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Original Article

The Role of Coronary Artery Calcium Score as a Systemic Marker of Atherosclerosis: A Cross-sectional Imaging Study

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Abstract

Background: The Coronary Artery Calcium Score (CACS) is widely used to assess coronary atherosclerosis. However, its utility in reflecting systemic atherosclerosis burden remains limited. Notably, no prior study has investigated the relationship between CACS and plaque morphology in the lower extremities. This research aims to address this gap by examining the association between CACS, Ankle-Brachial Index (ABI), and peripheral arterial plaque morphology as assessed by duplex ultrasonography.

Methods: One hundred consecutive patients who had lower extremity Doppler ultrasound and coronary CT angiography between November 2024 and May 2025 were included in this single-center, cross-sectional study. CACS was calculated using the Agatston method. ABI and Doppler-based plaque morphology were evaluated to determine the presence, severity, and complexity of Peripheral Artery Disease (PAD).

Results: CACS and ABI showed a moderately negative association ($r = -0.628$, $p < 0.001$), whereas CACS and plaque morphology showed a moderately positive correlation ($r = 0.619$, $p < 0.001$). CACS showed good discriminatory power for detecting peripheral plaque (AUC = 0.765), and excellent performance in identifying advanced plaque types (III-IV) at a threshold of 478.5 HU (AUC = 0.852; sensitivity 68%; specificity 91.7%).

Conclusions: This is the first study to demonstrate a direct association between coronary calcium burden and plaque morphology in the lower extremities. These findings highlight the potential role of CACS as a surrogate marker for systemic atherosclerosis and a valuable tool for identifying asymptomatic individuals who may benefit from peripheral arterial evaluation.

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Keywords: Coronary Artery Calcium Score, Peripheral Artery Disease, Plaque Morphology, Ankle-Brachial Index, Atherosclerosis

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Introduction

Atherosclerosis is a systemic disease that affects the entire vascular system without boundaries, with a diffuse burden that extends beyond the coronary arteries. However, research and clinical interventions have overwhelmingly focused on Coronary Artery Disease (CAD), often at the expense of other equally significant manifestations, such as Peripheral Artery Disease (PAD).[1-2] Although PAD is a sign of extensive atherosclerosis and bears an equally high risk of cardiovascular morbidity and mortality, CAD is unquestionably a life-threatening condition. Consequently, the dominance of CAD research has led to PAD research–a clear indicator of systemic vascular dysfunction–remaining under-recognized, despite its devastating consequences.[3-4] More specifically, the link between coronary calcium burden and peripheral plaque morphology remains under-explored. More than 200 million people worldwide suffer from PAD, which can manifest as atypical leg discomfort, critical limb ischemia, intermittent claudication, and sporadic acute limb ischaemia.[1-2,5-6] Beginning with endothelial degradation and the atherosclerotic process, PAD releases inflammatory factors until calcium and lipid particles are deposited in the artery's intima layer, creating calcification. Thus, calcium plays a vital role as a marker of atherosclerosis burden.[7] One technique for identifying PAD is the assessment of the Ankle-Brachial Index (ABI), a measure of the lower limb blood vessels' functional capacity.[7-8] Despite underlying PAD, arterial calcification and advanced plaque characteristics in patients with diabetes mellitus or chronic renal disease can cause deceptively normal or high ABI results. This phenomenon may occur because arterial stiffness or non-compressibility masks true perfusion deficits that might only be revealed through exercise ABI testing. In such cases, duplex ultrasonography offers added diagnostic value by visualizing the location, severity, and plaque morphology, allowing for better assessment of PAD progression.[9–11]

A noninvasive imaging method called Coronary Artery Calcium Scoring (CACS) evaluates coronary artery calcification.[7,12] Derived using the Agatston method, CACS is able to provide predictive value for cardiovascular mortality and adverse events.[7,12-13] Recent studies have presented promising data on the involvement of CACS in the presence and severity of coronary atherosclerotic lesions. Actually, a higher Syntax score, a metric used to assess CAD complexity, was independently associated with higher CACS levels.[14–19] Despite the established use of CACS in assessing coronary atherosclerosis, its extrapolation to other vascular territories remains limited. PAD often remains undiagnosed, especially in asymptomatic individuals. Although CACS is now widely performed and routinely used to assess coronary arteries, its potential role in evaluating lower extremity arteries, especially plaque morphology, remains largely unexplored. It may serve as a valuable tool for identifying patients who would benefit from further assessment of lower-limb arterial disease.[18]

This study aims to bridge the gap by evaluating the relationship between CACS and the presence of PAD, as assessed through ABI measurements and Doppler ultrasonography of the lower extremity arteries. By integrating functional and imaging-based evaluations of peripheral circulation, this study seeks to provide a more comprehensive understanding of systemic atherosclerosis and its clinical implications.

Methods

Study Design, Ethical Consideration, and Sample Size

One hundred consecutive patients who underwent coronary CT angiography at Dr. Hasan Sadikin General Hospital in Bandung, Indonesia, between November 2024 and May 2025 were included in a single-center, cross-sectional, observational analytic study. In order to reduce selection bias and more accurately represent the real-world clinical population, consecutive sampling was employed. This approach is commonly applied in observational studies to enhance external validity while maintaining feasibility in routine clinical practice. Retrospective data collection was done using the patient's medical record and the hospital's imaging registry. The Dr. Hasan Sadikin General Hospital in Bandung, Indonesia's Research Ethics Committee provided ethical permission (DP.04.03/D.XIV.6.5/425/2024) with waiver of informed consent for this retrospective chart review, in accordance with the principles of the Declaration of Helsinki. No patient re-contact was performed for this retrospective analysis.

Inclusion and Exclusion Criteria

The study's inclusion criteria included: (1) patients treated at Dr. Hasan Sadikin General Hospital who were included in the time period undergoing Coronary CT Angiography examination. (2) Patients with complete medical records, including CACS, ABI, and duplex ultrasonography of lower extremities measurements. (3) Patients (or their legal

representatives) must provide written informed permission to take part in the study. The following were the study's exclusion criteria: (1) incomplete medical record and registry data, (2) known PAD defined as prior formal diagnosis of PAD based on clinical symptoms (claudication, critical limb ischemia), prior lower extremity revascularization, or documented ABI <0.9 on prior lower extremity revascularization, or documented ABI <0.9 on previous examinations, and (3) patients who refused to provide written informed consent.

Data Collection Methods

Data were retrospectively obtained from the patient's Medical Records (MR) and imaging registry database. Variables collected included patient demographic data (e.g., age and gender) and risk factors (e.g., smoking status, menopause, family history, and obesity). Patient's objective clinical examination was collected, including physical examination (blood pressure in both arms and both legs) and Body Mass Index (BMI). Laboratory data on admission (Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, fasting blood glucose, ureum, creatinine and eGFR), Coronary CT Angiography report and duplex ultrasonography of lower extremities report.

Coronary CT imaging was performed using Siemens Scenario® preliminary multislice CT (128 slices, single source) with electrocardiogram-gated acquisition. Images were obtained after intravenous bolus injection of 70 mL of Ultravist. Data were transferred off line for 3D Multiplanar Reconstruction (MPR) and Maximum Intensity Projection (MIP) with post-processing of 75% of the cardiac cycle and a Dose Length Product (DLP) of 666.86 mGy. CACS acquisition was performed using a 3-mm slice thickness with retrospective ECG gating. The software (GE Healthcare SmartScore® Version 4.0) was used to determine the coronary artery calcium score. The Agatston technique was used to determine the calcium score level based on the presence of lesions that are automatically identified and colored by the software with an area larger than 1 mm^2 and a peak intensity more than 130 Hounsfield Units (HU). Using the Agatston method, the total CACS was determined for each marked lesion. During the procedure, all patients showed sinus rhythm, and patients with a heart rate above 60 beats per minute received beta-blockers to improve image quality.

ABI measurements were obtained after participants rested in a supine position for at least 5 minutes. Systolic blood pressure was recorded in both arms and both ankles using appropriately sized cuffs. In the lower limbs, pressure was measured over the dorsalis pedis and posterior tibialis arteries using a Philips Epiq CVx® machine equipped with a 12-3 MHz linear-array vascular transducer. The ABI was calculated by dividing the highest ankle systolic pressure by the highest brachial systolic pressure. The lower ABI value from both legs was used for analysis, with values below 0.9 or above 1.4 considered abnormal.[7] In addition, lower-extremity arterial evaluation was performed with the same ultrasound system. Duplex Doppler imaging enabled high-resolution visualization of the characterization of plaque morphology. The examination included a detailed assessment of the common femoral artery, proximal, mid, and distal segments of the Superficial Femoral Artery (SFA), as well as the popliteal artery and the anterior and posterior tibial arteries.[20]

Patients with a history of visits or treatment at Dr. Hasan Sadikin General Hospital will have data in their medical records, allowing their comorbidities to be traced. Patients who have possible comorbidities based on anamnesis (e.g., history of hypertension, diabetes mellitus, history of taking antihypertensive drugs or diabetes mellitus drugs), physical examination, or laboratory results will be consulted with an appropriate consultant or specialist for diagnosis. All data collected by cardiology residents during admission or during hospitalization will be checked and validated by the cardiology consultant and researchers. Missing data will be traced, but if not found or considered incomplete, then excluded from the study

Operational Definitions and Outcome Measures

CACS was performed using the Agatston method, which quantifies the total burden of coronary calcification by summing the area and peak attenuation (measured in Hounsfield units) of all calcified lesions within the coronary arteries. The total CACS was subsequently categorized into four groups: mild (CACS 1-100), moderate (CACS 101-300), severe (CACS 301-999), and extensive (CACS ≥1000).[13] The ABI was calculated by dividing the systolic blood pressure measured at the ankle by that of the upper arm, with values interpreted according to the 2017 European Society of Cardiology (ESC) guidelines on the diagnosis and treatment of peripheral arterial disease. A normal ABI was defined as 0.9-1.4.[21]

Plaque characterization in lower extremity arteries was performed using duplex ultrasonography and classified according to grayscale and Doppler

features, using a modified echogenicity-based system adapted from Sztajzel et al. (2005).[22] This classification system has been validated in carotid artery assessment and adapted for peripheral arteries.[23] No plaque was defined as a regular arterial segment with smooth walls, homogenous echogenicity, and laminar flow. Type I plaques were homogenously hypoechoic, indicating soft, lipid-rich content. Type II plaques showed predominantly hypoechoic areas mixed with echogenic spots, suggesting a combination of lipid and fibrous tissue. Type III plaques were predominantly echogenic with mixed echogenic and hypoechoic areas, reflecting fibrous or partially calcified tissue. Type IV plaques were uniformly hypoechoic with posterior acoustic shadowing, consistent with dense calcification. All Doppler evaluations were performed by a consultant cardiologist with expertise in vascular medicine, ensuring consistent, expert-level assessment. Nevertheless, this study did not include assessments of inter- and intra-observer variability, which should be acknowledged as a limitation. This classification supports a more detailed evaluation of atherosclerotic burden beyond the ABI.[22,23]

The medical history of all patients was recorded in detail. Systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg were considered indicators of hypertension. A fasting blood glucose level of >126 mg/dL was used to diagnose diabetes mellitus. Dyslipidemia was defined as total cholesterol ≥200 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥130 mg/dL, and/or triglycerides ≥150 mg/dL. Smoking status was defined as never, former, and current smoker.[7,24–27]

Statistical Analysis

CACS was considered the independent variable in this study, while the ABI and plaque morphology were treated as dependent variables. Numerical data are presented as mean ± standard deviation for normally distributed variables and median (interquartile range) for non-normally distributed variables. Categorical variables were coded and presented as frequency distributions and percentages. Normality of To ascertain whether the numerical data had a normal distribution, the Shapiro-Wilk test was used. When comparing numerical variables between two groups, normally distributed data were analyzed using the independent t-test, while non-normally distributed data were analyzed using the Mann-Whitney U test. ANOVA for normally distributed data and the Kruskal-Wallis test for non-normally distributed data were employed for comparisons involving more than two groups. The Chi-square test or Fisher's exact test was used to assess associations between categorical variables in cases when the predicted cell counts were low. The Pearson correlation test for regularly distributed data and the Spearman rank correlation test for non-normally distributed data were used to evaluate correlations between numerical variables. The strength and direction of the correlations, as well as the p-values, were interpreted according to Guilford's criteria. Using Receiver Operating Characteristic (ROC) curve analysis, the discriminatory ability of CACS to identify plaque was assessed. The Youden index was used to determine the optimal cut-off value. Due to the small sample size and severe imbalance between groups (n=12 without plaque vs. n=88 with plaque). In addition, multivariable logistic regression analyses were conducted to assess the independent association between CACS and PAD. Two models were constructed: Model 1 examined the presence of any peripheral plaque (plaque vs. no plaque), while Model 2 evaluated the presence of advanced plaque (type III-IV vs type no plaque-II). Both models were adjusted for major confounders, including age, sex, smoking status, diabetes mellitus, hypertension, and LDL cholesterol. Odds ratios (OR) with 95% confidence intervals (CI) and p-values were reported. All analyses were conducted using SPSS version 26.0 for Windows and R Studio.

Results

A total of 100 consecutive participants were included in this study. The baseline characteristics are presented in Table 1 using a mean ± standard deviation format. The mean age was 61.49±10.03 years, with 57% male and 43% female. The average blood pressure readings were 87±8 mmHg for the diastolic and 136±17 mmHg for the systolic. Lipid profile measurements showed a mean total cholesterol of 207.38±24.19 mg/dL, LDL of 145.27±24.93 mg/dL, HDL of 42.78±6.37 mg/dL, and triglycerides of 156.17±13.57 mg/dL. Mean fasting blood glucose was 101±21.41 mg/dL. Renal function markers revealed a mean serum creatinine level of 1.35±0.43 mg/dL and eGFR of 79.57±20.34 mL/min/1.73 m^2. In terms of clinical risk factors, 65 participants (65%) had hypertension, 13 (13%) had diabetes mellitus, and 7 (7%) reported a positive family history of cardiovascular disease. Regarding smoking status, 42% had never smoked, 20% had smoked in the past, and 38% were now smokers. The mean ABI across the study population was 1.13±0.14.

Lower extremity arterial plaque characteristics, assessed by Duplex ultrasonography, revealed a diverse distribution of plaque type. While 12 participants (12%) showed no evidence of plaque, a significant portion demonstrated early to advanced stages of atherosclerotic changes. Type I and II plaques were each observed in 22% of participants. More advanced plaque morphologies, type III plaques, which are often associated with fibrous and calcified components, were found in 24%, and type IV plaques were observed in 20%. This distribution underscores a substantial presence of asymptomatic peripheral atherosclerosis, reflecting the potential utility of plaque characterization for cardiovascular risk assessment in routine clinical practice.

Among participants with atherosclerotic plaque detected in the lower extremities (n = 88), systolic blood pressure, LDL cholesterol, triglyceride levels, fasting blood glucose, and CACS values were significantly higher compared to those without plaque (n = 12). Interestingly, ABI was also lower in the plaque group (1.13±0.14 vs 1.15±0.10); however, this difference did not reach statistical significance (p = 0.378). These results show that ABI alone may not be sufficiently sensitive to detect early or subclinical atherosclerosis in this study.

Correlations between CACS and plaque type, and between CACS and ABI were evaluated using the Spearman correlation test, which yielded the following results: r = -0.628 (p <0.001) and r = 0.619 (p <0.001), respectively. This suggests a significant correlation with a negative correlation direction

Table 1. Baseline Characteristic

Characteristic	Total N = 100	Coronary Artery Calcium Score					Doppler-based Plaque Findings		
		Mild (CAC 1-100 HU) N = 20	Moderate (CAC 101-300 HU) N = 30	Severe (CAC 101-300 HU) N = 35	Extensive (CAC ≥1000 HU) N = 15	p-value	No Plaque N = 12	Plaque N = 88	p-value
Age, years	61.49 ± 10.03	59.7 ± 11.27	58,93 ± 10.53	62.51 ± 9.75	66.6 ± 5.36	0.074	59.41 ± 10.79	61.77 ± 9.95	0.448
Male sex	57 (57%)	8 (14.03%)	17 (29.82%)	20 (35.08%)	12 (21.05%)	0.133	6 (50%)	51 (57.95%)	0.832
BMI (kg/m^2)	22.56 ± 3.54	21.77 ± 4.08	21.99 ± 2.96	22.84 ± 3.37	24.09 ± 3.97	0.290	22.47 ± 3.63	22.57 ± 3.54	0.988
Systolic blood pressure (mmHg)	136 ± 17	120.97 ± 12.39	131.22 ± 11.34	141.63 ± 17.44	150.96 ± 10.47	<0.001	127.75 ± 14.93	136.88 ± 16.93	0.078
Diastolic blood pressure (mmHg)	87 ± 8	78.71 ± 3.92	84.08 ± 6.76	91.39 ± 5.62	94.52 ± 5.41	<0.001	83.91 ± 5.77	87.59 ± 8.15	0.121
Total cholesterol (mg/dL)	207.38 ± 24.19	181.3 ± 12.99	198.9 ± 15.79	215.6 ± 18.98	239.93 ± 9.46	<0.001	195.75 ± 28.92	208.96 ± 23.22	0.081
LDL cholesterol (mg/dL)	145.27 ± 24.93	110.7 ± 9.31	139.53 ± 12.79	153.68 ± 12.35	183.2 ± 8.51	<0.001	133.83 ± 23.3	146.83 ± 24.48	0.090
HDL cholesterol (mg/dL)	42.78 ± 6.37	48.30 ± 5.18	44.86 ± 5.15	40.94 ± 4.80	35.53 ± 4.65	<0.001	44.58 ± 6.69	42.53 ± 6.32	0.298
Triglycerides (mg/dL)	156.17 ± 27.71	117.05 ± 13.57	153.3 ± 15.35	165.8 ± 17.08	191.6 ± 14.21	<0.001	135.92 ± 22.81	158.93 ± 27.27	0.006
Fasting blood glucose (mg/dL)	101 ± 21.41	84.3 ± 13.28	96.13 ± 17.61	103.74 ± 18.57	126.26 ± 19.23	<0.001	87.67 ± 19.57	102.76 ± 21.11	0.025
Ureum	36.6 ± 7.91	37.11 ± 9.23	38.27 ± 7.51	35.89 ± 7.14	34.23 ± 8.52	0.388	36.38 ± 9.48	36.64 ± 7.74	0.917
Creatinine	1.35 ± 0.43	0.98 ± 0.21	1.21 ± 0.25	1.43 ± 0.34	1.97 ± 0.47	<0.001	1.08 ± 0.36	1.40 ± 0.44	0.012
eGFR	79.57 ± 20.34	98.19 ± 5.63	90.96 ± 7.02	73.85 ± 11.6	45.31 ± 18.42	<0.001	90.5 ± 14.61	78.10 ± 20.58	0.021
Hypertension									
Yes	65 (65%)	5 (25%)	17 (56.6%)	29 (82.8%)	14 (93.3%)	<0.001	7 (58.33%)	58 (65.9%)	0.748
No	35 (35%)	15 (75%)	13 (43.4%)	6 (17.2%)	1 (6.7%)		5 (41.67%)	30 (34.09%)	

Diabetes Mellitus									
Yes	13 (13%)	0 (0%)	1(3.33%)	5 (14.2%)	7 (46.6%)	<0.001	0 (0%)	13 (14.77%)	0.356
No	87 (87%)	20 (100%)	29 (96.6%)	30 (85.7%)	8 (53.3%)		12 (100%)	75 (85.22%)	
Smoking Status									
Current	38 (38%)	5 (25%)	10 (33.3%)	15 (42.8%)	8 (53.3%)	0.198	3 (25%)	35 (39.77%)	0.239
Former	20 (20%)	2 (10%)	6 (20%)	8 (22.8%)	4 (26.6%)		1 (8.33%)	19 21.59%)	
No	42 (42%)	13 (65%)	14 (46.6%)	12 (34.2%)	3 (20%)		8 (66.67%)	34 (38.63%)	
Menopause									
Yes	40 (40%)	10 (50%)	12 (40%)	15 (42.9%)	3 (20%)	0.329	5 (41.7%)	35 (39.8%)	0.998
No	60 (60%)	10 (50%)	18 (60%)	20 (57.1%)	12 (80%)		7 (58.3%)	53 (60.2%)	
Family History									
Yes	7 (7%)	0 (0%)	3 (10%)	3 (8.6%)	1 (6.7%)	0.581	2 (16.7%)	5 (5.7%)	0.197
No	93 (93%)	20 (100%)	27 (90%)	32 (91.4%)	14 (93.3%)		10 (83.3%)	83 (94.3%)	
Ankle-brachial index	1.13 ± 0.14)	1.25 ± 0.10	1.16 ± 0.08	1.09 ± 0.12	0.98 ± 0.12	<0.001	1.15 ± 0.10	1.13 ± 0.14	0.378
Plaque type									
No plaque	12 (12%)	5 (25%)	4 (13.3%)	2 (5.7%)	1 (6.7%)	<0.001			0.002
I	22 (22%)	8 (40%)	7 (23.3%)	6 (17.1%)	1 (6.7%)				
II	22 (22%)	3 (15%)	9 (30%)	7 (20%)	3 (20%)				
III	24 (24%)	4 (20%)	5 (16.7%)	13 (37.2%)	2 (13.3%)				
IV	20 (20%)	0 (0%)	5 (16.7%)	7 (20%)	8 (53.3%)				
CACS									
Mild (1-100 HU)							5 (41.7%)	15 (17%)	0.002
Moderate (101-300 HU)							4 (33.3%)	26 (29.5%)	
Severe (301-999 HU)							2 (16.7%)	33 (37.5%)	
Extensive (≥1000 HU)							1 (8.3%)	14 (15.9%)	

Description: Categorical data is presented with the number/frequency and percentage, while numeric data is presented with the mean, median, standard deviation and range. P-value are unadjusted.

and moderate strength for CACS and ABI and positive correlation direction and moderate strength for CACS and plaque type based on the Guilford criteria.

Figure 1 shows the ROC curve analysis of CACS in detecting peripheral plaque. ROC analysis demonstrated that CACS had a good discriminatory ability in predicting the presence of any atherosclerotic plaque, with an AUC of 0.765 (95% CI: 0.671-0.859), a sensitivity of 73.86% and a specificity of 75% at an optimal threshold of 142.5 HU. However, the ability of CACS to identify type I and type II plaques morphology was limited, with a lower AUC of 0.678 (95% CI: 0.558-0.798), suggesting suboptimal discrimination between subjects without plaque and those with early plaque formation. In contrast, the performance of CACS in detecting type III and IV plaque was notably higher, with an AUC of 0.852 (95% CI: 0.776-0.928). At an optimal threshold 478.5 HU, the sensitivity was 68.2% and specificity was 91.7%, highlighting its stronger predictive value for more advance calcified plaque. Furthermore, Table 2 summarizes the ROC performance of CACS in detecting overall and type-specific peripheral plaques.

In the multivariable logistic regression for any plaque (Model 1), higher CACS (after square transformation to meet linearity assumption) remained a significant independent predictor of peripheral plaque (OR ≈ 1.00 per unit^2, p = 0.046), after adjustment for age, sex, smoking, diabetes mellitus, hypertension, and LDL cholesterol. None of the traditional risk factor were independently associated with plaque presence. For advanced plaque (Model 2) CACS was slso an independent predictor (OR 1.005, p = 0.003). Other clinical risk factors were not independently associated. The Nagelkerke R^2 of the models was 0.416 for Model 1 and 0.524 for model 2, indicating moderate explanatory power.

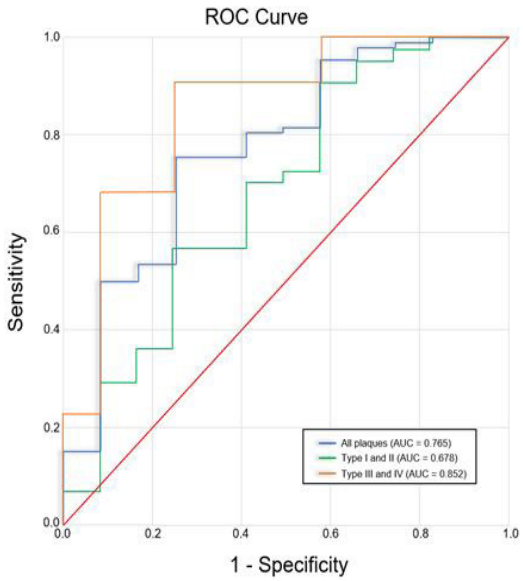

Figure 1. Receiver operating curve analysis of CACS in detecting peripheral plaque.

Table 2. ROC summary for CACS in detecting peripheral plaque.

Comparison	AUC	Std. Error[a]	Asymptotic 95% Confidence Interval[b]		Sensitivity (%)	Specificity (%)	Optimal Cut-off (HU)	p-value
			Lower	Upper				
CACS for plaque vs no plaque	0.765	0.077	0.615	0.916	73.86	75	142.5	<0.05
CACS for Type I and II plaques	0.678	0.094	0.494	0.862	90.9	41.7	35.5	0.06
CACS for Type III and IV plaques	0.852	0.068	0.718	0.986	68.2	91.7	478.5	<0.05

a. Under the nonparametric assumption
b. Null hypothesis: ture area = 0.5

Discussion

This study highlights three main findings. First, a statistically significant moderate inverse correlation was observed between CACS and ABI ($r = -0.628$, $p < 0.001$), underscoring the interplay between coronary and peripheral pathology. As previously acknowledged, arterial calcification and advanced plaque burden in specific populations may paradoxically coexist with preserved ABI values, potentially masking the diagnosis of PAD. In this study, ABI values were also lower in the plaque group, although the difference did not reach statistical significance. This subtle yet important observation underscores the limitations of ABI as a sole diagnostic tool in specific vascular phenotypes.[9–11]

Second, to further elucidate the phenomenon, we investigated the relationship between CACS and plaque morphology in the lower extremity arteries as assessed by duplex ultrasonography. The analysis revealed a moderate positive correlation ($r = 0.619$, $p < 0.001$), suggesting that increasing coronary calcium burden mirrors the progression of peripheral atherosclerotic plaque complexity.

Third, in a more granular exploration of this relationship, the ROC curve analysis revealed that CACS demonstrated good discriminatory power for detecting the presence of plaque in the lower extremities, with an AUC of 0.765, sensitivity of 73.86%, and specificity of 75% at an optimal threshold of 142.5 HU. This finding offers a novel perspective, suggesting that CACS may serve as a surrogate indicator of systemic atherosclerosis burden, particularly within the peripheral vascular territory. To further refine the diagnostic value of CACS, this study conducted a sub-analysis comparing its performance in identifying type I and II plaque morphology versus more advanced plaque (type III and IV) in the lower extremities.

Critically, the discriminatory ability of CACS for detecting softer plaques (type I and II) was suboptimal, with an AUC of only 0.678. This

Table 3. Multivariate logistic regression for association between CACS and PAD.

Variable	Odds Ratio (95% CI)	p-value
Model 1: Any plaque (plaque vs no plaque)		
CACS	1.00 (1.00–1.01)	0. 042
Age	0.999 (0.93–1.07)	0.98
Male sex	1.534 (0.22–10.71)	0.66
Hypertension	2.359 (0.45–12.24)	0.30
Diabetes mellitus	0.00 (0.00–Inf)	1.00
Smoking		
Current	0.00 (0.00–Inf)	1.00
Former	0.00 (0.00–Inf)	1.00
LDL cholesterol	0.097 (0.093–1.02)	0.28
Model 2: Advanced plaque (type III-IV vs no plaque-II)		
CACS(centered)	1.005 (1.002–1.009)	0.003
Age	0.98 (0.93–1.04)	0.656
Male sex	1.18 (0.289–4.892)	0.811
Hypertension	0.718 (0.208–2.473)	0.599
Diabtes mellitus	0.00 (0.00–Inf)	0.988
Smoking		
Current	5.062 (0.974–26.306)	0.054
Former	4.944 (0.561–20.188)	0.059
LDL cholesterol	1.00 (0.99–1.01)	0.726

represents a significant "blind spot" of CACS that has important clinical implications. This modest performance reflects the underlying pathophysiology: CACS, by definition, quantifies calcified plaque, which is often a marker of chronic, stable, long-standing atherosclerosis. However, acute cardiovascular events in both coronary and peripheral beds can arise from the rupture of non-calcified or minimally calcified, lipid-rich, vulnerable plaques. Therefore, a low or zero CACS score does not rule out the presence of potentially dangerous, non-calcified peripheral atherosclerotic disease. This limitation must be clearly understood when considering CACS as a screening tool for peripheral arterial disease. This modest performance may be attributed to the low calcium content typically present in lipid-rich or mixed soft plaques, which may not significantly elevate the overall coronary calcium score. In contrast, CACS exhibited markedly superior performance in predicting the presence of more advanced, calcified plaque (types III and IV), with an AUC of 0.852, a sensitivity of 68%, and a notably high specificity of 91.7% at an optimal threshold of 478.5 HU. While these findings provide evidence that CACS may reflect systemic vascular calcification in peripheral territories, the proposed threshold of 478.5 HU should be interpreted with caution due to the small sample size and lack of external validation. A more appropriate interpretation is that high CACS burden is associated with a higher likelihood of advanced peripheral plaque. It indicates a state of high systemic atherosclerotic burden, rather than recommending a specific clinical cutoff.

Atherosclerosis, a systemic arterial disease, is caused by endothelial dysfunction, lipid particle buildup, inflammatory cell recruitment, and intimal calcification. The development of atherosclerosis in the peripheral, carotid, or coronary arteries is consistent with the advancement of arterial calcification.[7,18] Although arterial calcification is widely studied and recognized as an independent risk factor for cardiovascular and cerebrovascular disease, the clinical relevance of coronary calcification in assessing lower extremity arterial disease remains largely unexplored.[18] Several studies have investigated the role of calcium scoring, whether derived from peripheral or coronary arteries, in the assessment of lower extremity PAD. In 2020, Yadav et al. conducted a comparative evaluation of a non-invasive technique, demonstrating that the arterial calcium scoring of lower extremities outperformed both color Doppler ultrasound and dual-energy CT (DECT) angiography in diagnosing PAD. Notably,

a calcium score threshold >842.2 yielded robust sensitivity and specificity for detecting atheromatous lesions, underscoring the diagnostic potential of local vascular calcification quantification.[28] By shifting the focus from local to systemic vascular beds, the Multi-Ethnic Study of Atherosclerosis (MESA) provided landmark evidence linking CACS with both ABI and clinical PAD. Our study builds upon this systemic perspective by demonstrating a statistically significant inverse correlation between CACS and ABI ($r = -0.628$, $p < 0.001$). This aligns with findings from Bakhsi et al., who reported that a 1-unit increase in log-transformed CACS was independently associated with a 1.15-fold higher odds of developing an abnormal ABI over time ($p < 0.001$). Importantly, this relationship remained robust after adjustment for traditional cardiovascular risk factors, suggesting that CACS extends beyond coronary risk prediction to serve as a marker of diffuse atherosclerotic burden.[7] Most recently, Maahs et al. introduced a novel ultrasound-based scoring system of femoral artery calcification, which demonstrated strong concordance with CT-based calcium quantification ($r = 0.64$). Beyond anatomical correlation, elevated ultrasound-derived scores were independently associated with adverse limb outcomes, including reduced amputation-free survival. This pivotal study validates duplex ultrasound not only as a hemodynamic assessment tool but also as a morphological risk stratification modality, further reinforcing the growing clinical value of calcium scoring across vascular territories.[20]

Building upon these findings, our study is, to our knowledge, the first to explore the association between CACS and plaque morphology in the lower extremities. Beyond its established role in stratifying coronary risk, our result suggests that CACS may also serve as a valuable prompt to broaden clinical vigilance toward other vascular territories. Specifically, CACS may enhance awareness of lower extremity arterial disease, enabling earlier identification of PAD. This novel perspective positions CACS not merely as a cardiac metric but as a gateway marker for systemic atherosclerotic burden, with meaningful implications for more comprehensive vascular risk assessment.

Study Limitation and Further Research

This study has several significant limitations that must be acknowledged and directly impact the interpretation and generalizability of our findings. First, this investigation was conducted retrospectively using a single-center hospital's imaging registry, which is inherently biased. The clinical indications for ordering both a coronary CT and a lower extremity duplex ultrasound are not random, as this patient cohort is likely enriched with individuals suspected of having complex, multi-site vascular disease. This represents a specialized, high-risk diagnostic population rather than a general screening population, which may limit the external validity of these results. Second, the unequal distribution between participants without peripheral plaque (n=12) and those with plaque (n=88) represents a significant limitation that affects the precision of our diagnostic accuracy estimates. This imbalance particularly impacts the stability of ROC curve analysis and the reliability of the proposed CACS cut-off values, which should be validated in larger, more balanced cohorts before clinical application. The small control group size means our diagnostic thresholds require external validation in diverse populations.

Third, CACS demonstrated limited utility in predicting type I and II plaques, as reflected by the low AUC in the ROC analysis, representing a critical clinical limitation. Fourth, not all relevant clinical variables and potential confounders were collected, including information regarding patients' prior medication use, which may have influenced the observed associations. Fifth, while we used an established plaque classification system, we did not assess inter-observer and intra-observer variability for plaque classification, which affects the reproducibility of our primary outcome measure. Sixth, although multiple statistical comparisons were performed, no correction for multiple comparisons was applied, increasing the potential for type I error. Finally, the assessment of lower extremity arterial plaques was limited to selected arterial segments. However, the femoral and popliteal arteries' evaluation may reasonably reflect the atherosclerotic burden in the lower extremities due to their exposure to high shear stress.[29-30]

Future studies should adopt a prospective, multicenter design with larger and more diverse populations to improve the external validity of the findings. Inclusion of a broader range of clinical variables could further minimize bias and strengthen the analysis. Moreover, more comprehensive vascular imaging of the entire lower extremity arterial tree is recommended to better characterize arterial plaque distribution. Despite these limitations, this study provides valuable preliminary evidence for the association between CACS and peripheral plaque morphology, representing the first investigation of this relationship. The findings suggest potential

clinical utility of CACS as a marker of systemic atherosclerotic burden, while highlighting areas that require further investigation before broader clinical application.

Conclusion

This study shows that CACS can reflect the systemic nature of atherosclerosis, including its presence in peripheral arteries. We found a moderate inverse relationship between CACS and ABI, a practical tool in daily clinical use. This study is the first to link CACS with plaque types in the lower extremities, as assessed by Doppler ultrasound. While CACS showed good discriminatory performance for detecting advanced peripheral plaque, it demonstrated significant limitations in identifying early, non-calcified plaques. A high CACS burden appears to be associated with advanced peripheral plaque and may indicate a high systemic atherosclerotic burden. However, the findings should be interpreted with significant caution due to the retrospective design, severe group imbalance, small sample size, and the specialized nature of the study population. The proposed CACS threshold requires external validation in larger, more balanced cohorts before any clinical application can be considered.

List of Abbreviations

ABI	Ankle-Brachial Index
AUC	Area Under Curve
BMI	Body Mass Index
CACS	Coronary Artery Calcium Score
CAD	Coronary Artery Disease
CT	Computed Tomography
DECT	Dual-Energy Computed Tomography
DLP	Dose Length Product
eGFR	estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
ESVS	European Society for Vascular Surgery
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein Cholesterol
HU	Hounsfield Units
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein Cholesterol
MESA	Multi-Ethnic Study of Atherosclerosis
MHz	Megahertz
MIP	Maximum Intensity Projection
MPR	Multiplanar Reconstruction
MR	Medical Record
PAD	Peripheral Artery Disease
ROC	Receiver Operating Characteristic
SFA	Superficial Femoral Artery
SPSS	Statistical Package for the Social Sciences

Ethical Clearance

Ethical approval was obtained from the Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia (Approval No. DP.04.03/D.XIV.6.5/425/2024) with a waiver of informed consent in accordance with the Declaration of Helsinki.

Publication Approval

All authors have reviewed and approved the final version of the manuscript and consent to its publication in the Indonesian Journal of Cardiology.

Authors Contributions

MSA: Conceptualized the research, designed the study methodology, supervised data collection and analysis, interpreted imaging and statistical results, and drafted the main manuscript; NYK: Conducted patient data collection, performed coronary CT and Doppler ultrasound data analysis, and contributed to manuscript writing and figure preparation; SH: Conducted statistical analysis, validated data accuracy, performed correlation and regression modeling, and contributed to critical revision of the manuscript; RP: Provided methodological supervision, contributed to study design refinement, reviewed the literature, and critically reviewed and approved the final version for publication. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Conflict of Interest

The authors affirm that no financial or commercial ties that might be interpreted as a potential conflict of interest existed throughout the course of this investigation. No commercial entity provided financial assistance or funding for this study.

Availability of Data and Materials

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The authors take full responsibility for the content, scientific accuracy, and integrity of all data and conclusions presented in this manuscript. All AI-generated content was thoroughly reviewed, edited, and validated by the authors. The use of AI did not involve the generation of scientific data, analysis, or conclusions, which remain entirely the work of the human authors. This disclosure is made in accordance with emerging guidelines for transparent reporting of AI-assisted academic writing.

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