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The Coronary Artery Calcium Score Paradox: Evaluating the Discordance Between Coronary Artery Calcium Burden and Coronary Artery Disease Severity on Computed Tomography Angiography.

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Abstract

Background: Coronary artery calcium (CAC) scoring is a non-invasive tool to estimate atherosclerotic burden and stratify cardiovascular risk. A CAC score of zero is traditionally considered indicative of low probability of obstructive coronary artery disease (CAD) and favorable prognosis. However, clinically significant non-calcified atherosclerosis may occur despite absent calcification, particularly among symptomatic individuals. This study aimed to investigate the relationship between CAC burden and CAD severity and evaluate the diagnostic performance of CAC scoring.

Methodology: In this retrospective observational study, 337 adults who underwent CAC scoring and coronary computed tomography angiography (CCTA) at Sheikh Zayed Hospital, Rahim Yar Khan, Pakistan (2018–2023) were included. CAC was quantified using the Agatston method and categorized as CAC = 0 or CAC > 0. CAD severity on CCTA was classified as normal, non-obstructive (<50% stenosis), moderate obstructive (50–70%), or severe obstructive (>70%).

Results: The cohort comprised 245 males (72.7%) and 92 females (27.3%), mean age 50.3 ± 11.2 years. CAC = 0 was observed in 190 (56.4%) patients, among whom 61 (32.1%) had CAD, including 13 with obstructive CAD ($p < 0.001$). Obstructive CAD with zero CAC was more frequent in patients <45 years (25.0% vs 6.0% in older patients; $p < 0.001$). CAC discriminated plaque well (AUC 0.808, 95% CI 0.762–0.855; $p < 0.001$). CAC >0 showed 88.2% sensitivity, 78.0% specificity, 66.0% positive predictive value, and 93.2% negative predictive value for obstructive CAD.

Conclusion: CAC scoring demonstrates good diagnostic performance and high negative predictive value for obstructive CAD. Nonetheless, a notable proportion of symptomatic patients, especially younger individuals, had CAD despite zero CAC, emphasizing the need to combine CAC assessment with clinical evaluation and anatomical imaging for accurate risk stratification.

Keywords

Coronary Artery Calcium Score, Coronary Artery Disease, Coronary CT Angiography, Obstructive Coronary Artery Disease, Non-Calcified Plaque, Agatston Score.

Introduction

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, imposing a substantial burden on healthcare systems and economies across both developed and developing countries[1]. Among the various forms of cardiovascular disease, coronary artery disease (CAD) represents the most prevalent manifestation and is responsible for a significant proportion of cardiovascular deaths globally[2,3]. CAD develops through progressive atherosclerotic plaque accumulation within the coronary arterial wall, resulting in luminal narrowing, impaired myocardial perfusion, and ultimately myocardial ischemia or infarction[2].

Coronary artery calcification is a hallmark of atherosclerotic disease and reflects the biological response of the arterial wall to chronic inflammation and plaque progression[4]. Calcification contributes to plaque stabilization but also serves as an indicator of cumulative atherosclerotic burden[5]. The development of coronary artery calcium (CAC) scoring using non-contrast computed tomography has revolutionized cardiovascular risk assessment by providing a rapid, non-invasive, and highly reproducible method for quantifying coronary calcification[6]. The Agatston scoring system remains the most widely accepted technique for CAC quantification and has become an integral component of contemporary cardiovascular risk stratification algorithms[7].

Numerous studies have demonstrated a strong relationship between increasing CAC burden and future cardiovascular events, establishing CAC as a powerful predictor of adverse cardiovascular outcomes[8-10]. Conversely, the absence of detectable coronary calcium, commonly referred to as the "power of zero," has traditionally been associated with an excellent prognosis, low prevalence of obstructive CAD, and a reduced risk of major adverse cardiovascular events[8,9]. Furthermore, previous studies have reported a prolonged “warranty period” of approximately 5–7 years for individuals with CAC = 0, during which cardiovascular event rates remain exceptionally low[11,12].

Despite these well-established associations, growing evidence suggests that the relationship between CAC and coronary artery disease may be more complex than previously assumed. Coronary calcification represents only one component of atherosclerotic plaque biology and primarily reflects mature or healed atherosclerotic lesions. Early-stage, lipid-rich, and non-calcified plaques may remain undetected by CAC scoring despite causing clinically significant coronary stenosis[5,11]. Consequently, symptomatic patients with a CAC score of zero may still harbor substantial coronary atherosclerosis, including obstructive disease, leading to a diagnostic discordance commonly referred to as the CAC paradox[11,13].

Recent reports have challenged the universal applicability of the "power of zero" concept. Case reports and observational studies have documented the presence of significant coronary stenosis in patients with zero CAC scores, particularly among younger individuals in whom non-calcified plaques predominate[11,13]. Basaran et al. reported that 15.7% of symptomatic patients with a CAC score of zero demonstrated evidence of coronary plaque formation on coronary CT angiography[14]. Such findings raise important concerns regarding the ability of CAC scoring alone to exclude clinically relevant coronary artery disease and highlight the potential limitations of calcium-based risk assessment in selected patient populations.

Given the increasing clinical reliance on CAC scoring as a gatekeeper for further diagnostic testing and therapeutic decision-making, a more comprehensive understanding of the relationship between coronary calcification and angiographic disease severity is warranted.

Therefore, the present study aimed to investigate the paradoxical discrepancy between coronary artery calcium burden and coronary artery disease severity, evaluate the diagnostic performance of CAC scoring for detecting obstructive and non-obstructive CAD, and explore the clinical implications of zero CAC scores in symptomatic patients undergoing coronary CT angiography.

Methodology

Study Design

This retrospective observational study was conducted to evaluate the relationship between coronary artery calcium (CAC) score and the severity of coronary artery disease (CAD), with particular emphasis on the diagnostic reliability of CAC scoring in detecting obstructive and non-obstructive coronary artery disease. The study involved a review of previously acquired imaging and clinical data from patients who underwent coronary computed tomography angiography (CCTA) and coronary artery calcium scoring at Sheikh Zayed Hospital, Rahim Yar Khan, Pakistan, between January 2018 and December 2023. The study was designed to assess the distribution of CAC scores across different categories of CAD severity and to determine the diagnostic performance of CAC in identifying coronary plaque burden and obstructive disease.

Ethics

Prior to data collection, ethical approval was obtained from the Institutional Review Board (IRB) of Sheikh Zayed Hospital, Rahim Yar Khan. As the study involved retrospective analysis of existing clinical and radiological records, no direct patient contact or intervention was required. Patient confidentiality and privacy were maintained throughout the study by removing all personal identifiers before data extraction and analysis. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Only anonymized data were used for statistical analysis, and access to the database was restricted to the research team.

Setting

The study was carried out at Sheikh Zayed Hospital, a tertiary-care referral center in Rahim Yar Khan, Pakistan, where coronary CT angiography and CAC scoring are routinely performed for the evaluation of suspected coronary artery disease. The radiology database served as the primary source of information. Imaging studies were performed as part of routine clinical practice using standardized institutional protocols for cardiac computed tomography. Data were collected from patients referred for assessment of chest pain, suspected ischemic heart disease, or other clinical indications warranting coronary imaging.

Participants

All adult patients aged 18 years or older who underwent both CAC scoring and coronary CT angiography during the study period were considered eligible for inclusion. Patients were included irrespective of sex, provided that complete imaging records and demographic information were available. Exclusion criteria comprised poor-quality or non-diagnostic scans, incomplete imaging studies, missing demographic or clinical information, previous coronary revascularization procedures including percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), and known congenital heart disease. These exclusion criteria were applied to minimize misclassification of coronary artery disease severity and to ensure accurate quantification of coronary calcium burden. After applying the eligibility criteria, a total of 337 patients were included in the final analysis.

Variables

The primary exposure variable was the coronary artery calcium (CAC) score measured using the Agatston scoring method. The primary outcome variable was coronary artery disease severity assessed on coronary CT angiography. CAD severity was categorized as normal (no luminal narrowing), mild or non-obstructive disease (<50% stenosis), moderate obstructive disease (50–70% stenosis), and severe obstructive disease (>70% stenosis). Additional variables included age, sex, presenting symptoms, and vessel-specific calcium scores involving the left main coronary artery (LM), left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA). For subgroup analyses, age was categorized into patients younger than 45 years and those aged 45 years or older based on previously established thresholds for premature coronary artery disease.

Data Sources / Measurement

Coronary artery calcium scores were obtained from non-contrast cardiac computed tomography scans and quantified according to the Agatston scoring system. The Agatston score incorporates both the

area and density of calcified plaques and is the standard method for CAC quantification. CAC measurements were recorded separately for the LM, LAD, LCX, and RCA arteries and were subsequently summed to derive total coronary calcium burden. For analytical purposes, CAC scores were evaluated both as continuous variables and as categorical variables. Patients were classified as having either a CAC score of zero (absence of detectable calcified plaque) or a CAC score greater than zero (presence of calcified plaque).

Coronary artery disease severity was determined using contrast-enhanced coronary CT angiography (CCTA). Degree of luminal stenosis was assessed by experienced radiologists according to institutional reporting protocols. Arterial segments were evaluated for the presence and severity of atherosclerotic plaque, and stenosis severity was categorized into normal, mild, moderate, and severe disease based on percentage luminal narrowing. Demographic information and presenting clinical characteristics were extracted from hospital electronic medical records and imaging reports.

Bias

Several measures were undertaken to minimize bias. Standardized institutional imaging protocols were used throughout the study period to ensure consistency in CAC and CCTA acquisition. Patients with incomplete records, poor-quality imaging studies, or prior coronary interventions were excluded to reduce information and misclassification bias. Objective imaging-based criteria were used for determining both CAC scores and CAD severity. However, as a retrospective single-center study, the possibility of selection bias and residual confounding cannot be completely excluded. Furthermore, incomplete documentation of certain cardiovascular risk factors may have limited adjustment for potential confounders.

Study Size

The study size was determined by the total number of eligible patients available in the institutional database during the study period. No formal sample size calculation was performed because the study utilized all available consecutive cases meeting the inclusion criteria between 2018 and 2023. Following application of the eligibility criteria, 337 patients constituted the final study population for analysis.

Quantitative Variables

Age and CAC scores were treated as quantitative variables. Age was summarized using means and standard deviations and was additionally categorized into clinically relevant age groups (<45 years and ≥45 years) for subgroup analyses [33]. CAC scores were analyzed as absolute continuous values and also categorized into conventional CAC score ranges (0, 1–10, 11–100, 101–400, and >400) to facilitate clinical interpretation. For diagnostic performance analyses, CAC scores were dichotomized into CAC = 0 and CAC > 0. CAD severity was analyzed as an ordinal categorical variable consisting of normal, mild, moderate, and severe disease categories.

Statistical Methods

Statistical analyses were performed using IBM SPSS Statistics version 27 and RStudio software. Data distribution was assessed prior to analysis. Continuous variables were summarized as mean ± standard deviation or median with interquartile range depending on normality assumptions, whereas categorical variables were presented as frequencies and percentages. Associations between CAC categories and CAD severity were evaluated using the Chi-square test. Because CAC scores demonstrated non-normal distribution, comparisons of CAC values across CAD severity categories for individual coronary vessels were performed using the Kruskal–Wallis test. When significant differences were identified, post-hoc pairwise comparisons with adjustment for multiple testing were conducted to identify specific group differences.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic accuracy of CAC scoring for detecting coronary plaque and obstructive CAD. The area under the ROC curve (AUC) and corresponding 95% confidence intervals were calculated. The optimal CAC threshold was determined using the Youden Index, which identified CAC >0 as the most appropriate cutoff value. Diagnostic performance measures including sensitivity, specificity, positive predictive value (PPV),

negative predictive value (NPV), and overall accuracy were calculated using 2×2 contingency tables. All statistical tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant.

Results

Participants

A total of 337 patients who underwent coronary computed tomography angiography (CCTA) with coronary artery calcium (CAC) scoring between 2018 and 2023 met the eligibility criteria and were included in the final analysis. Of these, 245 (72.7%) were male and 92 (27.3%) were female. The mean age of the study population was 50.34 ± 11.18 years. All included participants had complete CAC and CCTA data available for analysis. The demographic characteristics, presenting complaints, and CAC score distribution of the study population are summarized in Table 1.

Descriptive Data

The most frequently reported presenting complaint was left-sided chest pain, observed in 214 (63.5%) patients, followed by shortness of breath in 77 (22.8%) patients and palpitations in 46 (13.6%) patients. Analysis of coronary artery calcium burden revealed that more than half of the study population had a CAC score of zero (n = 190, 56.4%). Low CAC scores ranging from 1–10 and 11–100 were observed in 4.5% and 11.9% of patients, respectively. Higher calcium burdens were also prevalent, with 15.7% of patients demonstrating CAC scores between 101 and 400 and 11.6% exhibiting scores greater than 400, indicating the presence of moderate-to-severe coronary calcification in a substantial subset of participants (Table 1). Assessment of vessel-specific coronary artery disease severity demonstrated heterogeneous involvement across the major coronary arteries (Table 2). The left anterior descending artery (LAD) showed the highest disease burden, with severe stenosis present in 69 (20.5%) patients. In contrast, the left main coronary artery (LM) was least affected, remaining angiographically normal in 307 (91.1%) patients, with severe stenosis identified in only 6 (1.8%) cases. The left circumflex artery (LCX) and right coronary artery (RCA) demonstrated intermediate disease burden, with severe stenosis observed in 47 (13.9%) and 46 (13.6%) patients, respectively. These findings indicate that the LAD was the most frequently and severely affected coronary vessel within the study cohort.

Outcome Data

Patients were categorized according to coronary artery disease severity as normal (n = 149), non-obstructive CAD (n = 78), and obstructive CAD (n = 110). Gender distribution did not differ significantly across CAD severity categories (p = 0.151) (Table 3). However, CAC score distribution demonstrated a highly significant association with CAD severity (p < 0.001). Among the 190 patients with a CAC score of zero, 129 (67.9%) had normal coronary arteries, while 61 (32.1%) demonstrated evidence of coronary artery disease. Of these, 48 patients had non-obstructive CAD and 13 patients had obstructive CAD, highlighting that the absence of coronary calcification did not completely exclude the presence of clinically relevant atherosclerotic disease (Table 3). Increasing CAC burden was associated with greater CAD severity. Patients with CAC scores between 101 and 400 constituted 39.1% of the obstructive CAD group, while CAC scores greater than 400 were exclusively observed among patients with obstructive disease (35.5%). Intermediate CAC scores (11–100) were significantly more common in the non-obstructive CAD group than in the normal or obstructive groups (p = 0.002) (Table 3). Age-stratified analysis further demonstrated the paradoxical relationship between CAC and CAD severity. Among patients younger than 45 years, obstructive CAD was identified in 3 individuals despite a CAC score of zero, representing 25.0% of all obstructive CAD cases within this age group. In contrast, among patients aged 45 years or older, only 4 obstructive CAD cases occurred in the presence of zero CAC, accounting for 6.0% of obstructive disease in this age category (p < 0.001). These findings suggest that non-calcified atherosclerotic disease may contribute more substantially to obstructive CAD in younger individuals (Table 3).

Main results

The relationship between CAC distribution and coronary artery stenosis severity was further explored using Kruskal–Wallis post-hoc analysis.

Significant pairwise differences in CAC score ranks were observed across severity categories for all major coronary arteries (Table 4). Notably, statistically significant differences were observed between normal and moderate disease categories in the LM, LAD, LCX, and RCA arteries (all $p < 0.001$). Significant differences were also identified between normal and severe disease groups across all coronary vessels (all $p < 0.001$), indicating substantial variation in calcium burden according to angiographic disease severity. Receiver operating characteristic (ROC) analysis demonstrated that CAC score possessed good discriminative ability for identifying coronary plaque, with an area under the curve (AUC) of 0.808 (95% CI: 0.762–0.855; $p < 0.001$), as illustrated in Figure 1. The optimal threshold identified by the Youden Index was CAC >0.

Diagnostic performance analysis showed that for plaque detection, CAC >0 yielded a sensitivity of 69.0%, specificity of 86.9%, positive predictive value (PPV) of 86.4%, and negative predictive value (NPV) of 70.0% (Table 6). For the detection of obstructive CAD, CAC >0 demonstrated a higher sensitivity of 88.2% and an NPV of 93.2%, with corresponding specificity and PPV values of 78.0% and 66.0%, respectively (Tables 5 and 6). Overall, although increasing CAC burden was strongly associated with increasing CAD severity, a clinically important subset of patients with zero CAC still demonstrated coronary plaque and obstructive coronary artery disease. This discordance was particularly evident among younger individuals, emphasizing the limitations of relying solely on CAC scoring for excluding coronary artery disease in symptomatic patients.

Table 1: Frequency and distribution of baseline clinical characteristics, presenting complaints, risk factors and coronary artery calcium.

Variables	N(%)
Gender	
Male	245(72.7)
Female	92(27.3)
Presenting Complain	
Left sided chest pain	214(63.5)
Palpitations	46(13.6)
Shortness of breath	77(22.8)
Calcium Score[a]	
Zero	190(56.4)
1-10	15(4.5)
11-100	40(11.9)
101-400	53(15.7)
Age (years); Mean ± SD	50.34 ± 11.17

[a]Ca score using Agatston units

Table 2: Severity distribution of coronary artery stenosis.

Artery	Normal	Mild	Moderate	Severe
LAD	180 (53.4)	73(21.7)	15(4.5)	69(20.5)
LM	307(91.1)	16(4.7)	8(2.4)	6(1.8)
LCX	219(65.0)	48(14.2)	23(6.8)	47(13.9)
RCA	226(67.1)	37(11.0)	28(8.3)	46(13.6)

LAD: Left Anterior Descending; LM: Left Main; LCX: Left Circumflex; RCA: Right Coronary Artery

Table 3: Association of gender, age and coronary artery calcium score with severity of coronary artery disease (CAD).

Variables	Normal (N=149)	Non-obstructive (N=78)	Obstructive (N=110)	p-value
Gender				
Female	37	28	27	0.151
Male	112	50	83	
Ca score				
Zero	129	48	13	0.000*
1-10	4	6	5	0.221
11-100	12	18	10	0.002*
101-400	4	6	43	0.000*
Above 400	0	0	39	0.000*
Age Group (below 45)[a]				
Zero Ca score	73	13	03	0.000*
More than 0 Ca score	02	18	09	
Age Group (Above 45)				
Zero Ca score	60	37	04	0.000*
More than 0 Ca score	18	37	63	

[a]Shows gender stratification (below and above 45 years) and cross tabulation of ca score (zero or greater than zero) with CAD severity of disease (normal, non-obstructive and obstructive)

Table 4: Post hoc analysis of mean rank Ca distribution by coronary artery severity.

Artery	Group 1 - Group 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.
LM	Normal - Mild	55.628	13.374	4.159	0.000*	0.000
	Normal - Moderate	121.096	18.677	6.484	0.000*	0.000
	Normal - Severe	-171.596	21.498	-7.982	0.000*	0.000
	Mild - Moderate	-65.469	22.582	-2.899	0.004*	0.022
	Mild - Severe	-115.969	24.965	-4.645	0.000*	0.000
	Moderate - Severe	-50.5	28.164	-1.793	0.073	0.438
LAD	Normal - Mild	44.434	11.77	3.775	0.000*	0.001
	Normal - Moderate	150.575	22.796	6.605	0.000*	0.000
	Normal - Severe	-139.917	12.011	-11.65	0.000*	0.000
	Mild - Moderate	-106.141	24.047	-4.414	0.000*	0.000
	Mild - Severe	-95.483	14.242	-6.704	0.000*	0.000
	Severe - Moderate	10.658	24.165	0.441	0.659	1.000
LCX	Normal - Mild	62.796	12.562	4.999	0.000*	0.000
	Normal - Moderate	106.402	17.273	6.16	0.000*	0.000
	Normal - Severe	-174.183	12.671	-13.747	0.000*	0.000
	Mild - Moderate	-43.606	19.981	-2.182	0.029*	0.174
	Mild - Severe	-111.387	16.168	-6.889	0.000*	0.000
	Moderate - Severe	-67.781	20.049	-3.381	0.001*	0.004
RCA	Normal - Mild	48.68	13.4	3.633	0.000*	0.002
	Normal - Moderate	100.092	15.138	6.612	0.000*	0.000

	Normal - Severe	-161.713	12.222	-13.231	0.000*	0.000
	Mild - Moderate	-51.411	18.926	-2.716	0.007*	0.040
	Mild - Severe	-113.032	16.686	-6.774	0.000*	0.000
	Moderate - Severe	-61.621	18.111	-3.402	0.001*	0.004

LAD: Left Anterior Descending; LM: Left Main; LCX: Left Circumflex; RCA: Right Coronary Artery

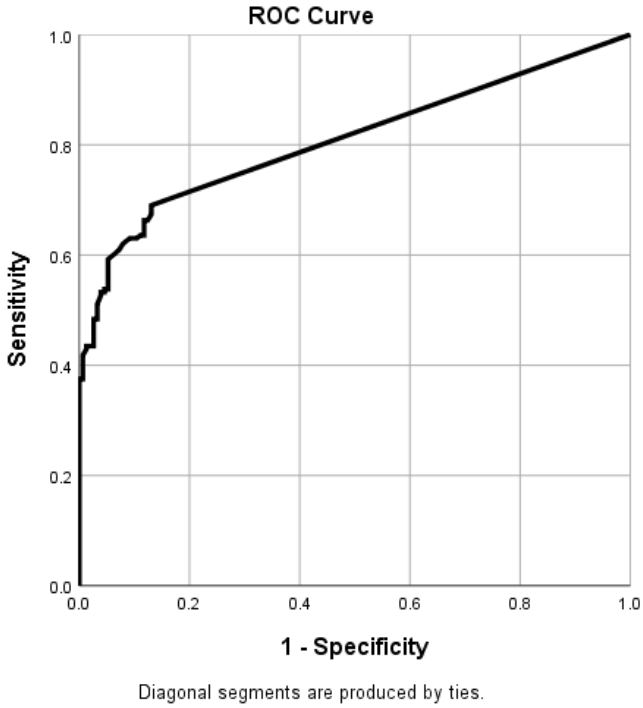

Figure 1: ROC curve of Ca score.

Table 5: 2x2 contingency table for obstructive and non-obstructive CAD.

	Obstructive CAD	Non Obstructive CAD	Total
CAC=0	13	177	190
CAC >0	97	50	147
Total	110	227	337

Table 6: Sensitivity, specificity, PPV and NPV values based on plaque presence/absence, and obstructive/non-obstructive disease.

Outcome Variable	CAC Threshold	Sensitivity	Specificity	PPV	NPV
Plaque presence vs absence	CAC >0 vs CAC =0	69.0%	86.9%	86.4%	70.0%
Obstructive vs non-obstructive CAD	CAC >0 vs CAC =0	88.2%	78.0%	66.0%	93.2%

Discussion

The present study evaluated the relationship between coronary artery calcium (CAC) burden and coronary artery disease (CAD) severity in a cohort of symptomatic patients undergoing coronary computed tomography angiography (CCTA). While CAC demonstrated good overall diagnostic performance for detecting coronary plaque and obstructive disease, our findings revealed a clinically important discordance between coronary calcification and angiographic disease severity. Most notably, a substantial proportion of patients with a CAC score of zero exhibited both non-obstructive and obstructive coronary artery disease, highlighting the limitations of relying exclusively on coronary calcification as a surrogate marker of atherosclerotic burden.

More than half of the patients in our cohort had a CAC score of zero, a prevalence comparable to that reported in large contemporary registries such as the Multi-Ethnic Study of Atherosclerosis (MESA) and the Heinz Nixdorf Recall (HNR) study[15,16]. These landmark studies established CAC scoring as a powerful marker of cardiovascular risk stratification and demonstrated exceptionally low cardiovascular event rates among individuals with absent coronary calcification. Similarly, our study confirmed that patients with CAC = 0 generally had a lower burden of obstructive disease. However, unlike population-based screening cohorts, our study focused on symptomatic individuals referred for coronary imaging, a population in whom the relationship between CAC and disease severity may be considerably more complex[17].

Coronary calcification is a biologically dynamic process representing a relatively advanced stage of atherosclerotic plaque evolution[18]. Calcified plaques often develop following chronic inflammation, lipid accumulation, cellular apoptosis, and osteogenic transformation within the vascular wall. Consequently, CAC primarily reflects cumulative plaque burden rather than current plaque vulnerability or luminal obstruction[18,19]. This distinction is clinically important because coronary stenosis may develop from non-calcified or partially calcified plaques that remain undetectable by conventional calcium scoring. Our findings support this concept and reinforce the understanding that absence of coronary calcium should not be interpreted as complete absence of coronary atherosclerosis.

The vessel-specific distribution of disease observed in our cohort is also consistent with previous anatomical and epidemiological studies. The left anterior descending artery (LAD) exhibited the highest burden of severe stenosis, whereas the left main coronary artery remained relatively spared. Similar findings have been reported in multiple angiographic and autopsy studies demonstrating preferential plaque accumulation within the LAD due to its unique hemodynamic characteristics, vessel geometry, and exposure to altered shear stress[20-22]. These observations further support the biological plausibility of the disease patterns observed in our population.

One of the most intriguing findings of this study was the apparent paradox observed in the post-hoc analysis, where angiographically normal vessels demonstrated significantly higher CAC score ranks than some moderately stenotic vessels. Although seemingly counterintuitive, this observation is supported by the complex pathophysiology of atherosclerosis. Coronary calcification does not necessarily correlate linearly with luminal narrowing because vascular remodeling can preserve luminal diameter despite substantial plaque accumulation. The Glagov phenomenon describes compensatory outward remodeling of the arterial wall that allows plaque growth without significant luminal compromise[23-30]. In addition, heavily calcified plaques often represent mature and biologically stable lesions that may not produce flow-limiting stenosis despite contributing substantially to total plaque burden[18,23,31]. Consequently, CAC should be regarded as a marker of cumulative atherosclerotic burden rather than a direct measure of stenosis severity.

The diagnostic performance analysis further highlights both the strengths and limitations of CAC scoring. We observed an area under the ROC

curve of 0.808 for plaque detection, indicating good discriminative ability. Furthermore, CAC >0 demonstrated high sensitivity (88.2%) and an excellent negative predictive value (93.2%) for identifying obstructive CAD. These findings are consistent with previous studies demonstrating the utility of CAC scoring as a reliable rule-out tool for clinically significant coronary disease[15,16,32]. The high negative predictive value supports the continued role of CAC scoring in risk stratification and patient selection for further diagnostic testing. Nevertheless, the central finding of this study is that a CAC score of zero did not completely exclude coronary artery disease. Among patients with zero CAC, approximately one-third demonstrated evidence of coronary atherosclerosis and a subset exhibited obstructive disease. Similar observations have been reported in several contemporary investigations and case reports challenging the absolute reliability of the "power of zero" concept[11,13,33,34]. The underlying explanation likely relates to the inability of CAC scoring to detect non-calcified plaques, which are more prevalent in younger individuals, early-stage atherosclerosis, and certain high-risk plaque phenotypes[5,11]. Therefore, reliance on CAC alone may result in underestimation of disease burden in selected patient populations.

A particularly important contribution of our study is the age-stratified analysis. We observed that obstructive CAD in the presence of CAC = 0 was proportionally more common among younger individuals (<45 years) than older patients. This finding aligns with emerging evidence demonstrating that younger adults are more likely to harbor lipid-rich and non-calcified plaques that have not yet undergone sufficient calcification to become detectable on CAC scanning[17,35]. Recent studies have similarly reported that a zero CAC score may not reliably exclude clinically significant coronary stenosis in younger symptomatic patients, particularly those with traditional cardiovascular risk factors[31,32]. These findings have important clinical implications because premature reassurance based solely on CAC = 0 may delay diagnosis and treatment in younger high-risk individuals.

Taken together, our findings support a more nuanced interpretation of CAC scoring. While CAC remains a valuable and readily accessible marker of atherosclerotic burden, its diagnostic utility is optimized when integrated with clinical presentation, cardiovascular risk factors, age, symptom characteristics, and complementary anatomical imaging findings. Emerging models combining CAC with clinical likelihood assessment have demonstrated superior predictive performance compared with either approach alone, supporting a multimodal strategy for CAD evaluation[24-26].

Limitations

Several limitations should be considered when interpreting the findings of this study. First, the retrospective observational design limits the ability to establish causal relationships and introduces the possibility of selection bias. Second, the study was conducted at a single tertiary-care center, which may limit the generalizability of the findings to other populations and healthcare settings. Third, complete information regarding certain cardiovascular risk factors, medication use, family history, lipid profiles, and comorbid conditions was not consistently available due to the retrospective nature of data collection, preventing adjustment for all potential confounders. Fourth, coronary artery disease severity was assessed using coronary CT angiography rather than invasive coronary angiography with physiological assessment, which remains the reference standard for evaluating hemodynamic significance of stenosis. Fifth, the relatively small number of younger patients with obstructive CAD may have limited the statistical precision of subgroup analyses. Finally, clinical outcomes such as major adverse cardiovascular events (MACE), myocardial infarction, revascularization, and mortality were not evaluated. Consequently, the prognostic significance of the observed CAC-CAD discordance could not be assessed. Future multicenter prospective studies incorporating longitudinal follow-up, comprehensive cardiovascular risk profiling, plaque characterization, and clinical outcome assessment are warranted to further clarify the implications of the CAC paradox and

refine the role of CAC scoring in contemporary cardiovascular risk assessment.

Conclusion

Coronary artery calcium scoring demonstrated a significant association with coronary artery disease severity and showed good overall diagnostic performance for detecting coronary plaque and obstructive CAD. The high negative predictive value observed in this study supports the established role of CAC as an effective tool for identifying patients at low likelihood of obstructive disease. However, our findings also reveal a clinically meaningful discordance between coronary calcification and coronary artery disease severity. A substantial proportion of symptomatic patients with a CAC score of zero exhibited coronary atherosclerosis, including obstructive disease, emphasizing that the absence of coronary calcification does not necessarily equate to the absence of clinically significant CAD. This phenomenon was particularly evident among younger patients, in whom non-calcified plaque appears to contribute more prominently to disease burden. Therefore, CAC scoring should not be interpreted in isolation. Rather, it should be integrated with patient age, symptom profile, cardiovascular risk factors, and anatomical imaging findings to achieve optimal diagnostic accuracy. Recognition of the "CAC paradox" is essential for avoiding false reassurance in symptomatic individuals and for improving individualized cardiovascular risk stratification. Further prospective studies are needed to define the mechanisms, prevalence, and long-term prognostic implications of this discordance and to establish more comprehensive approaches for coronary artery disease assessment.

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