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Non–traditional Lipid Profile and Obstructive Coronary Artery Disease Based on CAD–RADS Score

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Abstract

Background: The association between dyslipidemia and coronary artery disease (CAD) is undisputable. Current evidence suggests that, in comparison to conventional lipid parameters, a comprehensive non-traditional lipid profile serves as a more robust predictor of CAD. The evidence regarding the correlation between non-traditional lipid profile and severity of coronary lesions, as measured by the coronary artery disease-reporting and data system (CAD-RADS) score by Coronary Computed Tomography Angiography (CCTA), is still scarce. This study aimed to elaborate on the association between those parameters. Understanding these associations may improve risk stratification and management in CAD patients.

Methods: A cross-sectional single-center study was conducted in a large population of patients with suspected CAD. Data were obtained from medical records between January 2020 and February 2024. The CAD-RADS score was stratified into three groups: CAD-RADS 0 (no CAD), CAD-RADS 1-2 (stenosis <50%, classified as non-obstructive CAD), and CAD-RADS ≥3 (stenosis ≥50% in ≥1 coronary segment, classified as obstructive CAD). Logistic regression analysis analyzes the association between patients' lipid profiles and CAD-RADS scores. P-value <0.05 was considered statistically significant.

Results: A total of 543 (274 female) patients were included in this study. In the univariate analysis, the LDL/HDL ratio was significantly associated with the severity of CAD based on CAD-RADS scores. The multivariate analysis revealed that the LDL/HDL ratio was the most significant lipid parameter [Adj OR = 10.506, 95% CI (2.139-51.601), P 0,004] after adjustments for age, sex, smoker, and history of hypertension, diabetes mellitus, and chronic kidney disease. The LDL/HDL ratio cut-off value was 1.78 with a sensitivity of 68.90% and a specificity of 72.93%.

Conclusions: The LDL/HDL ratio was significantly associated with obstructive CAD, as assessed by the CAD-RADS score, with a cut-off value of 1.78 can be a predictor of obstructive CAD.

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Keywords: *lipid profile, coronary artery disease, CAD-RADS Score*.

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Introduction

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide.[1,2] Understanding the underlying factors that contribute to the severity of CAD is crucial for improving diagnostic and therapeutic strategies. Traditionally, the assessment of lipid profiles has been fundamental in predicting cardiovascular risk; however, emerging evidence suggests that beyond the standard lipid parameters, additional lipid-related biomarkers may provide a more comprehensive risk assessment.[3]

This is currently an active research area where lipid profiles, both traditional and non-traditional, have been identified as independent predictors for cardiovascular disease across various patient populations. Several studies have demonstrated that low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), and the TC/HDL-C ratio are strong predictors of cardiovascular disease.[2-4] Compared to individual lipid parameters, comprehensive non-traditional lipid indices such as non-HDL-C (total cholesterol minus HDL-C), TC/HDL-C (Castelli Risk Index-I), LDL-C/HDL-C (Castelli Risk Index-II), non-HDL-C/HDL-C (Atherogenic Index, AI), log TG/HDL-C (Atherogenic Index of Plasma, AIP), and TC × TG × LDL/HDL-C (Lipoprotein Combined Index, LCI) are regarded as superior predictors of CAD.[5-8]

Research has proven the effectiveness of Coronary Computed Tomography Angiography (CCTA) in evaluating patients with CAD.[9] The CAD-RADS score is a standardized method for classifying the severity of coronary artery disease using CCTA. This system offers a detailed evaluation of coronary artery stenosis, which is essential for clinical decision-making and risk stratification.[10] Although the relationship between traditional lipid profiles and CAD has been well-documented, there is a growing need to explore the association between more comprehensive lipid profiles and the extent of obstructive CAD as assessed by CAD-RADS.

This study aims to investigate the relationship between an expanded lipid profile and the severity of obstructive CAD based on the CAD-RADS score. By analyzing a broader range of lipid parameters, this research seeks to provide deeper insights into how these factors correlate with the anatomical and functional severity of CAD. The findings could enhance the current understanding of lipid-related mechanisms in CAD progression and support the development of more targeted therapeutic approaches

Materials and Methods

Design of the Study and Subject Recruitment

The minimum sample size was calculated using the unpaired analytical study sample size formula. Between January 2020 and February 2024, 747 consecutive adult patients who underwent CCTA at Hasan Sadikin General Hospital - Faculty of Medicine, Universitas Padjadjaran, were enrolled in this study.

Adults aged 18 years and older with suspected CAD who underwent CCTA were included in this study. Eligible participants must have complete traditional and non-traditional lipid profile data available, which includes total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), non-HDL, TC/HDL ratio, LDL/HDL ratio, Atherogenic Index (AI), Lipoprotein Combine Index (LCI), and Atherogenic Index of Plasma (AIP). Additionally, participants must provide written informed consent to participate in the study.

Patients who have undergone percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery are excluded from the study. PCI and CABG procedures can affect CTA results due to the presence of stents and surgical grafts, which may introduce artifacts, reduce image clarity, or obscure native coronary anatomy. By excluding these patients, researchers might obtain clearer CTA images for analyzing native coronary artery atherosclerosis. Patients who have experienced acute coronary syndrome (ACS) within the past three months, have incomplete lipid profile data, or have unsatisfactory CCTA data are also excluded from the study. Furthermore, individuals with severe comorbid conditions such as active cancer, severe liver disease, or chronic inflammatory diseases, as well as pregnant women and those with known allergies to contrast agents used in CCTA, are excluded from the study. These criteria ensure a homogeneous study population and enhance the validity and reliability of the study findings regarding the association between lipid profiles and obstructive CAD based on CAD-RADS scores.

Table 1. Baseline characteristic.

Variable	Non CAD (n=111)	Non Obstructive CAD (n=133)	Obstructive CAD(n=299)	P value
Age, mean±SD	49±10 (13.5)	55±10 (13)	60±9 (12)	<0.001
Sex				
Male, n (%)	27 (5%)	58 (11%)	184 (34%)	<0.001
Female, n (%)	84 (15%)	75 (14%)	115 (21%)	
Family History, n (%)	11 (2%)	8 (1%)	22 (4%)	0.509
Diabetes Mellitus, n (%)	3 (1%)	9 (2%)	51 (9%)	<0.001
Hypertension, n (%)	39 (7%)	58 (11%)	166 (31%)	<0.001
Dyslipidemia, n (%)	28 (5%)	41 (8%)	159 (29%)	<0.001
Active smoker, n (%)	16 (3%)	20 (14%)	105 (19%)	<0.001
Chronic Kidney Disease, n (%)	26 (5%)	41 (8%)	175 (32%)	<0.001
Total Cholesterol, n (%)				0.002
<200 (normal)	70 (13%)	87 (16%)	191 (35%)	
200-239 (borderline)	34 (6%)	33 (6%)	53 (10%)	
≥240 (high)	7 (1%)	13 (2%)	55 (10%)	
LDL, n (%)				<0.001
<130 (normal)	73 (13%)	90 (17%)	176 (32%)	
130-159 (borderline)	23 (4%)	28 (5%)	42 (8%)	
≥160 (high)	15 (3%)	15 (3%)	81 (15%)	
HDL, n (%)				0.055
≥40 (normal)	87 (16%)	102 (19%)	204 (38%)	
<40 (low)	24 (4%)	31 (6%)	95 (17%)	
Triglyceride, n (%)				0.018
<150 (normal)	76 (14%)	89 (16%)	176 (32%)	
150-199 (borderline)	26 (5%)	21 (4%)	58 (11%)	
≥200 (high)	9 (2%)	23 (4%)	65 (12%)	
Total Cholesterol, mean±SD, mg/dl	184±36	186±37	190±52	0.735
LDL, mean±SD, mg/dl	116±33	120±34	126±43	0.063
HDL, mean±SD, mg/dl	49±14	48±13	46±12	0.014
Triglyceride, mean±SD, mg/dl	133±62	153±115	163±118	0.215
Non HDL, mean±SD, mg/dl	136±36	136±37	145±51	0.379
CRI I, mean±SD	3.9±1.1	4±1.3	4.4±1.7	0.061
CRI II, mean±SD	2.57±0.9	2.58±0.95	3±1.4	0.005
AI, mean±SD	2.9±1.1	3±1.3	3.4±1.8	0.033
LCI, mean±SD	71137±55760	82391±111059	114264±169313	0.041
AIP, mean±SD	0.4±0.2	0.45±0.3	0.49±0.3	0.025

CAD: Coronary Artery Disease, SD: Standard Deviation, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, TC: Total Cholesterol, TG: Triglycerides, Non-HDL: Non-High-Density Lipoprotein Cholesterol; CRI: Castelli Risk Index (CRI-I: Total Cholesterol/HDL, CRI-II: LDL/HDL); AI: Atherogenic Index (Non HDL/HDL); LCI: Lipid Coefficient Index (TC.TG.LDL/HDL); AIP: Atherogenic Index of Plasma (log10[Trig/HDL]).

Table 2. Univariate and Multivariate Logistic Regression Model for Prediction of Obstructive CAD.

Variables		OR	(95% CI)	P value	Adj OR	(95% CI)	P value
Traditional lipid profile	TC	0.970	(0.917-1.027)	0.299	0.975	(0.908-1.048)	0.495
	TG	1.001	(0.993-1.009)	0.815	1.007	(0.997-1.016)	0.162
	HDL	1.007	(0.939-1.079)	0.847	1.015	(0.934-1.103)	0.726
	LDL	0.978	(0.948-1.008)	0.152	0.961	(0.928-0.996)	0.028
	Non HDL	1.051	(0.989-1.117)	0.109	1.06	(0.983-1.143)	0.133
Non-traditional lipid profile	TC/HDL	0.591	(0.157-2.222)	0.437	0.393	(0.068-2.276)	0.297
	LDL/HDL	4.393	(1.075-17.958)	0.039	10.506	(2.139-51.601)	0.004
	AI	0.432	(0.081-2.291)	0.324	0.459	(0.057-3.682)	0.464
	LCI	1.000	(1.000-1.000)	0.094	1.00	(1.000-1.000)	0.563
	AIP	0.361	(0.028-4.594)	0.432	0.076	(0.004-1.433)	0.086

Adj OR: Adjusted Odds Ratio, 95% CI: 95% Confidence Interval, TC: Total Cholesterol, TG: Triglycerides, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, AI: Atherogenic Index, LCI: Lipid Coefficient Index, AIP: Atherogenic Index of Plasma.

Traditional Cardiovascular Risk Factors

Dyslipidemia was defined based on patient history and was not limited to those already on statin therapy. Essential hypertension (EH), diabetes mellitus (DM), and chronic kidney disease (CKD) were defined according to features described in a previous report. EH was defined as systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg and/or a self-reported history of hypertension and/or use of anti-hypertensive drugs. DM was defined as fasting glucose levels ≥126 gr/dl, and/or a self-reported history of diabetes mellitus, and/or use of anti-diabetic drugs. CKD is defined as kidney damage or decreased kidney function for three months or more, irrespective of the cause, excluding patients on dialysis. Smoking was defined as daily cigarette smoking until the day of the interview.

Non-traditional lipid profile

Non-traditional lipid variables were calculated to provide a comprehensive assessment of lipid profiles in the study population. Non-HDL cholesterol was determined by subtracting HDL cholesterol from total cholesterol. Castelli's risk index-1 (CRI 1) was determined by the total cholesterol to HDL ratio (TC/HDL) and Castelli's risk index-2 (CRI 2) was determined by LDL to HDL ratio (LDL/HDL). The Atherogenic Index (AI), defined as the ratio of Non-HDL to HDL cholesterol, and the Atherogenic Index of Plasma (AIP), calculated as the logarithm of the ratio of plasma triglycerides to HDL cholesterol, were also included. Additionally, the Lipoprotein Combined Index (LCI) obtained from multiplying total cholesterol by triglycerides and LDL, then divided by HDL.

CCTA

CCTA is a non-invasive imaging modality to visualize coronary arteries. The protocol for CCTA in this study included the administration of a contrast agent to enhance the visualization of the coronary artery lumen and to identify the presence and extent of CAD. Patients underwent CCTA following standard preparation, including heart rate control with beta-blockers if necessary, to obtain high-quality images with minimal motion artifacts. The CAD-RADS is a standardized reporting system for CCTA findings, categorizing the severity of coronary stenosis from 0 (no stenosis) to 5 (total occlusion in at least one coronary segment). Obstructive CAD is defined as stenosis of ≥50% in at least one coronary segment on CCTA, corresponding to a CAD-RADS score of ≥3.

Statistical Analysis

The baseline characteristics of the study population will be summarized using descriptive statistics. The mean and standard deviation for continuous variables were compared using a k-independent samples t-test. The frequencies and percentages were compared using a Chi-square test for categorical variables. Univariate linear regression analysis will be performed to identify significant associations between each lipid parameter

Table 3. Multicollinearity of age, sex, hypertension, DM, smoking, CKD and LDL/HDL for Obstructive CAD.

Categorical variables	Coefficients beta	Coefficients std. error	t Value	P Value	R2	Adj R2
Constant	3.956339	0.389579	10.155	<0.001	0.09905	0.08418
Age	–0.024159	0.006498	-3.718	<0.001		
Sex	0.35918	0.145916	2.462	0.014		
Hypertension	-0.298539	0.12808	-2.331	0.02		
DM	0.121864	0.178713	0.682	0.495		
Smokers	-0.09115	0.157524	-0.579	0.563		
CKD	0.565755	0.133503	4.238	<0.001		

DM: Diabetes Mellitus, CKD: Chronic Kidney Disease

and obstructive CAD. Subsequently, multivariate logistic regression models will be constructed to adjust for potential confounding variables such as age, sex, hypertension, diabetes mellitus, chronic kidney disease, and smoking status. Include the identified confounding variables as covariates in the logistic regression model. The adjusted odds ratios (Adj OR) and 95% confidence intervals (CIs) will be calculated to determine the strength of the associations. Model performance will be evaluated using sensitivity, specificity, and accuracy metrics. Assumption made during analysis could be achieved by Linearity of Logits in which the relationship between the independent variables and the log odds of the dependent variable is assumed to be linear. This can be assessed through various diagnostic plots. The threshold for statistical significance will be established at $P < 0.05$. RStudio 4.3.2 will be employed to conduct all analyses.

Ethical Aspect and Research Approval

The data collection was categorized as low-risk as it was conducted using medical record data. After receiving approval and recommendations from the Ethics Committee Review Board of Hasan Sadikin General Hospital – Faculty of Medicine, Padjadjaran University, all procedures were performed in accordance with applicable guidelines and regulations. The registry number for this research was part of the CCTA registry, with the reference number LB.02.01/X.6.5.130/2023.

Results

Baseline characteristics

A total of 543 CAD patients were included in this study, out of a total of 747 CAD patients who underwent CCTA from 01 January 2020 to 28 February 2024. The remaining 139 patients were excluded due to incomplete fundamental clinical information, while nine patients were excluded due to missing or unsatisfactory CCTA data for analysis. Additionally, 56 additional patients were precluded as a result of history of PCI or CABG (Figure 1).

The baseline characteristics of the study population are shown in Table 1, which compares patients with obstructive CAD, non-obstructive CAD, and non-coronary artery disease (non-CAD). The mean age was significantly higher in the obstructive CAD group (60 years) compared to the non-CAD (49 years) and non-obstructive CAD (55 years) groups ($p < 0.001$). There was a higher proportion of males in the obstructive CAD group (34%) compared to the non-CAD (5%) and non-obstructive CAD (11%) groups ($p < 0.001$). The prevalence of diabetes mellitus, hypertension, dyslipidemia, active smoking, and chronic kidney disease was also significantly higher in the obstructive CAD group ($p < 0.001$ for each). Total cholesterol levels were higher in the obstructive CAD group, with more patients having cholesterol ≥240 mg/dl (10%) compared to the non-CAD (1%) and non-obstructive CAD (2%) groups ($p = 0.002$). LDL levels were also significantly higher in the obstructive CAD group, with more patients having LDL ≥160 mg/dl (15%) compared

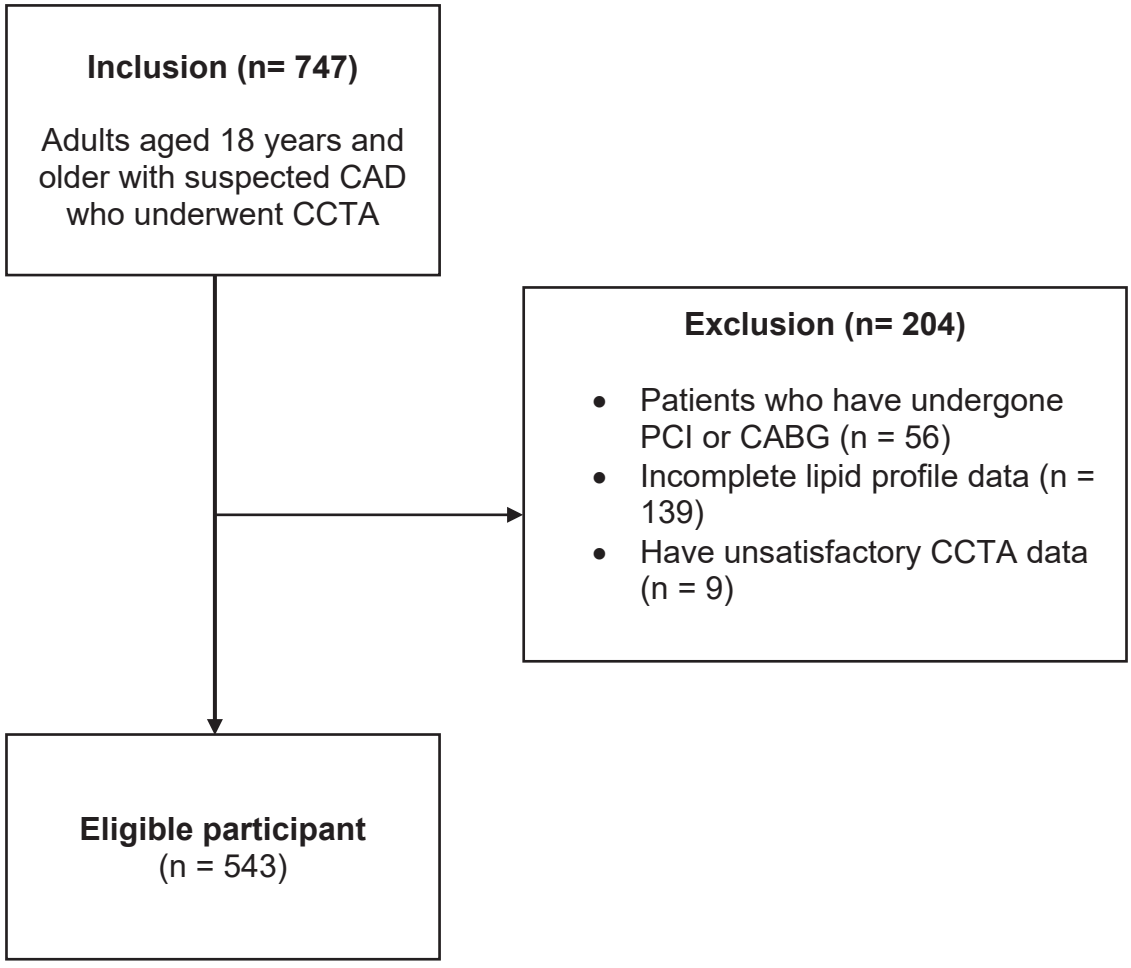

Figure 1. Patient Enrollment.

to the other groups (p < 0.001). Triglyceride levels were also higher in the obstructive CAD group, with more patients having triglyceride ≥200 mg/dl (12%) compared to the other groups (p 0.018). HDL levels were lower in the obstructive CAD group, with more patients having HDL <40 (17%) compared to the other groups (p 0.055). The mean of several non-traditional lipid measures, such as TC/HDL, AI, LCI, and AIP was higher in the obstructive CAD group and showed significant differences across the groups, indicating a worse lipid profile in the obstructive CAD group (p < 0.05 for each).

Univariate and Multivariate analysis

The univariate and multivariate logistic regression analysis table assesses the relationship between traditional and non-traditional lipid variables and obstructive CAD. There was no significant association between obstructive CAD and traditional lipid variables. (Table 2)

In contrast, among non-traditional lipid variables, only the LDL/HDL ratio was significantly associated with obstructive CAD [unadjusted OR 4.393, 95% CI (1.075-17.958), P 0.039), while non-HDL, TC/HDL, the AI, LCI, and AIP were not. After adjusting for potential confounding factors, which are established CAD risk factors, including age, sex, smoker, and history of hypertension, diabetes mellitus, and chronic kidney disease, we found that LDL/HDL ratio was significantly

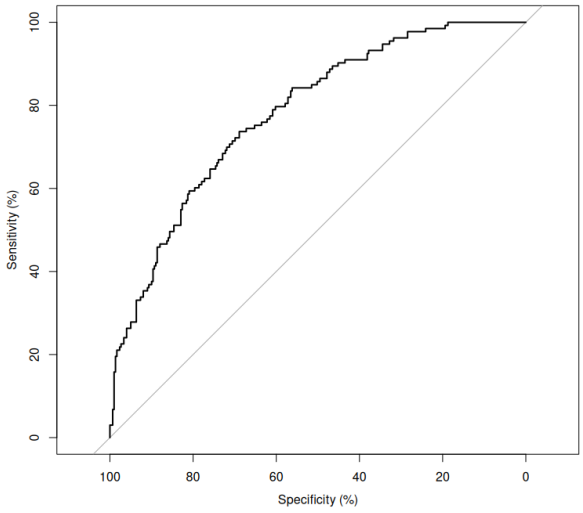

Figure 2. ROC curve of LDL/HDL Ratio.

associated with obstructive CAD [OR = 10.506, 95% CI (2.139-51.601), P 0,004] (Table 2). The variance inflation factor (VIF) is 1,1 in the multicollinearity regression model, which shows no collinearity between age, sex, hypertension, DM, smokers, CKD, and LDL/HDL ratio. (Table 3).

According to the ROC curve analysis, this study's cut-off value of LDL/HDL ratio was 1.78, with a sensitivity of 68.90% and specificity of 72.93. Area Under Curve (AUC) 77.99% (95% CI, accuracy 70.14%) shows fair performance in predicting obstructive CAD. (Figure 2).

Discussion

This study demonstrates a significant association between the LDL/HDL ratio and obstructive CAD as measured by the CAD-RADS score. The LDL/HDL ratio was a reliable marker across all models, even though other lipid measures did not show a significant correlation. This suggests that it might be useful for predicting obstructive CAD. Univariate analysis revealed that traditional lipid variables were not significantly associated with obstructive CAD, but the LDL/HDL ratio was a notable exception among non-traditional lipid variables. Multivariate analysis showed that the LDL/HDL ratio was consistently linked to obstructive CAD across all models, even after multiple covariates were taken into account. Other lipid measures did not show any significant associations.

Previous studies have demonstrated that dyslipidemia significantly influences coronary atherosclerosis, with reductions in HDL-C and increases in LDL-C being pivotal in the progression of atherosclerosis and the onset of CAD.[11-13] Elevated LDL-C levels are strong predictors of atherosclerotic cardiovascular diseases and lowering these levels can reduce the risks of events like AMI and ischemic stroke, while higher HDL-C levels are associated with a decreased risk. Research demonstrates that the LDL/HDL ratio serves as a robust predictor of CAD and long-term major adverse cardiac events (MACE), offering a more accurate risk assessment compared to solely measuring LDL or HDL.[14-17] Despite mixed results regarding the significance of lipid indices like AIP, AI, and LCI, their predictive values may vary with different scoring systems.[18-23] Additionally, adjusting for risk factors such as age, gender, hypertension, diabetes, chronic kidney disease and smoking status enhances the validity of CAD research findings, highlighting the complexity and multifactorial nature of CAD risk assessment.[1,24-27]

This study showed that the LDL/HDL ratio is associated with obstructive CAD based on the CAD-RADS score. Zhang et al. (2020) showed that the LDL-C/HDL-C ratio is a strong, independent indicator of MACE that will happen in people with CAD over the long term. The study highlighted the utility of the LDL-C/HDL-C ratio in evaluating CAD risk, especially for patients undergoing different types of treatments.[15] High levels of LDL can lead to plaque buildup in the artery walls, increasing the risk of atherosclerosis and eventually CAD. However, measuring LDL alone does not provide information about the beneficial cholesterol that can counteract LDL's harmful effects.[15,16] HDL helps transport cholesterol from the arteries back to the liver for disposal. High levels of HDL are associated with a lower risk of CAD. Measuring HDL alone is insufficient as it fails to indicate the extent to which HDL manages LDL.[15] The LDL/HDL ratio provides a better indication of CAD risk. A high ratio indicates that the amount of LDL is significantly higher than the HDL, suggesting a high risk for plaque formation in the arteries. Conversely, a low ratio indicates a better balance between LDL and HDL, meaning a lower risk of CAD.16 Several studies have shown that the LDL/HDL ratio is a better predictor of CAD compared to measuring LDL or non-HDL alone, as it reflects

the complex interaction between different types of cholesterol in the body.[17,18]

Moreover, the LDL/HDL ratio in this study had threshold value of 0.69 and cut-off value 1.78, which could be a predictor for obstructive CAD with a sensitivity of 68.90% and specificity of 72.93% and Area Under Curve (AUC) 77.99% (95% CI, accuracy 70.14%). The LDL/HDL ratio demonstrates moderate effectiveness as an indicator of obstructive coronary artery disease (CAD). It holds significant clinical relevance for preventing the progression of CAD and directing the treatment of coronary atherosclerosis. By applying this cut-off, we can implement effective strategies to lower the LDL/HDL ratio, consequently mitigating the advancement and severity of CAD. We have separately calculated LDL/HDL and CAD risk factors using the multicollinearity regression model. The findings revealed that the VIF is 1.1, indicating no multicollinearity between LDL/HDL and the variables of age, sex, hypertension, diabetes mellitus, chronic kidney disease, and smoking status. This finding is consistent with previous studies, which show that a higher LDL/HDL ratio was seen in patients with CAD than controls ($P < 0.05$). Their cut-off value of LDL/HDL ratio was 2.517, with a sensitivity of 64.5% and specificity of 61.3%, respectively, which may become a better predictor of CAD severity compared to LDL or HDL.[16]

A lower LDL/HDL ratio is beneficial in reducing the progression of atherosclerosis by minimizing LDL infiltration, enhancing cholesterol removal through HDL, decreasing inflammation, and stabilizing plaques. Conversely, a high LDL/HDL ratio promotes plaque growth and instability, increasing the risk of cardiovascular events. A high LDL/HDL ratio is associated with increased endothelial dysfunction and inflammation, both of which are central to atherosclerosis progression. Oxidized LDL particles trigger inflammatory responses by activating macrophages, which transform into foam cells and become part of the plaque structure. This ongoing inflammation contributes to plaque instability and the potential for rupture, leading to acute cardiovascular events. Conversely, a lower LDL/HDL ratio reduces this inflammatory cascade, thereby slowing the advancement of atherosclerosis. Changes in the LDL/HDL ratio can influence plaque composition. Higher LDL levels contribute to the formation of lipid-rich, unstable plaques that are more prone to rupture. HDL, on the other hand, has antioxidant and anti-inflammatory properties that help stabilize plaques by removing oxidized lipids and inhibiting further inflammatory cell infiltration. Studies show that lowering the LDL/HDL ratio is associated with an increase in fibrous cap thickness and a reduction in necrotic core size within plaques, making them less likely to rupture.[5-8,14-17,28]

This study found that there was a lack of significant association for AI, LCI, and AIP in multivariate models. To the best of the researchers' knowledge, no other studies have demonstrated that AI, LCI, or AIP are insignificant in predicting CAD. Numerous studies have emphasized the importance of the AIP and other lipid indices as predictors of CAD severity. A study involving 2,491 patients demonstrated a significant association between AIP and CAD severity as measured by the SYNTAX score, establishing AIP as an independent predictor.18 In the Chinese Han population, another study corroborated AIP's role as a strong predictor for CAD, emphasizing its clinical utility.[19] Further research involving 150 patients undergoing CABG revealed that both LCI and AI are significantly associated with CAD severity, with higher values observed in the CAD group compared to non-CAD controls.[20] The National Diabetes Survey of Pakistan identified a strong association between AIP and CAD risk factors, suggesting that higher AIP levels may serve as a marker for increased CAD severity.[21]

Lastly, a study of 896 patients with suspected CAD found a positive association between baseline AIP and the angiographic progression of CAD, underscoring AIP's potential in early risk stratification and monitoring of CAD progression.[22] Differences in research outcomes regarding the role of non-traditional lipids in CAD can be attributed to the use of different scoring systems. Various scoring systems used to assess the severity of CAD, such as CAD-RADS or other scoring methods, have different criteria and parameters for evaluating coronary artery narrowing and obstruction levels. This variation can lead to differences in classification and interpretation of results.

Metrics like AIP and AI may not demonstrate universal predictability across different populations. The predictive power of AIP and AI can vary due to factors like genetic background, lifestyle, and comorbidities, leading

to less consistent statistical significance compared to the more universally applicable LDL/HDL ratio. Some non-traditional lipid metrics may overlap with traditional measures like LDL and HDL, creating redundancy rather than additive predictive power. If LDL/HDL ratio already captures most of the atherogenic risk, additional indices may not significantly improve prediction due to shared variance. Non-traditional metrics like AIP and AI can be sensitive to other variables in the model or to smaller sample sizes, potentially limiting their statistical power. For instance, AIP's dependency on triglyceride levels may cause variability in significance depending on triglyceride distributions across the study population, especially in samples with lower overall cardiovascular risk.[21,23]

Limitations

A notable limitation of this study is that it was conducted in a single medical center, which may restrict the generalizability of the findings to other settings or populations with different characteristics. Additionally, the cross-sectional design of the study can establish associations but does not allow for the determination of causality. Furthermore, the study did not differentiate the duration of statin therapy among participants, which could significantly influence lipid levels and cardiovascular outcomes that leads to potential selection bias. Patients with longer exposure to statins may have more stabilized lipid profiles and potentially different clinical outcomes compared to those with shorter statin use. Although sample numbers achieved 543, larger samples are needed to adequately represent the broader population, which can affect the generalizability of the findings. Results derived from a small, specific group may not apply to different demographics or clinical settings. Future researchs for validation in larger, more diverse populations should consider stratifying patients based on their duration of statin therapy to better understand its effects on the study outcomes as well as longitudinal studies to assess the prognostic value of the LDL/HDL ratio in CAD progression.

Conclusions

The LDL/HDL ratio was significantly associated with obstructive CAD, as assessed by the CAD-RADS score, with a cut-off value of 1.78 can be a predictor of obstructive CAD. Adding LDL/HDL to traditional risk factors can further improve the comprehensive lipid-lowering treatment, guiding prevention strategies for obstructive CAD.

List of Abbreviations

CAD	Coronary Artery Disease
CAD-RADS	Coronary Artery Disease Reporting and Data System
CCTA	Coronary Computed Tomography Angiography
TC	Total cholesterol
TG	Triglycerides
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
CRI	Castelli's Risk Index
AI	Atherogenic Index
LCI	Lipoprotein Combine Index
AIP	Atherogenic Index of Plasma
PCI	Percutaneous Coronary Intervention
CABG	Coronary Artery Bypass Grafting
ACS	Acute Coronary Syndrome
EH	Essential Hypertension
DM	Diabetes Mellitus
CKD	Chronic Kidney Disease
MACE	Major Adverse Cardiac Events

Declaration

Ethics Approval and Informed Consent to Participate

All methods were carried out by relevant guidelines and regulations after obtaining approval and recommendations from the Ethics Committee Review Board of Hasan Sadikin General Hospital – Faculty of Medicine, Universitas Padjadjaran, with reference number LB.02.01/X.6.5.130/2023. Since this study used secondary data, written informed consent was not applicable.

Consent for publication

Ethics Committee Review Board of Hasan Sadikin General Hospital – Faculty of Medicine, Padjadjaran Universitywaived the need for informed consent with reference number LB.02.01/X.6.5.130/2023

Availability of data and materials section

The authors declare that the patients' personal data in this study will not be shared based on patients' confidentiality.

Competing Interest

The authors have declared that no competing interest exist.

Funding

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Authors' contributions

FFM did the conception and design of the study, acquisition of data, analysis and interpretation of the data, drafting the manuscript and revising the manuscript critically for important intellectual content.

AM did the acquisition of data, analysis and interpretation of the data, and drafted the manuscript and revising the manuscript critically for important intellectual content.

NYK, CA, and AA did the supervision critically for important intellectual content.

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References

1. Popa L, Petresc B, Cătană CS, Moldovanu C, Feier D, Lebovici A, et al. Association between cardiovascular risk factors and coronary artery disease assessed using CAD-RADS classification: a cross-sectional study in Romanian population. *BMJ Open*. 2020;10
2. Chen, S., Li, Z., Li, H., Zeng, X., Yuan, H., & Li, Y. (2023). Novel lipid biomarkers and ratios as risk predictors for premature coronary artery disease: A retrospective analysis of 2952 patients. *Journal of clinical hypertension (Greenwich, Conn.),* 25(12), 1172–1184. https://doi.org/10.1111/jch.14751
3. Alloubani, A., Nimer, R., & Samara, R. (2021). Relationship between Hyperlipidemia, Cardiovascular Disease and Stroke: A Systematic Review. *Current cardiology reviews*, 17(6), e051121189015. https://doi.org/10.2174/1573403X16999201210200342
4. Zheng, J., Sun, Z., Zhang, X., Li, Z., Guo, X., Xie, Y., Sun, Y., & Zheng, L. (2019). Non-traditional lipid profiles associated with ischemic stroke not hemorrhagic stroke in hypertensive patients: results from an 8.4 years follow-up study. *Lipids in health and disease*, 18(1), 9. https://doi.org/10.1186/s12944-019-0958-y
5. Okan, T., Doruk, M., Ozturk, A., Topaloglu, C., Dogdus, M., & Yilmaz, M. B. (2024). Evaluation of Plasma Atherogenic Index, Triglyceride-Glucose Index and Other Lipid Ratios as Predictive Biomarkers of Coronary Artery Disease in Different Age Groups. *Diagnostics (Basel, Switzerland),* 14(14), 1495. https://doi.org/10.3390/diagnostics14141495
6. Zhao, X., Wang, D., & Qin, L. (2021). Lipid profile and prognosis in patients with coronary heart disease: a meta-analysis of prospective cohort studies. *BMC cardiovascular disorders*, 21(1), 69. https://doi.org/10.1186/s12872-020-01835-0
7. Aggarwal, D. J., Kathariya, M. G., & Verma, D. P. K. (2021). LDL-C, NON-HDL-C and APO-B for cardiovascular risk assessment: Looking for the ideal marker. *Indian heart journal*, 73(5), 544–548. https://doi.org/10.1016/j.ihj.2021.07.013
8. Li, Y., Feng, Y., Li, S., Ma, Y., Lin, J., Wan, J., & Zhao, M. (2023). The atherogenic index of plasma (AIP) is a predictor for the severity of coronary artery disease. *Frontiers in cardiovascular medicine,* 10, 1140215. https://doi.org/10.3389/fcvm.2023.1140215
9. Knuuti J, Wijns W, Saraste A, et all. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020 Jan 14;41(3):407-477. doi: 10.1093/eurheartj/ehz425.

Erratum in: *Eur Heart J*. 2020 Nov 21;41(44):4242. PMID: 31504439

10. Cury RC, Leipsic J, Abbara S, Achenbach S, Berman D, Bittencourt M. CAD-RADSTM 2.0 – 2022 Coronary Artery Disease – Reporting and Data System An Expert Consensus Document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Cardiology (ACC), the American College of Radiology (ACR) and the North America Society of Cardiovascular Imaging (NASCI). *Radiol Cardiothorac Imaging*. 2022 Oct 1;4(4)
11. Wang Z, Sun Z, Yu L, Wang Z, Li L, Lu X. Machine learning-based prediction of composite risk of cardiovascular events in patients with stable angina pectoris combined with coronary heart disease: development and validation of a clinical prediction model for Chinese patients. *Front Pharmacol*. 2024 Jan 10;14:1334439. doi: 10.3389/fphar.2023.1334439.
12. Graby J, Sellek J, Khavandi A, Loughborough W, Hudson B, Shirodaria C, et al. Coronary CT angiography derived pericoronary inflammation and bespoke cardiovascular risk prediction in the lipid clinic: beyond the calcium score. *European Heart Journal*. 2022.
13. Sun T, Chen M, Shen H, PingYin, Fan L, Chen X, Wu J, Xu Z, Zhang J. Predictive value of LDL/HDL ratio in coronary atherosclerotic heart disease. *BMC Cardiovasc Disord*. 2022 Jun 17;22(1):273. doi: 10.1186/s12872-022-02706-6. PMID: 35715736; PMCID: PMC9206383.
14. Hernáez Á, Soria-Florido MT, Schröder H, Ros E, Pintó X, Estruch R, Salas-Salvadó J, et al. Role of HDL function and LDL atherogenicity on cardiovascular risk: A comprehensive examination. *PLoS One*. 2019 Jun 27;14(6):e0218533. doi: 10.1371/journal.pone.0218533. PMID: 31246976; PMCID: PMC6597156.
15. Zhang S, Zhao Y, Li X, Dai W, Chen X, Yang G, Liu L, Su Q. The LDL-C/HDL-C ratio and 4-year risk of coronary artery disease: *a retrospective study*. 2020.
16. Sun, T., Chen, M., Shen, H., PingYin, Fan, L., Chen, X., Wu, J., Xu, Z., & Zhang, J. (2022). Predictive value of LDL/HDL ratio in coronary atherosclerotic heart disease. *BMC cardiovascular disorders*, 22(1), 273. https://doi.org/10.1186/s12872-022-02706-6
17. Zhang, R., Fan, Y., Xue, Y., Feng, Y., Dong, C., Wang, Y., Kou, P., Li, G., Ma, A., & Wang, T. (2022). The LDL/HDL ratio predicts long-term risk of coronary revascularization in ST-segment elevation myocardial infarction patients undergoing percutaneous coronary intervention: *a cohort study*. Brazilian journal of medical and biological research = *Revista brasileira de pesquisas medicas e biologicas*, 55, e11850. https://doi.org/10.1590/1414-431X2021e11850
18. Ya Li, Yu-jiao Feng, Shu Li, Yulin Ma, Jiesheng Lin, J. Wan, Min Zhao. (2023). The atherogenic index of plasma (AIP) is a predictor for the severity of coronary artery disease. *Frontiers in Cardiovascular Medicine,* 10. DOI: 10.3389/fcvm.2023.1140215
19. Cai, G., Shi, G., Xue, S., & Lu, W. (2017). The atherogenic index of plasma is a strong and independent predictor for coronary artery disease in the Chinese Han population. *Medicine*, 96(37), e8058. https://doi.org/10.1097/MD.0000000000008058
20. Çelik, E., Çora, A. R., & Karadem, K. B. (2021). The Effect of Untraditional Lipid Parameters in the Development of Coronary Artery Disease: Atherogenic Index of Plasma, Atherogenic Coefficient and Lipoprotein Combined Index. *Journal of the Saudi Heart Association*, 33(3), 244–250. https://doi.org/10.37616/2212-5043.1266
21. Onat A, Can G, Kaya H, Hergenç G. "Atherogenic index of plasma" (log10 triglyceride/high-density lipoprotein-cholesterol) predicts high blood pressure, diabetes, and vascular events. *J Clin Lipidol*. 2010 Mar-Apr;4(2):89-98. doi: 10.1016/j.jacl.2010.02.005. Epub 2010 Feb 12. PMID: 21122635
22. Shui, X., Chen, Z., Wen, Z., Tang, L., Tang, W., Liao, Y., Wu, Z., & Chen, L. (2022). Association of Atherogenic Index of Plasma With Angiographic Progression in Patients With Suspected Coronary Artery Disease. *Angiology*, 73(10), 927–935. https://doi.org/10.1177/00033197221080911
23. Jung E, Kong SY, Ro YS, Ryu HH, Shin SD. Serum Cholesterol Levels and Risk of Cardiovascular Death: A Systematic Review and a Dose-Response Meta-Analysis of Prospective Cohort Studies. *Int J*

Environ Res Public Health. 2022 Jul 6;19(14):8272. doi: 10.3390/ijerph19148272
24. Guo Y, Yin F, Fan Y, Liu C, Luo Y, Tang Q, et al. Influence of age and gender on the presence of comorbidities and reduced quality of life in patients with coronary artery disease. *J Cardiovasc Transl* Res. 2020;13(3):19-25
25. Otaki Y, Gransar H, Cheng VY, Dey D, Labounty, et all. Gender differences in the prevalence, severity, and composition of coronary artery disease in the young: a study of 1635 individuals undergoing coronary CT angiography from the prospective, multinational confirm registry. *Eur Heart J Cardiovasc Imaging*. 2015 May;16(5):490-9
26. Toupendi NZ, Tiam EM, Ngou MT, et all. Relationship between cardiovascular risk factors and coronary artery disease assessed by CAD-RADS. *JESFC*. 2024 Jan; 117(1): 26-27
27. Wang C, Cheng G, Duanmu Y, Zhu Y, Xu L. Correlation of coronary plaque characteristics and obstructive stenosis with chronic kidney disease by coronary CT angiography. *Cardiovasc Diagn Ther*. 2015 Dec;5(6):435-43
28. Deventer HE, Miller W, Myers G, Sakurabayashi I, Bachmann L, Caudill S, et al. Non-HDL cholesterol shows improved accuracy for cardiovascular risk score classification compared to direct or calculated LDL cholesterol in a dyslipidemic population. *Clin Chem*. 2011;57(3):490-501. doi: 10.1373/clinchem.2010.154773