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Comparing Coronary Artery Calcium Score to Coronary CT Angiography Findings: Is CT Angiography Necessary in All Patients?

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ABSTRACT

Background: Ischemic Heart Disease (IHD) is the leading cause of death worldwide. The primary pathological process resulting in IHD is coronary artery atherosclerosis. Despite advances in CT scan technology, the Agatson method is still the most popular method for measuring coronary artery calcification. Various studies have shown that determining the degree of calcification using Coronary Artery Calcium Score (CACS) is the most reliable noninvasive method of risk assessment. Coronary CT Angiography (CCTA) might be required following CACS measurements. However, there is no consensus regarding a specific CACS cut-off for determining the need for CCTA.
Objectives: This study aimed to compare the severity of coronary calcification to CTA findings.
Methods: This retrospective study was conducted on 261 patients with cardiovascular risk factors or atypical symptoms. An ECG-gated multi-detector CT scan was performed to calculate CACS using the Agatston method. Then, CCTA was performed by injection of the IV contrast agent. The presence of significant coronary artery stenosis was defined as ≥ 50% diameter reduction in CCTA images. Univariate and multivariate analyses were performed using binary logistic regression.
Results: Among the patients, 58.2% had no stenosis and 17.6% had significant stenosis. According to the results of univariate analysis, higher age, hypertension, and lower estimated Glomerular Filtration Rate (eGFR) were associated with a significant increase in coronary artery stenosis. Following multivariate analysis, only GFR was suggested as an independent risk factor, which indicated the important role of GFR as a confounder. Approximately half of the cases (48.6%) had no calcification (CACS = 0), among whom only one patient (0.8%) had significant stenosis on CCTA images. In the minimal subgroup (0 < CACS ≤ 10), one patient (3.1%) showed significant stenosis (P < 0.01). The results revealed a gradual and independent association between higher CAC scores and increase in the incidence of significant stenosis.
Conclusions: Due to the low prevalence of significant stenosis in patients with CACS ≤ 10, CCTA is not recommended in this group, resulting in less radiation exposure and reduced health system costs. In patients with CACS > 10, the likelihood of significant stenosis requiring invasive treatment increases.

1. Background

Ischemic Heart Disease (IHD) is the leading cause of death worldwide and has preserved this position for the few last decades (1). The high prevalence of the disease has placed a large burden on healthcare systems across the world (2). The primary pathological process resulting in IHD is coronary artery atherosclerosis, which is a progressive chronic inflammatory disease that develops over a long period. This process is the result of fat deposition and recurrent intimal injuries, leading to the development of fibrocalcified plaques and increased arterial wall thickness (3). Therefore, calcification of the

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coronary artery walls has been mentioned as an indicator of atherosclerotic disease and is associated with Coronary Artery Disease (CAD) (4, 5).

The Role of Coronary Artery Calcium Score in Asymptomatic Patients

Coronary Artery Calcification (CAC) has been found to be associated with the risk of cardiovascular events, which was increased with increase in the Coronary Artery Calcium Score (CACS) (6, 7). In a systematic review of asymptomatic patients with suspicious symptoms of CAD and CACS = 0, mortality was reported to be lower than 0.5% in the follow-up phase (8), indicating a stronger predictive value for CACS in comparison to traditional risk stratifications. Various studies have shown that determining the degree of calcification using CACS is the most reliable noninvasive method of risk assessment in patients with intermediate cardiovascular risk factors (9, 10).

Non-enhanced CT scan has been found to be incapable of detecting non-calcified plaques (11), such a way that a surprisingly large number (38%) of symptomatic patients with zero CACS demonstrated significant stenosis. Thus, employing CACS for further evaluation of symptomatic patients was not recommended (12, 13).

The Role of Coronary CT Angiography

Coronary CT Angiography (CCTA) may be required following CACS measurements. To the best of our knowledge, there is no consensus regarding a specific CACS cut-off for determining the need for CCTA. In some centers, CTA is not a recommended procedure in asymptomatic patients with CACS = 0 due to the very low chance of CAD. In a prior study assessing CTA findings in high-risk patients or patients with atypical symptoms with CACS = 0, 5.2% of the participants had significant stenosis (14), which was higher than the rate observed in asymptomatic patients. On the other hand, invasive angiographic studies evaluating the importance of normal CACS indicated a high Negative Predictive Value (NPV) for ruling out significant stenosis, which was consistent with the findings of CCTA in similar studies (15-17).

Significant stenosis requiring invasive intervention can be assessed in CCTA. This view was supported by a systematic review, in which the sensitivity and specificity of detecting significant stenosis in 64 Multi-Detector Computed Tomography (MDCT) were 100% and 94%, respectively (18). Other clinical implications of CCTA include determining the number of involved vessels and the location of atherosclerotic plaques. In a study by Tota-Maharaj et al., the number of calcified coronary arteries was associated with increased mortality (19). This result was also applicable to asymptomatic patients (20).

2. Objective

Previous studies demonstrated the important role of CACS = 0 in ruling out CAD in asymptomatic patients. However, the exact significance of CACS in managing atypical patients who are referred for both CACS measurement and CCTA is unknown. The important question is whether CCTA is required following CACS assessment using non-contrast CT in these patients.

3. Methods

3.1. Patient Selection

This retrospective study was conducted on 261 individuals from September 2019 to October 2020. Most of the patients were asymptomatic with cardiovascular risk factors or manifested with atypical symptoms. The exclusion criteria of the study were previous Coronary Artery Bypass Graft (CABG) surgery, previous coronary stent placement, history of cardiac valve replacement, dialysis-dependent renal failure, and incomplete demographic and laboratory data.

3.2. CT Scan Protocol

The patients with an initial heart rate greater than 65 bpm received an oral dose of B-blocker (50 mg metoprolol) approximately one hour before imaging. An ECG-gated MDCT scan was performed using a 128-slice scanner (Siemens Medical Systems, Forchheim, Germany) without IV contrast injection to quantify CAC. Then, CCTA was performed by IV contrast agent injection (using 75 mL of 400 mg I/mL contrast material infused at 4 mL/s followed by a 50-mL saline flush). CCTA images were interpreted by a radiologist experienced in cardiac radiology.

3.3. Data Collection

Demographic information, medical history, and health-related behaviors were recorded using a self-administered questionnaire with the help of a trained employee. Demographic and blood pressure data were also recorded by a trained nurse. In addition, laboratory test results were collected from the patients' medical records.

Estimated Glomerular Filtration Rate (eGFR) was calculated using the Cockcroft-Gault formula based on the lowest serum creatinine level recorded from the patients within three months before imaging.

3.4. Measurement of Coronary Artery Calcification

CACS was calculated using the method described by Agatston et al. and was divided into the five following stages: no calcification (0), minimal calcification (1 - 10), mild calcification (11 - 99), moderate calcification (101 - 400), and extensive calcification (> 400). Moreover, the severity of coronary artery atherosclerosis was classified into three categories, namely mild stenosis (< 50% diameter reduction), moderate stenosis (50 - 70% diameter reduction), and severe stenosis (> 70% diameter reduction). According to the previous studies, the presence of significant coronary artery stenosis was defined as ≥ 50% diameter reduction (21, 22). The degree of stenosis was measured using the narrowest dimension of the lumen at the level of stenosis compared to a normal lumen diameter distally.

3.5. Statistical Analysis

Continuous variables were presented as mean ± SD. Associations between the dichotomous data were analyzed using chi-square test. In addition, independent sample t-test was used to compare the means of quantitative variables in the subgroups of coronary artery stenosis. Besides, Mann-Whitney U test and Kruskal Wallis test were used to determine the relationship between CACS and significant stenosis. Moreover, binary logistic regression was used to assess the significance of the relationship between demographic and clinical variables and significant coronary stenosis. All analyses were performed using the SPSS 22 software.

4. Results

Among the 261 study participants, 121 were female (46.4%) and 140 were male (53.6%). The mean age of the participants was 53.6 ± 11.2 years.

In terms of stenosis severity, 58.2% of the participants had no stenosis and 24.1%, 12.3%, and 5.4% had mild, moderate, and severe stenosis, respectively. Overall, 17.6% of the participants had significant stenosis.

According to the results of the univariate analysis (Table 1), older age was associated with a significant increase in coronary artery stenosis. Accordingly, the patients with significant stenosis were 7.2 years older than those without significant stenosis ($P < 0.001$).

The results revealed no significant difference among the coronary artery stenosis subgroups regarding sex distribution. Moreover, having a history of hypertension was associated with an increase in the prevalence of significant stenosis. Accordingly, the prevalence of hypertension was about 65% in the subgroup with significant stenosis and 40% in the subgroup without stenosis.

Renal failure leads to a notable increase in coronary artery stenosis. In the present study, the mean GFR (calculated based on the Cockcroft-gault method) was significantly lower in the patients with significant stenosis ($P < 0.001$). Moreover, the mean CACS was significantly higher in the patients with significant coronary artery stenosis, which suggested a direct relationship between higher CACS and increased severity of coronary artery stenosis observed in CCTA images ($P < 0.001$).

The results of multivariate analysis using logistic regression have been presented in Table 2. After considering the confounding factors, only GFR was suggested as an independent risk factor in increasing the incidence of significant coronary artery stenosis. Age and blood pressure did not have a significant effect on increasing coronary artery stenosis, which indicated the important role of GFR as a confounder.

Table 1. Basic Demographic and Medical Information in Relation to Significant Coronary Artery Stenosis; Univariate Analysis

Characteristics	Total	Significant Stenosis		P-value
		Yes	No	
Age (y)	53.6 ± 11.2	59.6 ± 6.9	52.4 ± 11.6	< 0.001
Male sex	140 (53.6%)	28 (60.9%)	112 (52.1%)	0.238
Creatinine (mg/dL)	1.01 ± 0.17	1.12 ± 0.21	0.99 ± 0.16	< 0.01
BUN (mg/dL)	14.7 ± 3.7	16.4 ± 4.5	14.3 ± 3.5	< 0.01
HbA1C (mmol/moL)	6.8 ± 1.7	6.9 ± 1.6	6.7 ± 1.8	0.444
Calcium (mg/dL)	8.8 ± 0.9	8.7 ± 0.8	8.8 ± 0.9	0.882
Phosphorus (mg/dL)	3.8 ± 0.6	3.9 ± 1	3.8 ± 0.5	0.533
Triglyceride (mg/dL)	168.3 ± 69.5	182 ± 79.1	164.8 ± 66.7	0.199
LDL cholesterol (mg/dL)	91.7 ± 24.1	91.2 ± 21.9	91.8 ± 24.7	0.889
HDL cholesterol (mg/dL)	46.2 ± 12.9	47.5 ± 12.7	46 ± 13	0.551
Hypertension	118 (45%)	30 (65%)	88 (40%)	< 0.001
Diabetes	37 (14%)	9 (19%)	28 (13%)	0.275
eGFR $_{(Cockgraft-gault)}$ (mL/min)	88.7 ± 21.6	73.6 ± 16.4	91.9 ± 21.2	< 0.01
CACS	79.6 ± 168.8	292.9 ± 243.2	33.9 ± 101.5	< 0.01

Abbreviations: eGFR, estimated glomerular filtration rate

Table 2. The Predictors of Significant Coronary Stenosis in Multivariate Analysis by Logistic Regression

Predictor	Odds Ratio (95% Confidence Interval)	P-value in Multivariate Analysis
Gender	0.62 (0.3 - 1.25)	0.188
Age	1.01 (0.96 - 1.05)	0.722
Hypertension	0.62 (0.3 - 1.3)	0.221
Diabetes	0.74 (0.3 - 1.82)	0.551
eGFR $_{(Cockcroft-gault)}$	0.96 (0.94 - 0.98)	< 0.001

Abbreviation: eGFR, estimated glomerular filtration rate

Table 3. Distribution of Different Coronary Artery Calcium Score (CACS) Subgroups in Relation to the Presence of Significant Coronary Artery Stenosis

Calcium Score	Total Number of Patients (%)	Significant Stenosis		P-value
		Yes	No	
Zero (CACS = 0)	127 (48.6%)	1 (0.8%)	126 (99.2%)	< 0.001
Minimal (0 < CACS ≤ 10)	32 (12.3%)	1 (3.1%)	31 (96.9%)	
Mild (10<CACS≤100)	48 (18.4%)	8 (16.7%)	40 (83.3%)	
Moderate (100 < CACS ≤ 400)	36 (13.8%)	22 (61.1%)	14 (38.9%)	
Extensive (CACS > 400)	18 (6.9%)	14 (77.8%)	4 (22.2%)	

Approximately half of the cases (48.6%) had no calcification (CACS = 0), among whom only one patient (0.8%) had significant stenosis on CCTA images. In the minimal subgroup (0 < CACS ≤ 10), one out of the 32 patients (3.1%) showed significant stenosis. Concordant with the increase in the severity of calcification in mild, moderate, and extensive subgroups, the percentage of identified patients with significant stenosis in CCTA increased and was reported as 16.7%, 61.1%, and 77.8%, respectively (P < 0.001, Table 3).

5. Discussion

The main goal of this study was to investigate the relationship between the severity of coronary artery calcification based on CACS and the degree of coronary artery stenosis detected in CCTA images.

The results of univariate analysis indicated that older patients with a history of hypertension and renal impairment were more likely to have significant coronary stenosis, which was concordant with the results of the previous studies. According to the results of multivariate analysis, GFR was the only independent predictor of significant stenosis. However, some other studies have assumed an independent role for higher age and hypertension in addition to GFR. This might be attributed to the fact that GFR was not considered a confounding factor in these studies (23, 24).

In the current study, only one out of the 127 patients with zero CACS showed significant stenosis. In addition, the prevalence of significant stenosis was 3.1% in patients with minimal calcification (CACS ≤ 0). These findings suggest that invasive interventions are probably not required in patients with CACS ≤ 10. Up to now, several studies have evaluated invasive angiographic findings in patients with CACS = 0, reporting a very low probability of significant stenosis in this group (22, 25). In a review article, the superiority of CCTA over conventional invasive coronary angiography in diagnosing atherosclerotic plaques without stenosis was highlighted. The authors pointed out the low risk (0 - 1%) of cardiovascular events in patients with normal CCTA or mild coronary artery involvement (26-29), which was in agreement with the results of a meta-analysis performed by Abdulla et al. (26). Furthermore, some studies have reviewed CCTA findings in patients without coronary artery calcification. Kelly et al. (21) and Cheng et al. (30) disclosed that 3.7% and 0.5% of patients had significant stenosis, respectively. These results were similar to those of the present investigation.

Few studies have evaluated the clinical significance of CACS = 1 - 10. In a research carried out by Shee Yen Tay et al., the use of CACS and CTA in screening asymptomatic patients with cardiovascular risk factors was investigated. The results revealed no significant difference between CACS = 0 and CACS = 1 - 10 regarding significant stenosis. Hence, it was suggested that asymptomatic patients with CACS = 0 did not need CTA, which was consistent with the results of the current study. They found significant stenosis in only 0.6% of asymptomatic patients with CACS ≤ 10 (24).

Non-enhanced CT scans have been found to be ineffective in detecting non-calcified plaques. Uretsky et al. disclosed that these plaques were rarely associated with significant stenosis (31). Therefore, it seems that CACS = 0 rules out the existence of significant stenosis and can eliminate the need for additional diagnostic procedures. Considering the prevalence of significant stenosis (43.1%) in patients with CACS > 10, the importance of CCTA is apparent in this group.

5.1. Conclusion

CACS measurement is an appropriate method for screening asymptomatic patients or those with atypical symptoms for CAD. Due to the low prevalence of significant stenosis in patients with CACS ≤ 10, CCTA is not recommended in this group, resulting in less radiation exposure and reduced health system costs. In patients with CACS > 10, the likelihood of significant stenosis requiring invasive treatment increases. Therefore, in order to determine the next treatment step, CCTA is recommended in this group.

5.2. Clinical Trial Registration Code

This study was not a clinical trial.

5.3. Ethical Approval

Ethical considerations of the study plans and protocols were approved by the Ethics Committee of Baqiyatallah University of Medical Sciences (code: IR.BMSU.BAQ.REC.1398.023).

Informed Consent

The participants were fully informed about the purpose of the study, the voluntary nature of participation, and that they could leave the study at any time. The participants were also assured about the confidentiality of their information. Written informed consent forms were also obtained from the participants.

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Authors' Contribution

Study concept and design: A.M., R.S., and R.S; analysis and interpretation of data: V.M., drafting the manuscript: A.M., R.S., and R.J.; critical revision of the manuscript for important intellectual content: A.M., R.S., and H.M. All authors read and approved the final manuscript.

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