Emergency Radiology (2022) 29:969–977
https://doi.org/10.1007/s10140-022-02082-w

ORIGINAL ARTICLE

Coronary artery calcification—does it predict the CAD-RADS category?

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Received: 16 June 2022 / Accepted: 28 July 2022 / Published online: 4 August 2022

Abstract

Purpose Coronary calcium scores (CCSs) in cardiac-gated computed tomography (CCT) are diagnostic for coronary artery disease (CAD). This study aims to investigate if CCSs can foretell CAD-reporting and data system (CAD-RADS) without performing computed tomography angiography (CTA).

Methods Profiles of 544 patients were studied who had gone through CCT and CTA; the number of calcified regions of interest (ROIs), the Agatston, area, volume, and mass CCSs were calculated. Among the CAD-RADS categories (1 to 5), the mean values were compared for each CCS separately. A cut-off for each CCS was declared using ROC curve analysis, more than which could predict significant CAD (CAD-RADS 3 to 5). Also, logistic regression models indicated the most probable CAD-RADS category based on the CCSs. $P < 0.05$ was considered significant.

Results Among 53% male and 47% female participants with a mean (SD) age of 62.57 (0.84) years, numbers of calcified ROIs were significantly different between each pair of CAD-RADS categories. While other CCSs did not show a significant difference between CAD-RADS 1 and 2 or 2 and 3. All CCSs were significantly different between the non-significant and significant CAD groups; cut-offs for the number of calcified ROIs, the Agatston, area, volume, and mass scores were 9, 128, 44mm^2, 111mm^3, and 22 mg, respectively. Formulae A and B predicted the most probable CAD-RADS category (accuracy: 79%) and the probability of significant/non-significant CAD (accuracy: 81%), respectively.

Conclusion CCSs could predict CAD-RADS with an accuracy of 80%. Further studies are needed to introduce more predictive calcium indices.

Keywords Coronary artery disease · Computed tomography angiography · Atherosclerosis · Vascular calcification

Introduction

Medical literature is full of studies struggling to generate diagnostic or prognostic tools with the highest benefits and lowest costs. Undoubtedly, coronary artery disease (CAD), as the most prevalent single cause of mortality worldwide, plays an influential role in inflicting a tremendous health-related and economic burden on most societies [1]. Thus, it has always been an enormous challenge to discover CAD immediately among large numbers of patients at risk and take preventive or therapeutic actions.

Since its introduction, computed tomography (CT) has evolved in many aspects to visualize internal organs on a 3D anatomic basis. Thereby, it created the chance for Agatston et al. to introduce the coronary artery calcification score (CACS) through the cardiac-gated CT (CCT) images to diagnose and predict CAD. Calcified regions in the direction of the coronary arteries can explicitly demonstrate the formation of atheroma and its location [2].

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The addition of an intravenous contrast agent further facilitated visualization of the intraluminal patency of the arteries through CT, giving birth to the coronary CT angiography (CCTA), which now stands as the modality of choice to assess CAD among stable patients experiencing cardiac symptoms, instead of invasive coronary angiography (ICA) which imposed an invasive procedure and massive X-ray exposure to the patient and operator [3].

Providing a standard universal reporting system for CCTA findings, coronary artery disease-reporting and data system (CAD-RADS) was developed, validated, and proven reliable in predicting the severity of CAD and its prognosis. This system describes the maximal degree of coronary artery stenosis in percent as follows: CAD-RADS 0: 0%, CAD-RADS 1: 1–24%, CAD-RADS 2: 25–49%, CAD-RADS 3: 50–69%, CAD-RADS 4A: 70–99%, CAD-RADS 4B: left main > 50% or three-vessel obstruction, CAD-RADS 5: 100%. It has now been accepted as the standard method of reporting CCTA results, proven to be superior in diagnostic and prognostic aspects to previous methods [4–7].

Due to partial volume effects and beam hardening, dense calcifications may menace the CCTA accuracy in estimating arterial stenosis [8]; CCT is regularly performed before CCTA, helping to map the calcified regions before contrast agent administration. Moreover, interpreting the CACS alongside the CCTA is reported to improve the mortality risk prediction in CAD patients [9].

Studies have shown that CACS can be used as a prognostic indicator of major adverse cardiac events (MACE) in symptomatic and asymptomatic patients; high CACS is associated with increased risk, while low CACS is associated with decreased risk for MACE [10–13]. Furthermore, coronary calcium scoring could direct downstream testing toward high-risk patients with no significant increase in the total number of tests in the whole population as EISNER controlled trial demonstrated [14]. Interestingly, during recent studies, CACS has been able to stratify the mortality risk of coronavirus disease 2019 (COVID-19) patients [15]. Concluding from the available evidence, CACS is a low-cost and highly beneficial tool for predicting the future MACE risk, as accurate as the combination of all other cardiovascular risk factors [16, 17].

Observed calcification in the CCT is generally reported as Agatston CACS, the accepted universal standard reporting method. Nevertheless, the Agatston CACS does not consider all the extracted information regarding calcium densities, so alternative measures are being developed to increase its prediction precision, including the total number of calcified regions of interest (ROIs), volume, mass, and area scores [17–19].

There are several known issues with CCTA, including the risk of allergic reaction to intravenous contrast agents, excessive radiation exposure, and financial costs; CCT may become the preferred method of estimating the risk of future MACE in some patients, especially if they are asymptomatic and clinically stable [20]. This fact raised the question of whether CACS or any other calcium score (separately or in combination) could indicate which category of CAD-RADS a patient belongs to without further performing CCTA. No answer in the medical literature is available to our knowledge. So, the current study aims to investigate if calcium scores extracted from CCT could predict patients' categories in CAD-RADS. This may convey a glorious prospective role for coronary calcium scores to participate in the CAD prevention and treatment scenario.

Materials and method

Patient selection and study design

Following approval by the regional and national research ethics committee, during a cross-sectional descriptive-analytic study, electronic profiles of the patients who had been referred by cardiologists to the CT angiography ward of a tertiary-care heart center from January 2021 to January 2022 due to CAD suspicion were extracted from an existing electronic database and included in the study. Profiles consisted of patients' names, genders, ages, CCTs, and CCTAs. It was ensured that all the CCTs had been obtained just before the CCTAs. Profiles belonging to patients who had experienced the following situations before CCTA were excluded due to CAD-RADS limitations or modifiers (which could confound the categorization) [21]:

1. Percutaneous cardiac instrumentation (PCI) (modifier S)
2. Any surgery or invasive procedure on the heart or coronary vessels (modifier G)
3. Any congenital cardiac anomalies
4. Non-identifiable CAD-RADS (modifier N)

Moreover, profiles with missing or unavailable data within any of the required variables or profiles belonging to patients with the Agatston CACS = 0 were excluded.

Observed vulnerable plaque in CCTA (modifier V in CAD-RADS) was not excluded, nor was it applied in the reporting since it was observed not to contribute incrementally to prognostic function [4, 22]. Also, both CAD-RADS 4A and 4B were assessed as CAD-RADS 4, not as separate categories.

CT scan protocol

CCT

CCT for all the eligible cases had been performed without intravenous contrast injection, using a 256-slice MDCT

scan (Brilliance TM 256, Philips Medical System, Cleveland, OH, USA) and a particular workstation for reporting. The imaging protocol had been as follows: the thickness of cuts, 2.50 mm; detector size, 0.625 mm; gantry rotation time, 0.27 ms; tube voltage, 120 kV; and tube current, 84 mAs/slice. If any patient had been experiencing a heart rate of more than 75 beats per minute, oral β-blocker medication (50–100 mg of metoprolol) had been administered to them an hour before image acquisition. Additionally, sublingual nitroglycerin (0.4 mg) had been administered a minute before the image acquisition to dilate coronary arteries.

CCTA

CCTA had been performed following the CCT using the same scanner device and protocol except for the following:

1) Tube current: 180–200 mAs/slice.
2) The thickness of the source image cut: 0.67 mm.
3) Utilizing intravenous contrast media: According to the patient's BMI, 70 to 90 cc of iodinated contrast media (Visipaque, GE Healthcare, Ireland, Cork, Ireland) at a concentration of 320 mg iodine/mL with a flow rate of 5–6 cc/s had been injected. Then, 40 mL of normal saline had been infused with a flow rate of 4 mL/s.

Quantitative assessments

The reconstructed images were sent to the Philips workstation to provide CCT and CCTA reports. All reconstructed image formats were authorized for image analysis, containing axial or oblique maximum intensity projections (MIP) and curved multi-plane reconstructions (MPR).

Utilizing the semi-automated software (Extended Brilliance workspace; Philips Medical Systems), the calcified ROIs were manually marked; the Agatston CACS, number of calcified ROIs, calcification mass, volume, and area scores were automatically calculated. A calcified ROI was defined as an area within the coronary artery direction with at least 130 HU attenuation and 1.03 mm^2 area [23].

All epicardial coronary arteries with diameters of 1.5 mm or more were evaluated based on the CAD-RADS; the final assigned scores ranged from 0 to 5. A professional radiologist (senior author) and a senior radiology resident physician (the second author) were involved in manually marking the calcified ROIs, estimating the CAD-RADS, and reporting the overall results.

Statistical analysis

Demographic features (sex and age) were extracted from the included profiles and entered into the R statistics software (version 4.1.1, R Foundation for Statistical Computing, Vienna, Austria) for further analysis. Also, for every patient, the Agatston CACS, the number of calcified ROIs, mass, volume, area scores, and CAD-RADS category were entered. To assess whether the aforementioned calcium scores differ significantly among different categories of CAD-RADS, the one-way ANOVA test was used, and pairwise comparisons were performed using the least significant difference (LSD) post hoc test.

CAD-RADS categories 3, 4, and 5 were defined as significant CAD [22, 24]. The independent *T* test was used to assess whether the calcium scores differ significantly between the groups with significant and non-significant CAD. A significant *P* value was assumed to be less than 0.05.

A cut-off value was estimated using the receiver operating characteristics (ROC) curve for each of the calcium scores, above which predicted significant CAD based on CAD-RADS.

A multinomial logistic regression model estimated the probability of falling every individual patient into each quintuple CAD-RADS category. Yet, a logistic regression model assessed the likelihood of every patient having significant CAD.

Results

Medical profiles of 544 patients [289 (53%) male and 255 (47%) female] were found eligible to enter this study. The mean ± standard deviation (SD) age of the studied population was 62.57 ± 0.84 years (male group = 60.99 ± 1.24 and female group = 64.36 ± 1.08).

For mean values of calcium scores in the whole population, 95% confidence intervals ($Mean \pm \frac{Std.}{\sqrt{n}} Z_{\alpha/2}$) were 400.56 ± 58.14 Agatston units, and 19.29 ± 1.91, 139.74 ± 19.59 mm^2, 353.84 ± 49.1 mm^3, and 83.51 ± 12.48 mg for the Agatston CACS, the number of calcified ROIs, area, volume, and mass scores.

No statistically significant difference was observed in any of the above calcium scores between genders ($P \geq 0.05$), depicting that the variable gender would not be expected to confound the results.

None of the eligible profiles indicated CAD-RADS 0. Therefore, this category was not included in the further analysis.

All calcium scores were significantly different among the quintuple categories of CAD-RADS (1 to 5); post hoc tests showed that the numbers of calcified ROIs were significantly different between each pair of categories. However, regarding other calcium scores, no significant differences

were found between the CAD-RADS 1 and 2 and also the CAD-RADS 2 and 3 (Table 1).

All calcium scores differed significantly between the non-significant and significant CAD groups (Table 1). ROC curve analysis for every calcium score estimated that the cut-off values—more than which indicated significant CAD and less than which indicated non-significant CAD—for the number of calcified ROIs, the Agatston CACS, area, volume, and mass scores were 9, 128, 44mm^2, 111mm^3, and 22 mg respectively. These cut-offs and their sensitivities, specificities, positive predictive values, and negative predictive values are represented in Table 2.

To predict if the CAD is significant or not using calcium scores, formula A was generated with 81% accuracy (only the Agatston CACS and the number of calcified ROIs proved effective for prediction). Also, formula B was developed to predict the CAD-RADS category with 79% accuracy (only the Agatston CACS proved effective for forecast).

Formula A: The significant probabilities were estimated using the Agatston CACS from the testing set, and the maximum value was considered CAD-RADS category.

X = the Agatston CACS $Y = CAD - RADS$ category

$$g_1(x) = -1.47 + 0.021x$$

$$g_2(x) = -2.365 + 0.023x$$

$$g_3(x) = -2.109 + 0.024x$$

$$g_4(x) = -3.827 + 0.025x$$

$$\boldsymbol{P}(\mathrm{Y} = 1) \cong \frac{1}{1 + e^{g_1(X)} + e^{g_2(X)} + e^{g_2(X)} + e^{g_3(X)} + e^{g_4(X)}}$$

Table 1 Distribution of calcium scores among CAD-RADS categories

Calcium score	CAD-RADS				
	Non-significant CAD ($n=256$)		significant CAD* ($n=288$)		
	1 ($n=132$)	2 ($n=124$)	3 ($n=73$)	4 ($n=171$)	5 ($n=44$)
The number of calcified ROIs	5.42 ± 0.92	11.11 ± 2.29†	17.70 ± 3.39†	30.88 ± 4.00†	41.55 ± 9.04†
Area score (mm^2)	16.27 ± 0.89	64.78 ± 20.94	104.92 ± 23.83	240.20 ± 42.20†	388.70 ± 112.15†
Volume score (mm^3)	40.80 ± 9.7	162.40 ± 52.36	262.45 ± 59.62	614.20 ± 105.34†	972.23 ± 280.34†
Mass score (mg)	8.20 ± 2.44	35.71 ± 12.48	57.52 ± 13.30	149.01 ± 28.03†	232.75 ± 69.05†
The Agatston CACS (AU)	34.17 ± 8.51	173.01 ± 60.88	292.63 ± 67.58	709.87 ± 125.80†	1118.00 ± 333.85†

Data are reported as 95% confidence intervals for means ($Mean \pm \frac{Std.}{\sqrt{n}} Z_{\alpha/2}$). *AU*, Agatston unit; *CACS*, coronary artery calcium score; *CAD*, coronary artery disease; *CAD-RADS*, coronary artery disease-reporting and data system; *ROI*, region of interest

*All of the calcium scores were significantly higher among patients with significant CAD, compared to patients with non-significant CAD. $P<001$ was retrieved for each calcium score separately through an independent sample T test

†Estimated to be significantly higher than the previous CAD-RADS category, using the least significant difference post hoc test following one-way analysis of variances (ANOVA) test

Table 2 Cut-off values, sensitivities, specificities, and positive and negative predictive values of calcium scores for diagnosing significant CAD

Calcium score	Cut-off value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
The number of calcified ROIs	9	77.43	79.30	80.8	75.70
Area score	44 mm^2	73.61	81.25	81.5	73.2
Volume score	111 mm^3	75.00	81.25	81.8	74.3
Mass score	22 mg	75.00	79.69	80.6	73.9
The Agatston CACS	128 AU	73.61	81.64	81.9	73.3

Following ROC curve analysis, AUC was calculated at 0.83 for the number of calcified ROIs and 0.84 for every other calcium score (AUC > 0.5 was significant). Values more than the cut-off indicate significant CAD (CAD-RADS 3, 4, and 5), and values less than the cut-off indicate non-significant CAD (CAD-RADS 1 and 2)

AU, Agatston unit; *AUC*, area under the curve; CACS, coronary artery calcium score; CAD, coronary artery disease; *CAD-RADS*, coronary artery disease-reporting and data system; *ROC*, receiver operating characteristics; *ROI*, region of interest

$$\boldsymbol{P}(\mathrm{Y}=2)\cong\frac{e^{g_1(X)}}{1+e^{g_1(X)}+e^{g_2(X)}+e^{g_2(X)}+e^{g_3(X)}+e^{g_4(X)}}$$

$$\boldsymbol{P}(\mathrm{Y}=3)\cong\frac{e^{g_2(X)}}{1+e^{g_1(X)}+e^{g_2(X)}+e^{g_2(X)}+e^{g_3(X)}+e^{g_4(X)}}$$

$$\boldsymbol{P}(\mathrm{Y}=4)\cong\frac{e^{g_3(X)}}{1+e^{g_1(X)}+e^{g_2(X)}+e^{g_2(X)}+e^{g_3(X)}+e^{g_4(X)}}$$

$$\boldsymbol{P}(\mathrm{Y}=5)\cong\frac{e^{g_4(X)}}{1+e^{g_1(X)}+e^{g_2(X)}+e^{g_2(X)}+e^{g_3(X)}+e^{g_4(X)}}$$

Formula B: The significant probabilities were estimated using the number of calcified ROIs and the Agatston CACS from the testing set. Probabilities of more than 0.5 were considered to be significant.

X_1 = the Agatston CACS X_2 = number of calcified ROIs $e = 2.718$

$$\boldsymbol{P}(\mathrm{Significant})\cong\frac{e^{-1.304+0.002X_1+0.068X_2}}{1+e^{-1.304+0.002X_1+0.068X_2}}$$

$$\boldsymbol{P}(\mathrm{NonSignificant})=1-\boldsymbol{P}(\mathrm{Significant})$$

Discussion

"CACS should be obtained for many more patients than it is today." This conclusion was made at the clinical lipidology roundtable discussion in 2019 [16], representing the recent growing interest in how CCT and calcification findings can diagnose CAD or predict its outcome, as CCT is a relatively cheap, easy, and accurate diagnostic tool. Because CAD-RADS extracted from CCTA has been demonstrated to be an excellent diagnostic and prognostic tool [24, 25], the current study aimed to assess calcium scores' ability to predict CAD-RADS, which was assumed to be a gold standard. All coronary calcium scores indicated significant CAD based on the CAD-RADS, and the appropriate cut-off value for each score could be introduced; formulae were generated to estimate the CAD-RADS category based on calcium scores without further need to perform CCTA. These results further support the potential to diagnose and predict CAD using calcium scores as accurately as possible (Fig. 1).

Although all of the calcium scores differed significantly between categories 3 and 4, as well as 4 and 5 of CAD-RADS, they could not demonstrate significant differences between categories 1 and 2 and also 2 and 3. This finding supports Bittner et al. [25] and Lee et al. [26] conclusions regarding the incremental prognostic value of CAD-RADS over other systems like CACS. Also, the concordance of different calcium scores in differentiating the CAD-RADS categories confirms the high correlations reported in previous studies among these scores [27].

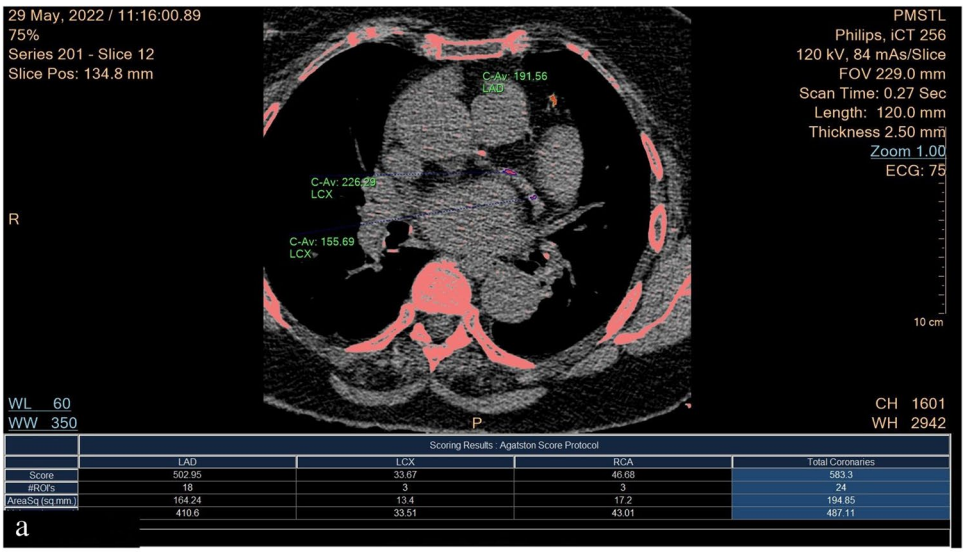
The only calcium score that significantly differed between every two groups of CAD-RADS categories was the number of calcified ROIs. This feature was superior to the Agatston CACS, the standard method of reporting coronary calcification. This was also concordant with previous studies that discussed the limitations of the Agatston CACS, one of which was its disability to demonstrate the calcification spread across coronary arteries [28, 29].

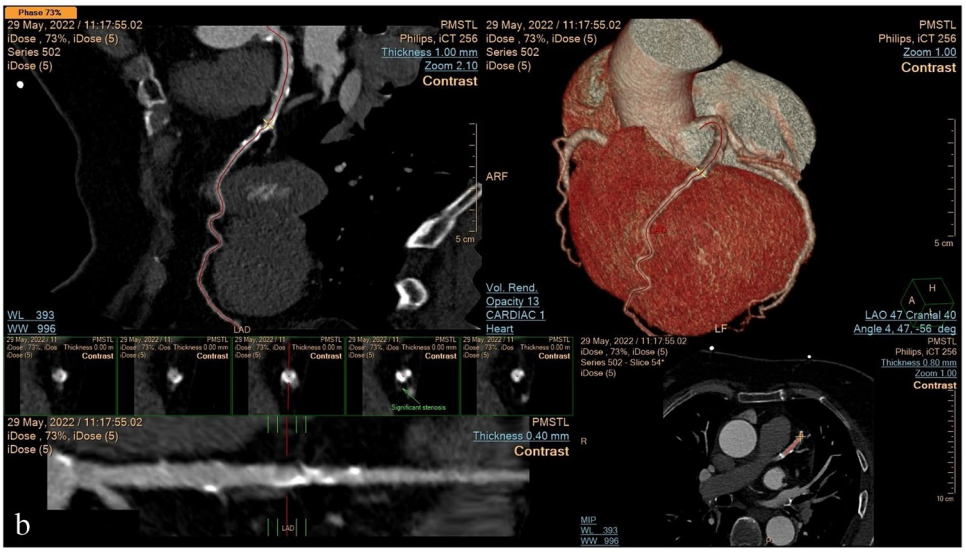
The current study introduces two novel findings regarding the calcium scores:

1) Cut-off values for each calcium score more than which indicated significant CAD (CAD-RADS 3, 4, and 5) and less than which indicated non-significant CAD (CAD-RADS 0, 1, and 2): cut-offs for the number of calcified ROIs, the Agatston CACS, area, volume, and mass scores were 9, 128, 44mm^2, 111mm^3, and 22 mg respectively.
2) Formulae that could estimate the CAD-RADS category based on the calcium scores with approximately 80% accuracies (Formulae A and B).

These findings provide a background for the future landscape of the clinical roles of calcium scores among CAD patients. This study showed that other calcium scores, particularly the number of calcified ROIs, could be used alongside the Agatston CACS to improve CCT functions, despite their similar predictive abilities. Looking back to the literature, as a struggle to strengthen the diagnostic and prognostic values of calcium scores based on available data obtained from CCT, the spatially weighted calcium score (SWCS) was introduced in 2021 by integrating calcium density information in neighborhood voxels of the calcified ROIs, however, could not add to the predictive value of Agatston CACS > 0 [18]. Also, as vulnerable atherosclerotic plaques exhibited lower calcium densities and lower volume scores, it is logical that different calcium scores show different potentials in prognostication [28, 30]. We suggest that future approaches for reporting CACS be based on all the available evidence from the body of literature to build up a robust diagnostic and predictive tool for CAD. Whatever that tool would be, its report should be simple and definite as the clinicians sometimes get confused with the different calcium scores and do not yet have a radiological culture to interpret the results.

A semi-automated software conducted calcium scorings in this study; calcified ROIs were manually marked. It should be emphasized that with a fully-automated software, it will probably be easier to measure and report calcium scores. Yet based on the authors' experience, the fully-automated





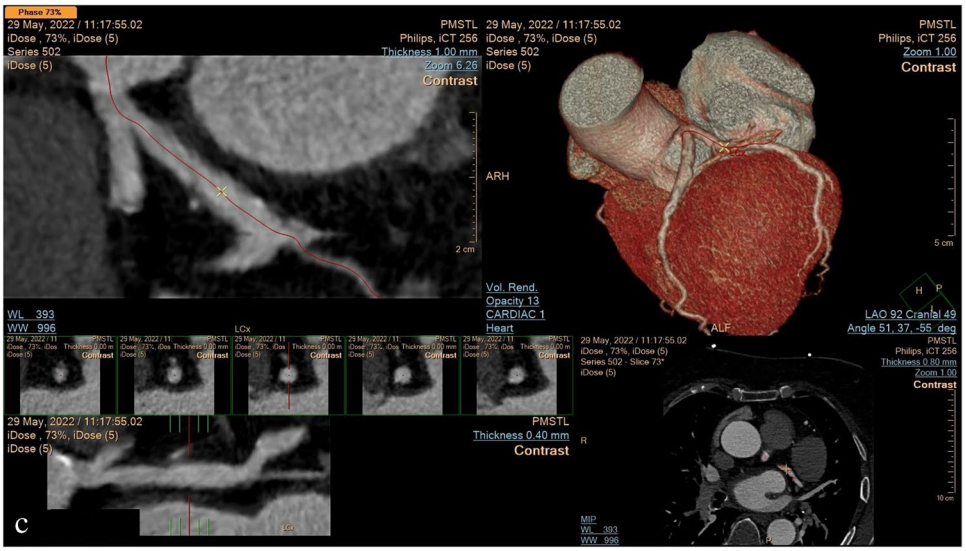


Fig. 1 Cardiac-gated computed tomography (CCT) and coronary computed tomography angiography (CCTA) of a coronary artery disease (CAD) patient. A 62-year-old female patient with the chief complaint of exertional chest pain had been referred by a cardiologist to the CCTA ward. She had been diagnosed with primary hypertension and non-familial hypercholesterolemia as risk factors for CAD. **a** A cut of the CCT of the patient shows calcified regions of interest (ROIs) in the directions of the left anterior descending (LAD) and left circumflex (LCX) arteries (demarcated pink areas). The table shows the measured calcium scores. Based on both the obtained cut-off values and formula B, she was diagnosed with significant CAD. Formula A estimated the CAD-reporting and data system (CAD-RADS) to be 4. **b** CCTA picture of the patient shows mild (25–49%) and severe (70–99%) stenotic calcified plaques within the proximal and mid-part LAD, respectively. **C** CCTA picture shows minimal or mild stenotic calcified plaques within the LCX direction. Based on the CCTA findings, the patient was finally diagnosed with CAD-RADS 4A, concordant with the earlier estimates after CCT. So, she went through invasive coronary angiography and percutaneous coronary instrumentation of the LAD mid-part

measurements need to be closely supervised by radiologists and their accuracies should not be inferior to the semi-automated ones.

The generated formulae in this study can be utilized as calculators for estimating the CAD-RADS among patients who are not candidates for CCTA due to allergy to contrast agents, susceptibility to X-ray radiation, or their wishes. Further studies are suggested for integrating demographic features and cardiovascular risk factors into this formula.

The current study was not conducted without limitations. First, the sample size was limited to 544 patient profiles, which was relatively small for such a study. Second, the CAD-RADS was assumed as a gold standard tool for diagnosis and prognostication of CAD. In light of the CAD-RADS and CCTA limitations, the most appropriate tool would have been the ICA along with cardiovascular risk factors in patient histories. However, a relatively small number of patients suspicious of CAD had gone through ICA within our available database. The third was excluding patient profiles that CAD-RADS modifiers should have interpreted. Although previous studies have claimed that CAD-RADS categories alone without modifiers play the primary functional role [31], modifiers extend the reporting system's inclusiveness. Fourth, CAD-RADS 4A and 4B were not analyzed as separate categories in this study because cases of CAD-RADS 4B were much fewer than sufficient to accurately participate in the analyses. Finally, variables other than calcium scores were not applied within the formulae to calculate CAD-RADS categories. Previous studies have reported that calcium scores gradually increase along with aging, so the functional abilities of calcium scores are not expected to be the same for different age groups [32–34]. Although the age range of participants in this study was narrow (60 to 64 years) and did not seem to confound our results, a more comprehensive age range could have distorted it.

Putting all the limitations together, further studies are needed to be conducted prospectively during a long period and include larger sample sizes. Data may be available from cohorts or registries that already exist. Additionally, it is more appropriate to consider ICA in conjunction with clinical risk factors as the gold standard. The incremental values of CAD-RADS modifiers and CAD-RADS 4 subcategories are suggested for further investigation in future studies, especially their correlation with calcium scores and other cardiovascular risk factors. Locations of calcified ROIs (proximal–distal or the involved vessels) probably influence the severity and final prognosis of CAD; it is recommended as a subject for future studies to investigate the effect of calcified ROIs' locations on diagnostic and prognostic abilities of calcium scores. As the final and most critical suggestion, further studies are recommended to modify the formulae presented in this study. This will enable us to additionally consider confounding variables like age, gender, and ethnicity, expanding their applicability to a broader range of people.

Conclusions

All of the coronary calcium scores, including the number of calcified ROIs, the Agatston CACS, mass, volume, and area scores, were able to predict significant CAD based on the CAD-RADS. Moreover, the CAD-RADS category based on calcium scores could be estimated by two novel formulae generated. These results support the potential for calcium scores to represent robust diagnostic and prognostic functions among asymptomatic or symptomatic patients suspicious of CAD, even without further need to perform CCTA.

Acknowledgements The authors appreciate the Isfahan University of Medical Sciences for providing the required equipment to conduct this study.

Author contribution All authors contributed to the study's conception and design. Material preparation and data collection were performed by Maryam Moradi and Ebrahim Rafiei. The collected data was primarily analyzed by Hossein Haghbin. The first draft of the manuscript was written by Sina Rasti. All authors commented on previous versions of the manuscript, and further read and approved the final manuscript.

Funding This work was supported by Isfahan University of Medical Sciences (grant number 340065). The university provided the required equipment for this study; no other financial or non-financial support was received from this or any other institution.

Data availability The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the research ethics board of the Radiology Department in Isfahan University of Medical Sciences and the national research ethics committee (code: IR.MUI.MED.REC.1400.138).

Consent to participate This study used available data from electronic patient profiles retrospectively. Considering the retrospective nature, the need for individual patient consent was waived by the research ethics committee as a data protection safeguard was in place.

Conflict of interest The authors declare that they have no conflict of interest.

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