic balance in the

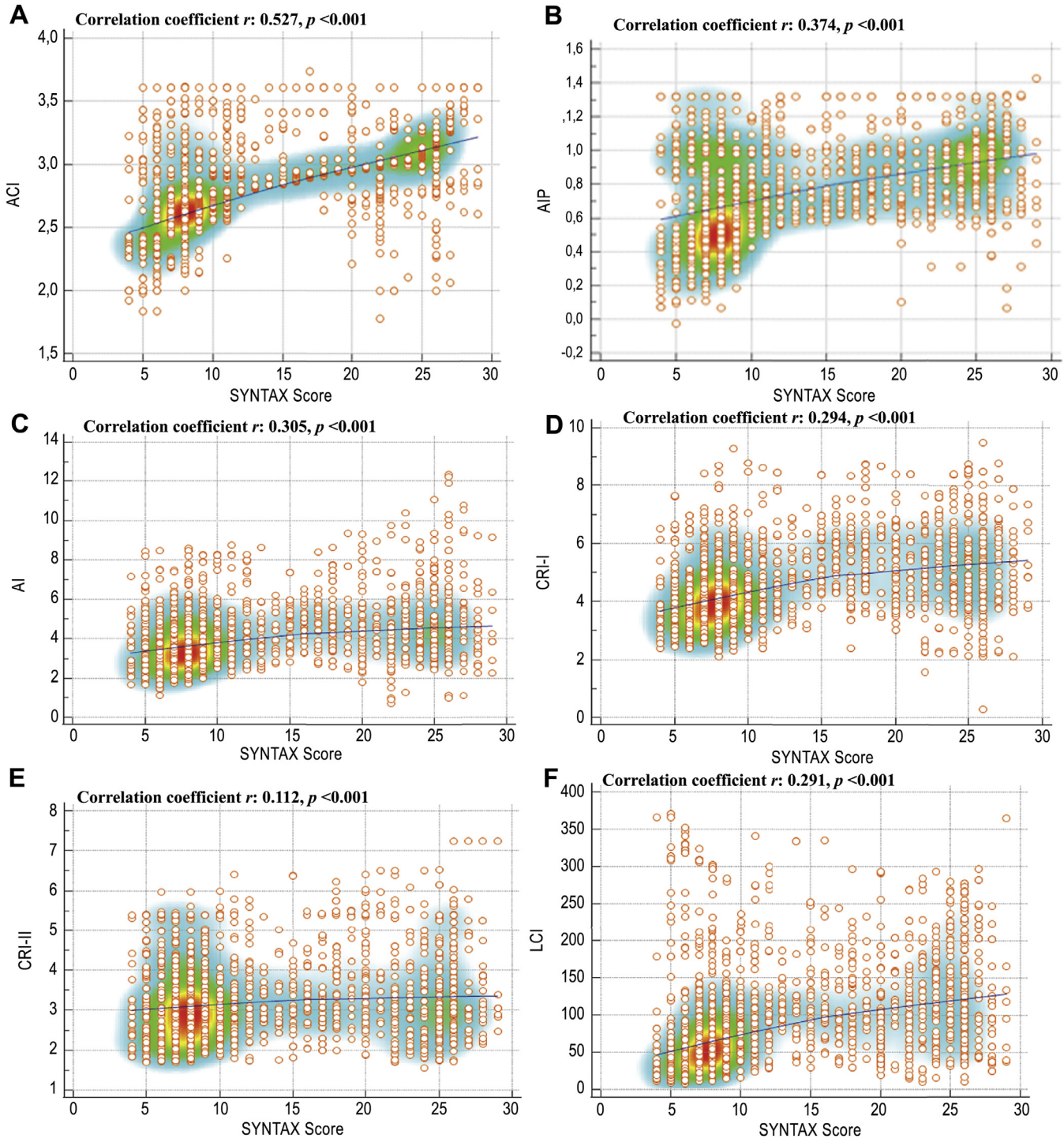


**Figure 2.** Representation of the relationship between SYNTAX Score and non-traditional lipid profiles in scatter diagram with heat map; ACI shows a stronger positive correlation with SYNTAX Score than other non-traditional lipid profiles (Correlation coefficient *r*: 0.527, *p* <0.0001). ACI: atherogenic combined index; AI: atherogenic index; AIP: atherogenic index of plasma; CRI-I, Castelli risk index-I; CRI-II, Castelli risk index-II; LCI: lipoprotein combined index.

blood. For example, AIP can be obtained by proportioning TG from atherogenic particles and HDL-C from antiatherogenic particles (8,9), and it does not consider lipoprotein particles such as non-HDL-C, which are responsible for a significant proportion of the atherogenic burden in the blood (29,30). In this context, since non-HDL-C contains various atherogenic cholesterol particles such as LDL-C, VLDL-C, and intermediate-density lipoproteins, it should

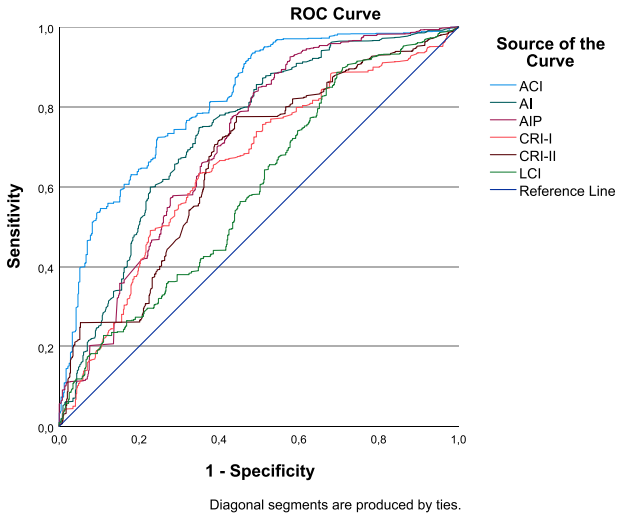


**Figure 3.** The ACI predicts the presence of CAD with 74% sensitivity and 73% specificity at the best cut-off value (2.62). When non-traditional lipid profiles were pairwise compared with ROC analysis to predict the presence of CAD, the ACI was superior to all other non-traditional lipid profiles in predicting the presence of CAD. ACI, atherogenic combined index; AI, atherogenic index; AIP, atherogenic index of plasma; AUC: area under the curve; CAD: coronary artery disease; CI: confidence interval; CRI-I: Castelli risk index-I; CRI-II: Castelli risk index-II; ΔAUC: differences between areas under the curve; LCI, lipoprotein combined index; ROC: receiver operating characteristic.

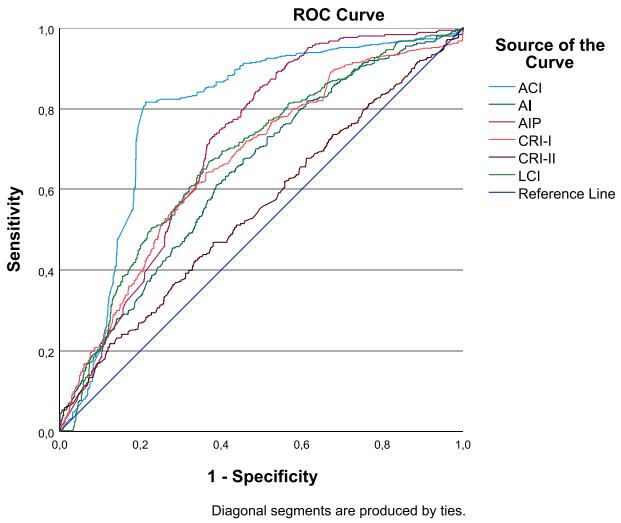


**Figure 4.** The ACI predicts severe CAD with 81% sensitivity and 80% specificity at the best cut-off value (2.95). When non-traditional lipid profiles were pairwise compared with ROC analysis to predict the severity of CAD, the ACI was superior to all other non-traditional lipid profiles in predicting severe CAD. ACI, atherogenic combined index; AI, atherogenic index; AIP, atherogenic index of plasma; AUC: area under the curve; CAD: coronary artery disease; CI: confidence interval; CRI-I: Castelli risk index-I; CRI-II: Castelli risk index-II; ΔAUC: differences between areas under the curve; LCI, lipoprotein combined index; ROC: receiver operating characteristic.

have a place in lipid formulations to effectively reflect the atherogenic balance in the blood. Similarly, AI ratios the atherogenic non-HDL-C particle to the non-atherogenic HDL-C particle (17) and does not take into account the cumulative effect of a significant atherogenic particle in the blood, such as TG, on atherosclerosis (31). CRI-I ratio TC and HDL-C (15). However, in the CRI-I formulation, the inclusion of HDL-C in TC complicates its reflection of the antiatherogenic balance, because HDL-C, an antiatherogenic particle, serves as both the numerator and denominator, making CRI-I less effective in assessing atherogenic risk. CRI-II is obtained by dividing the atherogenic LDL-C particle by the non-atherogenic HDL-C particle (15). The disadvantage of this formulation is that it does not include atherogenic particles such as TG and VLDL and intermediate-density lipoprotein. LCI is obtained by dividing the product of TC, TG, and LDL-C particles by the antiatherogenic particle HDL-C (32). However, this formulation has some disadvantages in terms of reflecting the atherogenic balance more accurately, such as the fact that TC contains HDL-C, which is an antiatherogenic particle, and LDL-C, which is already included in the formulation. Therefore, as supported by our results, we think that ACI can more comprehensively reflect the cumulative, additive, and synergistic atherogenic and antiatherogenic balance between traditional lipid fractions and can be effectively used in CAD risk prediction.

## Limitations

This study had some limitations. a) The study design is cross-sectional, which inherently limits the ability to establish causality. The observed associations between ACI and the presence and severity of CAD may be influenced by confounding variables, and longitudinal studies are needed to confirm the predictive value of ACI over time. b) Although our study was not a single-center study, the small number of participating centers may affect the generalizability of the findings to larger populations. Variations in patient demographics, lifestyle, and healthcare practices in different regions may affect the external validity of the results. c) The study included patients who underwent coronary angiography, which may introduce selection bias by overrepresenting individuals with more severe symptoms or risk factors. This may affect the generalizability of the findings to individuals with less severe or asymptomatic CAD. d) The exclusion criteria, such as the exclusion of patients with a history of certain medical conditions or interventions, may limit the applicability of the results to a broader patient population. Generalization of results to individuals with comorbidities or specific medical histories should be made with caution. e) The decision not to include traditional lipid profiles in the regression models might overlook potential interactions or dependencies be-

tween ACI and traditional lipid parameters. Future studies considering a comprehensive analysis including both traditional and novel lipid indices may provide a more complete picture. f) Log-transformation of lipid indices was used due to non-normal distributions, which may introduce complexity in the interpretation of results. Although log transformation is a common statistical approach, its implications on clinical significance should be carefully considered. g) The study does not explicitly address potential ethnic or racial differences in the predictive value of ACI. Given that cardiovascular risk factors may vary among different ethnic and racial groups, the findings may not be universally applicable. h) Although the study emphasizes the need for cost-effective diagnostic tools, it does not assess the specific cost-effectiveness of implementing ACI in routine clinical practice. A comprehensive economic analysis would be beneficial to evaluate the financial feasibility of incorporating ACI into cardiovascular risk assessment. i) The novel lipid biomarker ACI, while promising, requires external validation in diverse populations to confirm its generalizability and reliability across different settings and patient groups. j) The study focuses primarily on the association of ACI with the presence and severity of CAD. Future research should explore the clinical utility of ACI in predicting cardiovascular events and outcomes to establish its role in risk stratification and preventive interventions.

## Conclusions

In conclusion, this study validates the ACI as a novel and robust lipid biomarker for the assessment of CAD. Derived from a logarithmic transformation of key atherogenic lipoprotein ratios, the ACI provides a nuanced evaluation of cardiovascular risk by explicitly incorporating TG, VLDL, and intermediate-density lipoprotein. Elevated ACI levels were consistently observed in CAD patients compared to controls and strongly correlated with CAD severity as measured by the SYNTAX score. Multivariate analyses confirmed ACI as an independent predictor of CAD presence and severity, surpassing established lipid indices in predictive accuracy. These findings underscore the potential of ACI to improve risk stratification and guide preventive interventions in clinical practice while highlighting the need for further longitudinal validation and exploration in diverse populations to consolidate its clinical utility.

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No funding was received for the conduct of this study.

## Conflict of Interest

The authors report that there are no competing interests to declare.

## Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2024.103065.

## References

1. 3rd Goldsborough E, Osuji N, Blaha MJ. Assessment of Cardiovascular Disease Risk: A 2022 Update. Endocrinol Metab Clin North Am 2022;51:483–509 Epub 2022 Jul 4. PMID: 35963625. doi:10.1016/j.ecl.2022.02.005.
2. Ray KK, Ference BA, Séverin T, et al. World Heart Federation Cholesterol Roadmap 2022. Glob Heart 2022;17:75. doi:10.5334/gh.1154.
3. Leong DP, Joseph PG, McKee M, et al. Reducing the Global Burden of Cardiovascular Disease, Part 2: Prevention and Treatment of Cardiovascular Disease. Circ Res 2017;121:695–710. doi:10.1161/CIRCRESAHA.117.311849.
4. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation 2006;113:2335–2362. doi:10.1161/CIRCULATIONAHA.104.482570.
5. Lyngbakken MN, Myhre PL, Røsjø H, et al. Novel biomarkers of cardiovascular disease: Applications in clinical practice. Crit Rev Clin Lab Sci 2019;56:33–60. doi:10.1080/10408363.2018.1525335.
6. Rochette L. Emerging New Biomarkers for Cardiovascular Disease. Int J Mol Sci 2022;18(23):3274. doi:10.3390/ijms23063274.
7. Ridker PM, Rifai N, Cook NR, et al. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA 2005;294:326–333.
8. Fernández-Macías JC, Ochoa-Martínez AC, Varela-Silva JA, et al. Atherogenic Index of Plasma: Novel Predictive Biomarker for Cardiovascular Illnesses. Arch Med Res 2019;50:285–294. doi:10.1016/j.arcmed.2019.08.009.
9. Li Y, Feng Y, Li S, et al. The atherogenic index of plasma (AIP) is a predictor for the severity of coronary artery disease. Front Cardiovasc Med 2023;10:1140215. doi:10.3389/fcvm.2023.1140215.
10. Falk E. Pathogenesis of atherosclerosis. J Am Coll Cardiol 2006;47(8):C7–C12 Suppl. doi:10.1016/j.jacc.2005.09.068.
11. Rader DJ, Puré E. Lipoproteins, macrophage function, and atherosclerosis: beyond the foam cell? Cell Metab 2005;1:223–230. doi:10.1016/j.cmet.2005.03.005.
12. Gaggini M, Gorini F, Vassalle C. Lipids in Atherosclerosis: Pathophysiology and the Role of Calculated Lipid Indices in Assessing Cardiovascular Risk in Patients with Hyperlipidemia. Int J Mol Sci 2022;24:75. doi:10.3390/ijms24010075.
13. Matsuura Y, Kanter JE, Bornfeldt KE. Highlighting Residual Atherosclerotic Cardiovascular Disease Risk. Arterioscler Thromb Vasc Biol 2019;39:e1–e9. doi:10.1161/ATVBAHA.118.311999.
14. Si Y, Liu J, Han C, et al. The correlation of retinol-binding protein-4 and lipoprotein combine index with the prevalence and diagnosis of acute coronary syndrome. Heart Vessels 2020;35:1494–1501. doi:10.1007/s00380-020-01627-8.
15. Drwiła D, Rostoff P, Nessler J, et al. Prognostic value of non-traditional lipid parameters: Castelli Risk Index I, Castelli Risk Index II, and triglycerides to high-density lipoprotein cholesterol ratio among patients with non-ST-segment elevation myocardial infarction during 1–year follow-up. Kardiologiia 2022;62:60–66.
16. Bora K, Pathak MS, Borah P, Hussain MI, Das D. Association of the Apolipoprotein A-I Gene Polymorphisms with Cardiovascular Disease Risk Factors and Atherogenic Indices in Patients from Assam, Northeast India. Balkan J Med Genet 2017;20:59–70. doi:10.1515/bjmg-2017-0002.

17. Mao Q, Zhao J, Zhao X. Association of non-HDL-C-to-HDL-C ratio with coronary lesions and its prognostic performance in first-onset NSTEMI. Biomark Med 2023;17:29–39. doi:10.2217/bmm-2022-0548.
18. Jia S, Liu Y, Yuan J. Evidence in Guidelines for Treatment of Coronary Artery Disease. Adv Exp Med Biol 2020;1177:37–73. doi:10.1007/978-981-15-2517-9_2.
19. Collet JP, Thiele H, Barbato E, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;42:1289–1367. doi:10.1093/eurheartj/ehaa575.
20. Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis 2019;290:140–205. doi:10.1016/j.atherosclerosis.2019.08.014.
21. Gheorghe A, Griffiths U, Murphy A, et al. The economic burden of cardiovascular disease and hypertension in low- and middle-income countries: a systematic review. BMC Public Health 2018;18:975. doi:10.1186/s12889-018-5806-x.
22. Joseph P, Leong D, McKee M, et al. Reducing the Global Burden of Cardiovascular Disease, Part 1: The Epidemiology and Risk Factors. Circ Res 2017;121:677–694.
23. Gaziano TA. Economic burden and the cost-effectiveness of treatment of cardiovascular diseases in Africa. Heart 2008;94:140–144. doi:10.1136/hrt.2007.128785.
24. Xiang Q, Tian F, Xu J, et al. New insight into dyslipidemia-induced cellular senescence in atherosclerosis. Biol Rev Camb Philos Soc 2022;97:1844–1867. doi:10.1111/brv.12866.
25. Khatana C, Saini NK, Chakrabarti S, et al. Mechanistic Insights into the Oxidized Low-Density Lipoprotein-Induced Atherosclerosis. Oxid Med Cell Longev 2020;2020:5245308. doi:10.1155/2020/5245308.
26. Maguire EM, Pearce SWA, Xiao Q. Foam cell formation: A new target for fighting atherosclerosis and cardiovascular disease. Vascul Pharmacol 2019;112:54–71. doi:10.1016/j.vph.2018.08.002.
27. James RW. Rapports lipides/lipides et lipides/apolipoprotéines: qu'apportent-ils au bilan cardiovasculaire? [Serum lipid and apolipoprotein ratios: do they add to cardiovascular risk assessment?]. Rev Med Suisse 2006;2(632–634):637.
28. Toprak K. Atherogenic Index of Plasma is an Independent Risk Factor for Contrast Induced Nephropathy in Patients With Non-ST Elevation Myocardial Infarction. Angiology 2023;74:427–434. doi:10.1177/00033197221110723.
29. Sniderman A, Williams K, de Graaf J. Non-HDL C equals apolipoprotein B: except when it does not!. Curr Opin Lipidol 2010;21:518–524. doi:10.1097/MOL.0b013e32833ee80c.
30. Aggarwal DJ, Kathariya MG, Verma DPKLDL-C. NON-HDL-C and APO-B for cardiovascular risk assessment: Looking for the ideal marker. Indian Heart J 2021;73:544–548.
31. Peng J, Luo F, Ruan G, et al. Hypertriglyceridemia and atherosclerosis. Lipids Health Dis 2017;16:233. doi:10.1186/s12944-017-0625-0.
32. Drwila D, Rostoff P, Nessler J, et al. Prognostic significance of atherogenic index of plasma, atherogenic coefficient and lipoprotein combined index among elderly patients with non-ST-segment elevation myocardial infarction in 1-year follow-up. Bratisl Lek Listy 2022;123:872–877. doi:10.4149/BLL_2022_139.