DOI: http://dx.doi.org/10.48305/arya.2023.39234.2832

Coronary artery calcification score as the determinant of coronary artery disease in chronic kidney disease patients: A preliminary study

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Original Article

Abstract

BACKGROUND: Coronary computed tomography angiography (CCTA) is a noninvasive cardiovascular imaging procedure that visualizes coronary artery calcifications (CAC), a marker of subclinical atherosclerosis. Due to different calcification patterns in patients with chronic kidney disease (CKD) compared to the general population, this study aims to present diagnostic cut-off values for CAC to detect early coronary artery disease (CAD) in CKD patients.

METHODS: This cross-sectional study included 807 patients: 407 with CKD and 400 controls with normal kidney function who underwent CCTA during 2019-2021. CAC score measurements were performed for all left main coronary arteries to investigate CAD. The Coronary Artery Disease Reporting and Data System (CAD-RADS) was used as the gold standard to determine the value of CAC, and diagnostic values were measured.

RESULTS: The number of female patients was 443 (54.9%), and 364 (45.1%) were male. The mean age in the case group was 63.95 ± 10.26 years, and in the control group, it was 53.80 ± 11.84 years. At the cut-off point of 85, the CAC score had a sensitivity and specificity of 84.7% and 83%, respectively, among patients with CKD to detect CAD (Area Under the Curve (AUC): 0.919, 95% CI: 0.89-0.94; P-value < 0.001). Considering a cut-point of 85 for CAC, the frequency of healthy subjects with CAD-RADS less than two was significantly higher than the cases (P-value = 0.012), while the two groups were similar regarding CAD-RADS 3-5 (P-value = 0.83).

CONCLUSION: According to this study, the CAC score is a valuable means to detect CAD among CKD subjects. There is no significant difference in CAC between patients with substantial CAD-RADS in CKD and non-CKD patients. The cut-point of 85 for the CAC score was found valuable to diagnose CAD with over 80% sensitivity and specificity.

Keywords: Computed Tomography Angiography; Coronary Artery Disease; Atherosclerosis; Chronic Renal Insufficiency

Date of submission: *7/7/2022*, ***Date of acceptance:*** *2/8/2023*

Introduction

Sudden cardiac death or non-fatal myocardial infarction may occur with no precursor sign or symptom, including chest pain or dyspnea on exertion, highlighting the importance of expeditious detection of underlying subclinical coronary atherosclerosis[1-3].

In addition to conventional cardiovascular disease risk factors, coronary artery calcification (CAC) is a marker of subclinical atherosclerosis and provides supplementary prognostic information in assessing conventional risk factors[4,5]. Therefore, clinical guidelines have progressively recommended that a scoring system for CAC can improve cardiovascular

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risk estimation in asymptomatic people and serve as a guide for cardiologists' decision-making to initiate or adjourn preventive therapies[6]. However, CAC cannot represent the whole spectrum of atherosclerosis[7].

Coronary computed tomography angiography (CCTA) is a noninvasive modality of cardiovascular imaging by which both calcified and non-calcified atherosclerotic plaques can be visualized[8]. This instrument has high diagnostic performance for localization, size, and the histologic component of atherosclerotic plaques or excludes coronary luminal stenosis[9]. No other modalities, even invasive ones, have demonstrated similar capability to identify coronary artery wall thickening and patency[10]. Therefore, CCTA is extensively utilized for symptomatic patients in particular circumstances[11]. Increasing numbers of studies have presented high sensitivity, specificity, positive predictive value, and negative predictive value via CCTA with sufficiently high image quality by which coronary calcium score can be calculated and coronary artery stenosis can be identified[12,13].

Nevertheless, the utility of CCTA to evaluate CAC in asymptomatic patients with mild-to-moderate cardiovascular risk is a matter of debate, and currently, the guidelines have presented an uncertain but potentially practical clinical application[14].

Chronic kidney disease (CKD), a predisposing condition to cardio-metabolic risks, is closely interrelated with cardiovascular disease (CVD) to the extent that the disorder of one organ causes discrepancies between the cardiovascular and urinary systems, eventually leading to the collapse of both[15]. CKD patients are up to 50% at increased risk of CAD development[16].

Atherosclerosis is characterized by plaque formation in the intimal layer of the coronary arteries; however, the pathophysiology of vascular disease in CKD is quite different from atherosclerosis in the general population[17]. Vascular calcification may occur in the intima or media layer of the vessel wall. This pattern is more common in CKD patients than in the general population, a condition that can affect the precision and utility of CCTA to diagnose the plaques[17]. However, there is no consensus information about the values of CAC in early CAD diagnosis among this critical group of patients. The current study aims to present diagnostic cut-off values for CAC to detect premature CAD in CKD patients.

Methods

Study population

This cross-sectional study was conducted on 807 patients, including 407 cases with chronic kidney disease and 400 controls with normal kidney function, who underwent CCTA at Isfahan University of Medical Sciences affiliated centers from May 2019 to June 2021.

The study proposal was presented to the Ethics Committee of Isfahan University of Medical Sciences and was approved with the code IR.MUI.MED.REC.1400.636. As the study protocol involved assessing previous medical records in the imaging centers, written consent was not explicitly obtained. However, general consent regarding the use of anonymous data had been recorded for all patients at the initial step

Patients older than 18 with indications for CCTA (according to the clinical judgment of an experienced cardiologist) were included in the study. Patients with a history of contrast-induced hypersensitivity, CKD classified as stages 4 or 5[18], and a history of severe hypersensitivity reactions were excluded. Low-quality images were also ruled out from the study.

Patients were entered into the study as cases and controls based on inclusion criteria until the desired number of participants was achieved. Baseline creatinine was checked for all patients, and those with an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 were allocated to the case group; otherwise, they were placed in the control group. A nephrology consultant was primarily requested for patients with CKD classification stages 3a or 3b to decide on CCTA performance.

Data collection

The patients' demographic (age, height, weight, current smoking, and alcohol consumption) and medical conditions (treated hypertension, diabetes mellitus, or dyslipidemia) were entered into the study checklist.

CCTA was performed for the patients using a 256-slice multidetector computed tomography scan (Brilliance TM 256; Philips medical system), and a stated workstation was used for their reports. The protocol of the imaging study was as collimation of 96-128 mm, detector size of 0.625 mm, rotation time of 0/27ms, voltage of 120 kV, and 180-200 mAs. A

panel calculated the CAC scores consisting of two expert cardio radiologists. The operators manually marked and calculated the scores using the Agatston scoring method[19]. The CAC score quantification comprised the four major coronary arteries, including the left main coronary artery (LMCA), the left anterior descending (LAD), the left circumflex (LCX), and the right coronary artery (RCA).

Coronary Artery Disease Reporting And Data System (CAD-RADS) was used as the gold standard to determine the values of CAC for CAD diagnosis in patients. According to the maximum degree of stenosis in different coronary territories, patients were classified into CAD-RADS 0 (no plaque or stenosis); CAD-RADS 1 (1–24% stenosis); CAD-RADS 2 (25–49% stenosis); CAD-RADS 3 (50–69% stenosis); CAD-RADS 4A (70–99% stenosis); CADRADS 4B (left central>50% stenosis or 3-vessel obstructive disease>70%); and CAD-RADS 5 (total occlusion)[20]. In the current study, significant CAD was defined as CAD-RADS≥3.

Statistical analysis

The obtained data were entered into the Statistical Package for Social Sciences (version 16, IBM Corporation, Armonk, NY, USA). The quantitative variables were presented as mean and standard deviation (SD), and qualitative variables were reported as absolute numbers and percentages. The Chi-square test was used to compare categorical variables, and the quantitative variables were compared using an independent T-test. The receiver operating curve (ROC) was depicted to determine a cut-off value with optimal sensitivity and specificity for CAC in CKD patients with significant CAD-RADS in coronary arteries requiring intensive medications or interventions. Sensitivity, specificity, and area under the curve (AUC) were measured. After considering the CAC score cut-off point, logistic regression was performed to evaluate risk factors. A P-value of less than 0.05 was considered significant.

Results

Eight hundred seven patients were enrolled in two groups: cases (n=407) with CKD and controls (n=400) with normal kidney function. The studied population comprised 443 females (54.9%) and 364 males (45.1%) with a mean age of 67.36±9.89 years.

The demographic and medical characteristics of the studied groups are demonstrated in Table 1.

According to Table 2, CKD patients differed from the controls regarding their CAC scores in different CAD-RAD staging of 1 (P-value=0.034), 2 (P-value=0.025), and 5 (P-value=0.007).

Based on Figure 1 (a), at the cut-off point of 85, the CAC score had a sensitivity and specificity of 84.7% and 83%, respectively, among patients with CKD to identify CAD (AUC: 0.919, 95% CI: 0.89-0.94; P-value < 0.001). For healthy cases, the threshold was also 85, with a sensitivity of 85.1% and specificity of 89.5% (AUC: 0.947, 95% CI: 0.91-0.97; P-value < 0.001) (Figure 1 (b)).

Besides, Table 3 shows that considering a cut-point of 85 for CAC, the frequency of healthy

Table 1. Demographic and medical characteristics of the studied population

Demographic characteristics	Case group (n=407)	Control group (n=400)	P-value
Age (years)	63.95±10.26	53.80±11.84	0.002*
Gender (male), n (%)	156 (38.3)	208 (52)	<0.001**
Current smoking	41 (10.1)	57 (14.2)	0.06**
Alcohol consumption	11 (2.7)	13 (3.3)	0.64**
Medical characteristics			
Hypertension	245 (60.2)	174 (43.5)	<0.001**
Dyslipidemia	192 (47.2)	160 (40)	0.04**
Diabetes mellitus	101 (24.8)	101 (25.3)	0.60**

* T-test

** Chi-square

The continuous variables were reported as mean±SD, and categorical variables were reported as numbers (percentage). A p-value lower than 0.05 was considered significant, and the difference between the two groups of the study was significant in age, gender, hypertension, and dyslipidemia.

Table 2. The Comparison of CAC between the cases and controls

	Coronary artery calcium score		P-value
	Case group (n=407)	Control group (n=400)	
CAD-RAD 0	0.28±0.25	0.22±0.19	0.709
CAD-RAD 1	70.54±21.45	27.71±5.66	0.034
CAD-RAD 2	178.80±27.68	109.69±22.42	0.025
CAD-RAD 3	423.95±64.64	347.87±75.35	0.264
CAD-RAD 4	853.12±100.027	793.38±151.81	0.99
CAD-RAD 5	982.60±182.86	1623.44±502.52	0.007

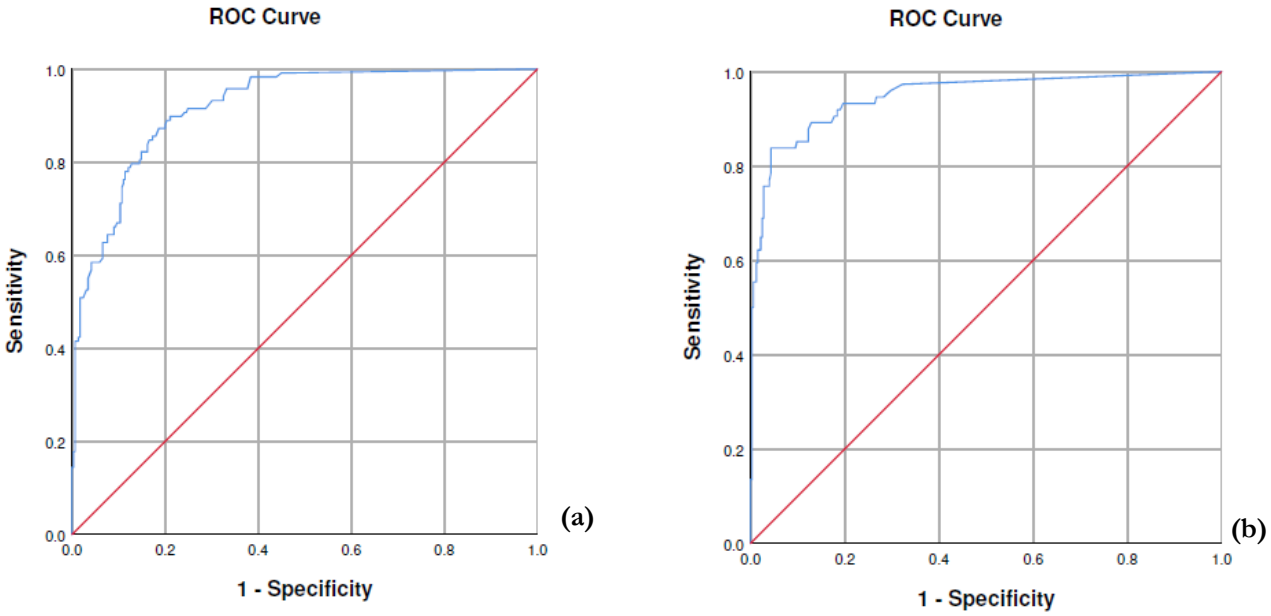

Figure 1. ROC curve of CAC in healthy and CKD patients; (a): CKD patients(AUC: 0.919, 95%CI: 0.89-0.94; P-value<0.001), (b): healthy patients (AUC: 0.947, 95%CI: 0.91-0.97; P-value<0.001)

Table 3. The Comparison of studied groups according to CAD-RADS

		Low CAC score	High CAC score	P-value
CAD-RADS 0-2	Case group	240 (83.3%)	48 (16.7%)	0.012
	Control group	294 (90.2%)	32 (9.8%)	
CAD-RADS 3-5	Case group	19 (16%)	100 (84%)	0.83
	Control group	11 (14.9%)	63 (85.1%)	

Table 4. The logistic regression analysis with a CAC score greater than 85 as the dependent variable

Variables	OR	95%CI	P-value
Age	1.101	1.081-1.122	<0.001*
Male	3.463	2.341-5.123	<0.001*
Dyslipidemia	1.337	0.923-1.937	0.124
Hypertension	1.518	1.054-2.184	0.025*
Diabetes Mellitus	1.589	1.070-2.358	0.022*
Smoking	1.110	0.646-1.907	0.706
Alcohol Consumption	0.603	0.198-1.835	0.373

OR, odds ratio; CI, confidence interval

* P-value lower than 0.05 is considered as significant

subjects with CAD-RADS less than two was remarkably more than the cases (P-value=0.012), while the two groups did not differ based on CAD-RADS 3-5 (P-value=0.83).

The logistic regression was executed to evaluate the effects of sex, age, smoking, alcohol consumption, and comorbidities on the diagnosis of CAD, based on the CAC score cut-off point of 85. Males were 3.463 times more likely to have a minimum CAC score of 85. The probability of a CAC score of more than 85 multiplies by 1.101 for every 1-year advancement in age. Hypertension and diabetes mellitus significantly affected the exhibition of CAD, while the effects of dyslipidemia, smoking, and alcohol consumption were not significant in our study. The details are summarized in Table 4.

Discussion

Atherogenesis is an ongoing pathological process in humans that leads to CAD, mainly diagnosed in the late stages using invasive modalities such as coronary angiography or even following the incidence of cardiovascular diseases. Therefore, numerous investigations are in progress to present a straightforward, concise, and accessible modality for the early diagnosis of CAD[20].

The current study aims to explain the values of the CAC scoring system in the early detection of CAD using CCTA as a noninvasive modality. Accordingly, we found the CAC is significantly higher in CKD patients with non-significant CAD (CAD_RADS: 1, 2), but in patients with significant CAD (CAD-RADS 3, 4, 5), no apparent difference in CAC is noticed. Also, we find a cut-point of 85 with sensitivity and specificity of 85.1% and 89.5% to detect CAD in healthy cases, respectively.

Surfing the literature represents that CAC is progressively notified as a marker applied to determine coronary heart disease, cardiovascular disease, and all-cause mortality. It is well elucidated that at any level of CAC volume, CAC density is inversely associated with CAD[21]. In this regard, a meta-analysis, including 20 studies, presented that zero-to-low CAC scores were negligibly associated with inducible myocardial ischemia. In contrast, the intermediate-to-high scores of CAC were independently related to increased and various frequencies of inducible myocardial ischemia[22]. Interestingly, Tison and colleagues declared that extra-coronary calcifications, such as the thoracic aorta, aortic valve, aortic root, and mitral valve calcification, were remarkably correlated with increased risk of cardiovascular events and all-cause mortality[23].

Despite the significance of the CAC score in determining CAD, limited studies have been conducted to find a cut-point. Kaczmarska and colleagues presented that the CAC score of 10 had the sensitivity and specificity of 79% and 75% to diagnose obstructive CADs, while the sensitivity descended to 48% and specificity increased to 92% by selecting 100 as the cut-point. They emphasized the better outcomes of 10 as the threshold for a low CAC score; the non-appearance of coronary calcification does not imply the rule out of coronary artery disease, as non-calcified obstructive coronary plaques might present with negative Agatston score results. The cut-point of 10 rather than 100 discriminates low calcified or non-calcified obstructive plaque. On the contrary, prominent calcification may stabilize the plaques, while the lipid-rich may lead to plaque rupture by an ongoing extensive inflammatory process[24]. Growing evidence demonstrates that non-calcified plaques may lead to acute coronary syndrome incidence[25].

However, scientists have unanimously presented that zero to minimal CAC scores (≤10) are at negligible risk (less than 1%) for coronary artery involvement and cardiovascular events among asymptomatic patients. Therefore, it seems that these patients do not require further imaging[26-28]; However, Plank et al. represented that a CAC score of zero cannot exclude CAD and recommended performing CCTA for patients with a borderline treadmill-stress test or diabetes mellitus[29]. Contrarily, the CONFIRM registry reported that 3.5% of symptomatic patients had a CAC score of zero and questioned the negative predictive value of the CAC score. Therefore, this score is recommended for low-to-intermediate cardiovascular risk patients[30].

Nevertheless, the practicality of CAC scoring was to the extent that it has been applied to reclassify cardiovascular risk factors. Accordingly, the Multi-Ethnic Study of Atherosclerosis(MESA) in the United States of America on a large population presented that a CAC score of zero was the most substantial negative risk major for cardiovascular disease with a net reclassification improvement (NRI) of 13.75[31]. Another analysis of the patients

with intermediate-risk cardiovascular disease regarding the Framingham Risk Score >5 and<20 found the greatest NRI for CAC score than the other six risk factors (0.659). Besides, CAC had the highest NRI for the total number of correctly recategorized participants for CVD events[32].

Similar outcomes have been proposed for all-cause mortality. For instance, A large population-based study presented that by controlling diverse cardiovascular risk factors, including age, gender, ethnicity, and traditional cardiovascular risk factors, a CAC score of zero was associated with a 10-year survival of 99.4% that decreased to 87.7% when the score increased to over 1000[33]. Another 15-year follow-up study on asymptomatic individuals presented a range of 3-28% for the risk of all-cause mortality among people with 0-100 CAC[34]. Another retrospective cohort study stated that a CAC score of zero in patients with low-to-intermediate risk of cardiovascular disease confers low annual all-cause mortality (less than 1%), and this warranty may extend up to 15 years[35].

Besides, due to the substantial limitations of more invasive modalities, particularly those requiring contrast application, in CKD patients, a large number of CKD cases also entered into the study. It was found that a similar cut-point of 85 for CAC can diagnose CAD with a promising sensitivity of 84.7% and specificity of 83% in CKD patients.

Numerous studies have demonstrated that CKD patients are at amplified risk for CAD and have higher CAC scores than the healthy population[36]. These findings were confirmed by Yiu et al., who presented a higher prevalence, more diffuse, and greater extent of coronary calcium in moderate CKD patients and CAD in patients with moderate CKD than in patients without significant CKD. Accordingly, they continued that the optimal cut-off CAC score of 140 had a sensitivity and specificity of 73% and 70% for CAD diagnosis in moderate CKD patients, while this threshold was 50 with both sensitivity and specificity of 75% in a healthy subject. Besides, the incidence of CAD was 2.8 times greater in the first group[37]. The other study by Fujimoto et al. presented a cut-point of 1000 for a CAC score with 68% sensitivity and 69% specificity to diagnose obstructive CAD in CKD patients under hemodialysis[38]. Or Robinson and his colleagues demonstrated a cut-point of 400 with 83% and 85% sensitivity and specificity for diagnosing CAD in a population of 37 CKD patients[39]. The diversities in the cut-points may be attributed to the size of the study population, the severity of CKD, or the population's ethnicity.

The evaluation of risk factors' effect on CAC showed that age, sex, hypertension, and diabetes mellitus are related to CAC scores greater than 85. These results are coherent with previous studies, but smoking, alcohol consumption, and dyslipidemia did not significantly correlate with an incidence of CAC greater than 85[40-45]. The methods of previous studies signify that their evaluation was not in accordance with a CAC score of 85, but it was based on 100 and 400 cut-off points between normal, mild, and moderate conditions, which are not comparable to the results of our study. Further studies with a greater sample size, considering 85 as the cut-off point for CAC score, are recommended.

Conclusion

According to this study, the CAC score is a practical way to identify CAD among healthy and CKD subjects. There is no significant difference in CAC of patients with significant CAD-RADS in CKD and non-CKD patients. The cut-point of 85 for the CAC score was found valuable to diagnose CAD with over 80% sensitivity and specificity.

Conflict of interests

The authors declare no conflict of interest.

Funding

There is no funding in this study.

Author's Contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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How to cite this article: Moradi M, Talebi A, Shavakhi S, Tarrahi MJ, Meraji Far F. **Coronary artery calcification score as the determinant of coronary artery disease in chronic kidney disease patients: A preliminary study.** ARYA Atheroscler. 2024; 20(3): 12-20.