ORIGINAL ARTICLE

Association of High Agatston Coronary Artery Calcium Score with Critical Coronary Artery Disease: A Cross-Sectional Study from Rawalpindi, Pakistan

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ABSTRACT

Objective: To determine the association and pattern of critical coronary artery disease in patients with high calcium scores.

Study Design: Analytical cross-sectional study.

Place and Duration of Study: The study was conducted at the Department of Cardiology, Armed Forces Institute of Cardiology/National Institute of Heart Diseases (AFIC/NIHD), Rawalpindi, Pakistan from May 2025 to August 2025.

Methods: A total of 250 patients between the ages of 25 and 70 years, belonging to both genders, with the diagnosis of coronary artery disease (CAD), having a coronary artery calcium score (CACS) of >400, were included. Patients with a previous history of coronary artery bypass grafting, unstable angina, valvular heart disease, previous myocardial infarction, and chronic kidney disease were excluded. All patients underwent coronary angiography, and the frequency of patients with critical stenosis and the pattern of CAD was ascertained. Data analysis was done using SPSS version 26, taking a *P*-value of less than 0.05 as significant.

Results: The mean age of patients was 57.4±9.2 years. Out of 250 patients, 161 (64.4%) had CACS of 400-1000, while 89 patients (35.6%) had CACS above 1000. A total of 184 patients (73.6%) had significant CAD. CACS of more than 1000 was significantly associated with a higher risk of critical CAD (*P*=0.004). Age >50 years (*P*=0.035) and male gender (*P*=0.019) were found to be significantly associated with a higher CACS as well as the presence of critical CAD.

Conclusion: A high and very high CACS was significantly associated with the presence of critical coronary artery disease and multivessel involvement in this study. A higher score may help identify patients at risk and help in risk stratification; however, further longitudinal studies are required to establish predictive and causal relationships.

Keywords: *Atherosclerosis, Coronary Artery Disease, Coronary Artery Stenosis, Computed Tomography Angiography.*

How to cite this: *Farhan S, Khan MN, Sadiq MW, Hashmi MO, Shah SA. Association of High Agatston Coronary Artery Calcium Score with Critical Coronary Artery Disease: A Cross-Sectional Study from Rawalpindi, Pakistan. Life and Science. 2025; 6(4): 464-470. doi: http://doi.org/10.37185/LnS.1.1.1008*

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Received: Aug 31, 2025; Revised: Sep 22, 2025
Accepted: Sep 26, 2025

Introduction

Coronary artery disease (CAD) is globally the largest cause of death, placing a significant strain on economies and healthcare systems, even if its mortality rates have declined in high-income nations in recent decades. According to estimates for 2022, 315 million people worldwide suffer from CAD.[1,2] Notably, the underdeveloped or low to middle-income countries account for more than 75% of CAD-related deaths, highlighting a disproportionate impact on these areas where access to diagnostic

and preventive resources is frequently restricted.[3] The Global Burden of Disease study for 2019 estimated that Pakistan's age-standardized incidence of CAD was 918.2 patients per 100,000 population.[4]

The evaluation of CAD typically involves a combination of clinical assessment and diagnostic modalities, such as electrocardiography (ECG), echocardiography, stress testing, and anatomical imaging, such as coronary angiography. The pathophysiology of CAD revolves around the formation of atherosclerotic plaque, which comprises fatty deposits, inflammation, and calcification in the intimal layer of coronary arteries. This narrowing of the arterial lumen reduces blood flow and results in clinical manifestations of CAD.[5] To assess the severity and distribution of coronary stenosis, the gold standard remains invasive coronary angiography (ICA). However, ICA is associated with procedural risks and is not suitable for all patients, especially in low-resource settings.[6]

Nowadays, Computed tomography angiography (CTA) has become a dependable non-invasive imaging technique that offers precise visualization of coronary anatomy.[7] Coronary Artery Calcium Score (CACS) calculated by the Agatston method is a useful tool obtained from non-contrast gated acquisition, which serves as a robust marker of coronary atherosclerosis and has a strong association with future coronary events.[7] Conversely, CACS >400 Agatston units can significantly impair scan interpretation due to blooming artifacts affecting the diagnostic accuracy.[8] The European Society of Cardiology (ESC) 2012 guidelines on cardiovascular disease prevention also recommended determination of CACS for risk assessment in asymptomatic patients[9,10]

The rationale of this study was that there is a paucity of data in the Pakistani population on the association of high CACS with critical CAD. In the current era of evidence-based practices, this study will not only help bridge that gap but also, in a developing country like ours, in which the healthcare resources are constrained and which happens to be the 5th populous nation globally, this cost-effective and readily available test will help to stratify the patients at high risk of developing critical CAD. Early identification of these patients will improve patient outcomes and optimize resource utilization by channeling treatment to those who need it most.

Methods

The study was conducted at the Department of Cardiology, Armed Forces Institute of Cardiology/National Institute of Heart Diseases (AFIC/NIHD), Rawalpindi, Pakistan from May 2025 to August 2025 on a total of 250 patients with the diagnosis of CAD after approval from Institutional Ethical Review Board (IERB) of AFIC vide letter: 9/2/R&D/2025/347, dated 23rd April 2025. The WHO sample size calculator was employed for sample size calculation, taking the study by Liaquat A et al. as the parent study.[11] The confidence level was taken as 95%, absolute precision was 0.05, and the anticipated population proportion was taken as 79.6% (patients with CACS>400 who had significant CAD). The sample size was determined to be 250 patients. We employed non-probability consecutive sampling for data collection. Informed consent was taken from all patients before inclusion in the study.

Patients of both genders between the ages of 25-70 years with a body mass index (BMI) of <30 Kg/m2 with the diagnosis of CAD who underwent CT coronary angiography at our department were made part of the study. The CACS was calculated for all the patients in Agatston units. Only those having a CACS of more than 400 were added to the sample.

Patients with a history of PCI with stenting, post-coronary artery bypass grafting (CABG), chronic kidney disease with serum creatinine levels of more than 1.5 mg/dL, unstable angina, valvular heart disease, and a history of previous myocardial infarction (MI) were not included in the study.

The clinical details and patients' demographics were documented on a structured data collection proforma, including age, gender, BMI, and the presence or absence of the following cardiovascular risk factors: family history of CAD, diabetes mellitus, hypertension, and history of smoking. All patients then underwent multi-detector computed tomography (MDCT) with prospective ECG gating on a Canon Aquilion One 320-slice CT scanner. The protocol involved a section thickness of 3.0 mm and an interval of 1.5 mm, respectively, with the scan range from below the arch of the aorta to the cardiac base.

The Agatston method, using vendor-provided software, was used to calculate the CACS. Calcified plaque was defined using the standard of a lesion with a density of ≥130 Hounsfield Units (HU) and an area of ≥1 mm². The Agatston score was computed as the product of the calcified plaque area and a weighted factor based on peak plaque attenuation. Patients with CACS <400 underwent CTCA, while patients with CACS>400 were recruited, and invasive coronary angiography was performed. Patients were further grouped as CACS: 400–1000 (high score) and >1000 (very high score).

Coronary angiography was performed by a qualified Interventional cardiology team in collaboration with the research team. The procedure was conducted under local anesthesia with procedural sedation. Vascular access was obtained via the right radial artery using the Seldinger technique, and a 6-F arterial sheath was placed. Intravenous unfractionated heparin, dosed according to the patient's body weight, was administered for anti-coagulation. Angiographic images of both coronary arteries were acquired using Judkins diagnostic catheters. These angiograms were analyzed by cardiologists with a minimum of 5 years post-fellowship experience to determine the presence or absence of critical CAD. Neither the interventional cardiology teams nor those analyzing the angiograms were blinded to the CACS of patients.

Critical CAD was defined as the presence of more than 70% intra-luminal narrowing in vessels more than 1.5 mm in diameter and more than 50% in the left main stem (LMS). Based on angiographic findings, patients were categorized as having single vessel coronary artery disease (SVCAD), double vessel coronary artery disease (DVCAD), and triple vessel coronary artery disease (TVCAD), with further classification based on involvement of the left anterior descending artery (LAD), left circumflex (LCX), and right coronary artery (RCA). Additionally, LMS involvement was also documented. Data analysis was performed by using the Statistical Package for the Social Sciences (SPSS) version 26. Mean and standard deviation/median were determined for numerical variables like age, and CACS, while qualitative variables like gender, obesity, diabetes, hypertension, smoking, family history of CAD, and pattern of CAD were expressed as frequency and percentages. Data stratification was performed by age and gender. Post-stratification chi-square test was applied to analyze the categorical variables, while the independent sample T-test was applied to analyze the numerical variables, taking a *P*-value of less than 0.05 as statistically significant. (Figure.1).

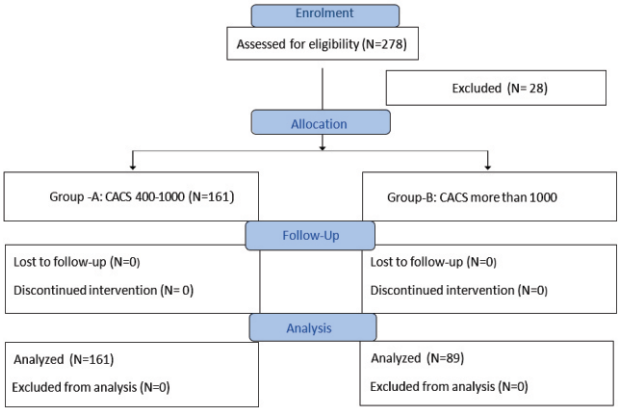

Fig.1: Patient's flow diagram

Results

A total of 250 patients were part of our study sample. Out of 250 patients, 161 patients (64.4%) had CACS of 400-1000, while 89 patients (35.6%) had CACS above 1000. The overall mean age of patients was 57.4±9.2 years. There were 163 male patients (65.2%), while 87 were female (34.8%). The overall mean BMI of patients was 27.6 ± 1.6 kg/m^2. The mean CACS in patients with CACS between 400 and 1000 was 672.2±167.3, while that in patients with CACS >1000 was 1306.3±156.3. The distribution of the patients according to their demographic data is shown in Table 1.

Although age, gender, a history of hypertension, diabetes mellitus, and smoking were not significantly related to the CACS, a positive family history of CAD was significantly related to the value of CACS (*P*=0.041). Of all the patients included in the study, 184 patients (73.6%) were found to have significant CAD as per the operational definition, making CACS significantly associated with CAD. The distribution of the patients according to critical CAD, disease pattern, and vessels involved is shown in Table 2. Analysis of the data revealed that CACS of more than 1000 was significantly associated with critical CAD (*P*=0.004). Moreover, a higher CACS was also associated with the involvement of more vessels.

Table 1: Demographic details of the patients

Variable	Group	*CACS (400-1000) N=161	*CACS (>1000) N=89	*Chi Square* value (χ^2)	*P*-value
Age Group	<50 years	44 (71.0%)	18 (29.0%)	1.551	0.213
	>50 years	117 (62.2%)	71 (37.8%)		
Gender	Male	111 (68.1%)	52 (31.9%)	2.794	0.095
	Female	50 (57.5%)	37 (42.5%)		
Diabetes	Yes	49 (62.0%)	30 (38.0%)	0.284	0.594
	No	112 (65.5%)	59 (34.5%)		
Hypertension	Yes	70 (59.3%)	48 (40.7%)	2.514	0.113
	No	91 (68.9%)	41 (31.1%)		
Smoking	Yes	65 (59.6%)	44 (40.4%)	1.916	0.166
	No	96 (68.1%)	45 (31.9%)		
Family History	Yes	76 (58.5%)	54 (41.5%)	4.166	0.041
	No	85 (70.8%)	35 (29.2%)		

**Coronary Artery Calcium Score (CACS)*

Table 2: Distribution of patients according to Coronary Artery Disease (CAD)

Variable	Group	CACS (400-1000) N=161	CACS (>1000) N=89	*Chi-Square* Value (χ^2)	*P*-value
Critical CAD	Yes	109 (67.7%)	75 (84.3%)	8.097	0.004
	No	52 (32.3%)	14 (15.7%)		
CAD pattern	SVCAD	96 (59.6%)	9 (10.1%)	63.395	<0.001
	DVCAD	28 (17.4%)	20 (22.5%)		
	TVCAD	37 (23.0%)	60 (67.4%)		
		Vessels Involved			
LAD	Yes	96 (59.6%)	81 (91.0%)	27.307	<0.001
	No	65 (40.4%)	8 (9.0%)		
RCA	Yes	83 (51.6%)	76 (85.4%)	28.352	<0.001
	No	78 (48.4%)	13 (14.6%)		
LCX	Yes	72 (44.7%)	68 (76.4%)	23.352	<0.001
	No	89 (55.3%)	21 (23.6%)		
LMS	Yes	15 (9.3%)	6 (6.7%)	0.494	0.482
	No	146 (90.7%)	83 (93.3%)		

Coronary Artery Calcium Score (CACS), Coronary Artery Disease (CAD), Single Vessel Coronary Artery Disease (SVCAD), Double Vessel Coronary Artery Disease (DVCAD). Triple Vessel Coronary Artery Disease (TVCAD), Left Anterior Descending Artery (LAD), Left Circumflex (LCX), Right Coronary Artery (RCA)

Table 3: Coronary Artery Calcium Score (CACS) by Age and Gender Stratification

Variable	Group	CACS (400-1000) N=161	CACS (>1000) N=89	*Chi-Square* Value (χ^2)	*P*-value
Age Group					
<50 years	Yes	26 (16.1%)	15 (16.9%)	3.352	0.067
	No	18 (11.2%)	3 (3.8%)		
>50 years	Yes	83 (51.6%)	60 (67.4%)	4.467	0.035
	No	34 (21.1%)	11 (12.4%)		
Gender					
Male	Yes	77 (47.8%)	45 (50.6%)	5.545	0.019
	No	34 (21.1%)	7 (7.9%)		
Female	Yes	32 (19.9%)	30 (33.7%)	3.030	0.082
	No	18 (11.2%)	7 (7.9%)		

Data stratification for age and gender is shown in Table 3. Age more than 50 (*P*=0.035) and male gender (*P*=0.019) were found to be significantly associated with a higher CACS, as well as the presence of critical CAD.

Discussion

CACS measured by the Agatston method has been proposed as a direct measure of the burden of atherosclerotic narrowing of the coronary arteries.[12] South Asian population has the highest prevalence of CAD. With the increasing population and the burden of CAD, CACS can serve as a non-invasive marker of CAD severity.[13] In this research protocol of ours, we studied the association of high calcium score (400-1000) and very high calcium score (>1000) with the presence of critical CAD. In our study sample, 73.6% of patients had critical CAD. Liaquat A et al. and Mokhtar J et al. also reported that in patients with a CACS of more than 400 Agatston units, the frequency of critical CAD was 79.6% and 79.3% respectively.[11,14]

The mean age of the study sample was 57.4±9.2 years. Liaquat A et al. also reported a comparable mean age of 53.2±12.0 years in their study.[11] Another study by Grandhi GR et al. reported a mean age of 53.5±10.8 years.[15] A higher mean age of 69.8±7.9 years and 71.7±7.5 years was reported by Peng AW et al. in patients with CACS of 400-1000 and >1000, respectively, in the Multiethnic Study of Atherosclerosis (MESA).[16] Our study showed a male preponderance with 163 male patients (65.2%) while 87 patients (34.8%) were female. Liaquat A et al. reported a higher frequency of male patients (77.6%) from a study from Islamabad.[11] However, in the study by Grandhi GR et al. from the USA, only 46.0% patients were male.[15]

Stratification of data also revealed that higher CACS in males gender and those aged more than 50 years was associated with a significantly higher frequency of critical CAD. The results of our study showed a non-significant association of diabetes (*P*=0.594), hypertension (*P*=0.113), and a history of smoking (*P*=0.166). However, family history was significantly associated with critical CAD in patients with high calcium scores (*P*=0.041). On the contrary, Liaquat A et al. reported a significant relation of diabetes mellitus (<0.001) and hypertension (*P*<0.001) with critical CAD in these patients.[11]

A study by Elnagar B et al., published in 2024, reported that a CACS of >400 Agatston units was associated with critical CAD and adverse cardiac events in a statistically significant proportion (*P*<0.001).[17] Another study by Miller RJ et al. reported that CACS >400 was independently associated with significant CAD. The study reported that patients with a CACS of >400 had a more 50% chance of significant CAD in all patients.[18] Peng AW et al. also reported that a very high CACS (>1000) was associated with almost twice the risk of adverse cardiac events and critical CAD as compared to patients with CACS between 400-999.[16] AlShumrani GA et al. reported that a CACS of >250 was 100% specific for the presence critical CAD and the presence of critical stenosis increased as the score increased by a significant proportion (*P*<0.001).[19]

Most previous research has focused on event prediction rather than actual angiographic

correlation with critical stenosis. Others have combined CACS with the fibrinogen-to-albumin ratio for its association with critical CAD.[20] Additionally, the anatomical distribution of disease (single, double, or triple-vessel involvement) in relation to CACS thresholds remains poorly characterized. In this study, we also examined the pattern of CAD involvement in patients with CACS >400. The findings of our study are comparable to those reported in the national and international literature. The limitations of this research protocol included a small sample size, the exclusion of overweight individuals, the inclusion of patients with stable coronary artery disease, and lack of blinding. Further studies with larger sample sizes are recommended to gather more evidence, which will help achieve the goal of improving the standard of care for patients with CAD.

Conclusion

The findings of our study revealed that high and very high CACS are significantly associated with the presence of critical CAD. Moreover, it is even more significant in male patients, patients aged more than 50 years, and those with a family history of CAD. A high CACS is a non-invasive test that can help to segregate patients at increased risk of having critical stenosis and direct further management.

Acknowledgement: None

Conflict of Interest: The authors declare no conflict of interest

Grant Support and Financial Disclosure: None

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Author Contributions

SF: Conception and design of the work, writing the original draft, proofreading, and approval for final submission
MNK: Manuscript writing for methodology design and investigation
MWS: Data acquisition, curation, and statistical analysis
MOH: Validation of data, interpretation, and write-up of results
SAS: Revising, editing, and supervising for intellectual content