https://doi.org/10.15218/zjms.2022.007

Prevalence and extent of coronary artery disease among patients with a zero calcium score

Received: 18/03/2020 Accepted: 06/06/2021

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Abstract

Background and objective: Coronary artery calcium is a specific indicator of and an independent risk factor for atherosclerosis. However, calcium scoring may miss non calcified plaques, which were indicated to be of clinical importance. This study aimed to identify the presence of non calcified plaques in patients with zero coronary artery calcium score who have been examined with computed tomography coronary angiography and find out any association between the presence of non-calcified plaques and risk factors and presenting symptoms in those patients.

Methods: In this retrospective study, we analyzed the computed tomography images of 9826 consecutive patients attending the cardiac center in Erbil, Iraq, between January 2016 and September 2020. Of these patients, we included 2805 patients with a zero coronary artery calcium score in the study. Coronary calcium-scoring scans were followed by computed tomography coronary angiography (256 MSCT Philips ICT). The coronary artery calcium scores were calculated, and the presence of non calcified plaques and significant stenosis (>50% of vessel diameter) were evaluated.

Results: Of the 2805 patients with a zero coronary artery calcium score, 896 (31.9%) had atherosclerotic plaques; 143 patients (5.1%) had significant coronary stenosis. Among coronary risk factors, diabetes mellitus (OR = 2.1; 95% CI 1.4-3.3), hypertension (OR = 1.3; 95% CI 1.07-1.58)), male sex (OR = 1.9; 95% CI 1.5-2.3) and old age (OR was 3.2 for the age group 35-44 years reaching 27.7 in the age group ≥ 75 years) were significantly correlated with the presence of atherosclerosis and obstructive coronary artery disease.

Conclusion: Although coronary artery calcium scoring is a safe and reliable test to exclude obstructive coronary artery disease, the absence of coronary artery calcium does not absolutely exclude the presence of atherosclerosis. Computed tomography coronary angiography is mandatory for determining the atheroma burden from zero coronary artery calcium score plaques.

Keywords: Coronary calcium scoring; CT coronary angiography; Coronary artery disease stenosis.

Introduction

Coronary artery disease (CAD) is the most important cause of death worldwide, more common in western countries. It seems to be increasing in frequency in the non-industrialized countries as well.[1]

The recent technical development of multi-detector computed tomography (MDCT) has rendered the diagnosis of CAD and calculation of calcium score feasible. This improved the prediction of cardiac events over the conventional risk score.[2] Coronary artery calcium (CAC) score is useful for coronary artery disease risk stratification. A zero CAC score is associated with a very low likelihood of CAD and future cardiac events.[3]

Coronary artery calcification is highly

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https://doi.org/10.15218/zjms.2022.007

specific for atherosclerosis and is thought to be originated as part of the healing mechanism of usually subclinical plaque rupture events.[4] Calcification is one of the components of atherosclerotic plaques and develops late in the atherosclerotic process. As ruptured culprit plaques are not necessarily calcified.[5] As a result, the absence of calcium does not necessarily exclude atherosclerosis. Henneman et al. reported that 39% of patients who present with acute coronary syndrome have a zero calcium score.[6]

Although invasive coronary angiography is the current gold standard test for coronary artery disease[7] however, there are limitations to catheter angiography. It provides information only on the lumen and cannot demonstrate the atherosclerotic changes in the arterial wall. It also carries a non-negligible risk of complication and adds high costs to the patient.

Recently, the use of coronary CT angiography (CTCA) in the imaging of coronary arteries continues to rise for many reasons. Firstly, and in contrast to catheter angiography, it is a noninvasive imaging tool that can simultaneously evaluate the arterial wall and the arterial lumen. Secondly, both calcified and non-calcified plaques can be detected by CTCA with high accuracy. As a result, CTCA has become a favorable noninvasive diagnostic option for detecting coronary artery disease in patients with low to moderate risk.

This study aimed to evaluate the frequency and extent of CAD in patients with zero CAC score using 256 MSCT CTCA and determine the demographic characteristics and the cardiovascular risk factors that affect the formation of non-calcified plaques in these patients.

Methods

A retrospective review of cases was conducted in the department of radiology of the surgical specialty hospital (cardiac center) located in Erbil, Iraqi Kurdistan region, from January 2016 to September 2020.

Study population

A total of 9826 cases were referred to the mentioned department for CTCA and determination of their CAC score during the period mentioned above. In the CAC score examination conducted immediately before CTCA, a total of 2805 cases with no detection of calcified plaques in the coronary arteries (CAC score=zero) were included in the study. Cases were excluded from the study when the CTCA examination was suboptimal and the coronary arteries could not be sufficiently evaluated. Patients with a coronary stent or by-pass grafts were also excluded.

Cardiac CT scanning protocol

A 256-slice MSCT (Briliant ICT, Philips Medical System) was used to assess the patients. All patients had their blood pressure and heart rate measured with the administration of sublingual nitroglycerin before the scan. For patients with an initial heart rate above 65 b/m, beta-blockers were given if no contraindications were present. To calculate CAC score and in advance of CTCA, unenhanced electrocardiographically gated CT images were acquired. This was obtained using the following parameters: collimation, 4 × 3.0 mm; gantry rotation time, 0.25 sec; tube voltage, 120 kV; and tube current, 300 mA, a prospectively triggered at 75% of the RR interval.

The patients' renal functions were assessed prior to the scan by serum creatinine level, and instructions were given to stop caffeine, tobacco, and any other stimulants for 24 hours prior to the scan. Ante-cubital fossa was used to gain intravenous access with a 20G cannula to inject 70-75 ml of non-ionic contrast containing 350 mg of Iodine/ml at a rate of 5-6ml/sec. This was followed by an injection of 40 ml of normal saline. The scan was obtained in a single breath-hold from the pulmonary hilum to the base of the heart. The data were retrospectively gated and reconstructed at 40% and 78% of the RR interval, with reconstructions obtained to assess

https://doi.org/10.15218/zjms.2022.007

different segments further.

Cardiac CT data analysis

CAC score was calculated using the Agatston scoring method, and zero CAC score patients were enrolled in this study. Two experienced observers have carried out interpretations of the CTCA images. As per the American Heart Association model,[8] the coronary arteries were divided into 15 segments, and curved multiplanar reformation (c-MPR) and cross-sectional (CS) images were used to assess segments with a diameter of > 2 mm. The classification of degree of stenosis was as follows: mild <50%, moderate 50-70%, and severe > 70% (Figure 1). The degree of stenosis was divided into four groups, namely i) free of stenosis (normal), ii) mild, iii) moderate, and iv) severe.

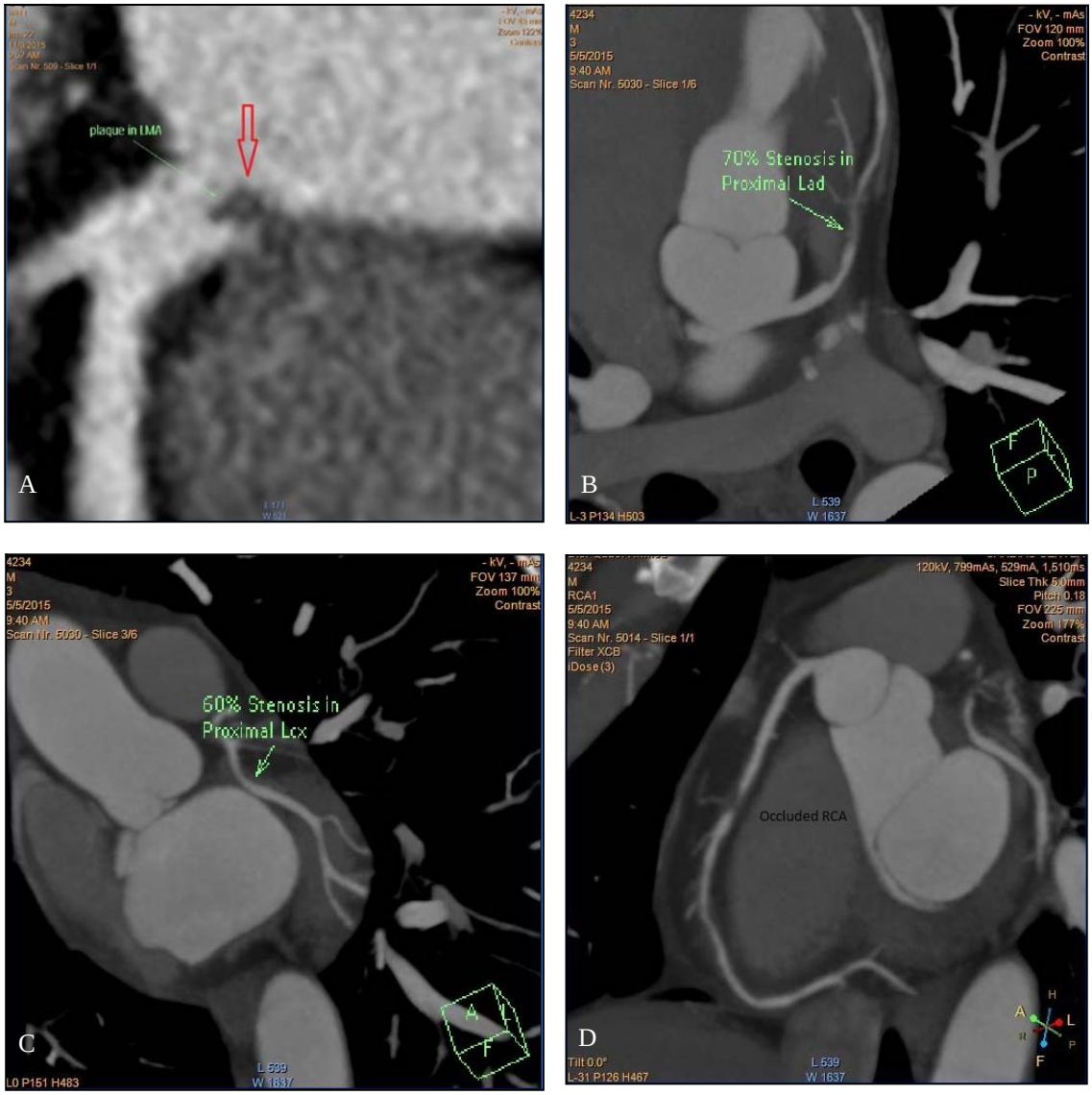

Figure 1 Examples of the severity of stenosis (non-calcified plaque) in different segments of the major coronary arteries A) Left main artery B) Left descending artery C) Left circumflex artery D) Right coronary artery

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Cardiovascular risk factors

The presence of cardiovascular risk factors (diabetes mellitus, hypertension, family history, and smoking) was based on patients' medical records: Diabetes was defined as fasting glucose ≥ 126 mg/dl and hemoglobin A1c ≥ 6.5% or the use of antidiabetic treatment. Hypertension was defined as blood pressure ≥ 140/90 mmHg or the use of antihypertensive medications. Informed consent was obtained from all patients.

Statistical analysis

The data were entered and analyzed using the statistical package for the social sciences (SPSS version 19.0). Chi-square test of association was used to compare proportions and to test for the significance of the associations. Factors significantly associated with the findings (by Chi-square test) were entered in a multivariate binary logistic regression model. The 'CT finding' was either 'normal', 'obstructive', or 'non-obstructive'. Patients with obstructive and non-obstructive lesions were combined into one category, named positive finding. As a result, the finding became binary (either normal or positive) and considered a dependent variable in the regression model. A *P* value of ≤0.05 was considered statistically significant.

Results

The mean (±SD) age of the studied sample was 47.8 ± 11 years, ranging from 14 to 82 years. More than half of the study participants were 35 to 54 years old, and more than half (60.1%) were females.

One third of the sample had hypertension, and 8.8% had both hypertension and diabetes. A relatively small proportion (7%) of the patients were smokers, and 2.9% were drinkers. A family history of ischemic heart disease was found in 20.1% of cases (Table 1).

Table 1 Distribution of sample by demographic and clinical characteristics

	No.	(%)
Age (years)		
< 35	310	(11.1)
35-44	821	(29.3)
45-54	859	(30.6)
55-64	648	(23.1)
65-74	145	(5.2)
≥ 75	22	(0.8)
Sex		
Male	1120	(39.9)
Female	1685	(60.1)
Hypertension &/or diabetes		
None	1519	(54.2)
Hypertension	928	(33.1)
Diabetes	110	(3.9)
Hypertension and diabetes	248	(8.8)
Smoking		
No	2608	(93.0)
Yes	197	(7.0)
Alcohol drinking		
No	2723	(97.1)
Yes	82	(2.9)
Family history of IHD		
No	2226	(79.4)
Yes	579	(20.6)
Total	**2805**	(**100.0**)

https://doi.org/10.15218/zjms.2022.007

Most patients with zero calcium score had normal CTCA results (68.1%), and only 5.1% had stenosis. In the majority of patients with significant stenosis, LAD artery was involved (81.1%), the second vessel involved was RCA (26.5%), then LCX artery (11.1%), but obstructive plaques did not involve LMA. Only a single vessel was involved in most patients with significant CAD (83.9%), while two-vessel disease occurred in 13.3 % of patients and three-vessel disease in 2.8% of patients (Table 2).

No significant association between the presence of symptoms and the findings was detected. As expected, most (93.3%) of asymptomatic patients had no findings (P = 0.134). No significant associations were detected between the findings of chest pain (P = 0.538), palpitation (P = 0.935), and shortness of breath (P = 0.955).

Table 3 shows significant associations between age and sex with the findings. The more the age, the more the proportions of obstructive and non-obstructive lesions. The pattern is consistent through all age groups except for the group of 65-74 years,

where more than half of them were normal (P <0.001). The proportion of normal findings among females (69.4%) was more than males (P = 0.049). It is evident in the table that 74.4% of those with no diabetes or hypertension were normal. This percentage decreased to 51.8% among people with diabetes and 52.8% among those with both diabetes and hypertension. This association was statistically significant (P <0.001). No significant association was detected between family history (P = 0.413), smoking (P = 0.321) and alcohol drinking (P = 0.436) with the findings (Table 3).

Table 2 Distribution of patients by CTCA results, the vessel involved, and the number of vessels involved in patients with critical stenosis

	No.	(%)
CTCA results		
Normal	1909	(68.1)
Obstructive	143	(5.1)
Non-obstructive	753	(26.8)
Total	2805	(100.0)
The vessel involved (N = 143)*		
LMA	0	(0.0)
LAD	116	(81.1)
LCX	16	(11.1)
RCA	38	(26.5)
No. of vessels involved in patients with critical stenosis		
Single vessel disease	120	(83.9)
Two vessel disease	19	(13.3)
Three vessel disease	4	(2.8)
Total	143	(100.0)

*More than one vessel may be involved in one patient.

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Table 3 Association between the CTCA results and the studied variables

		Findings						
		Normal		Obstructive		Non-obstructive		
Variables	**N**	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**	***P* value**
Symptoms								
Asymptomatic	15	14	(93.3)	0	(0.0)	1	(6.7)	
Symptomatic	2790	1895	(67.9)	143	(5.1)	752	(27.0)	0.134*
Chest pain								
Present	2675	1815	(67.9)	138	(5.2)	722	(27.0)	
Absent	130	94	(72.3)	5	(3.8)	31	(23.8)	0.539
Palpitation								
Present	27	19	(70.4)	1	(3.7)	7	(25.9)	
Absent	2778	1890	(68.0)	142	(5.1)	746	(26.9)	0.935
Shortness of breath								
Present	88	61	(69.3)	4	(4.5)	23	(26.1)	
Absent	2717	1848	(68.0)	139	(5.1)	730	(26.9)	0.955
Age								
<35	310	290	93.5	5	1.6	15	4.8	
35-44	821	675	82.2	23	2.8	123	15.0	
45-54	859	545	63.4	40	4.7	274	31.9	
55-64	648	314	48.5	51	7.9	283	43.7	
65-74	145	77	53.1	20	13.8	48	33.1	
≥75	22	8	36.4	4	18.2	10	45.5	<0.001
Sex								
Male	1120	739	66.0	69	6.2	312	27.9	
Female	1685	1170	69.4	74	4.4	441	26.2	0.049
Diabetes and / or hypertension								
None	1519	1130	74.4	62	4.1	327	21.5	
HT	928	591	63.7	40	4.3	297	32	
DM	110	57	51.8	13	11.8	40	36.4	
DM+HT	248	131	52.8	28	11.3	89	35.9	<0.001
Family history								
No	2226	1526	68.6	115	5.2	585	26.3	
Yes	579	383	66.1	28	4.8	168	29	0.413
Smoking								
No	2608	1782	68.3	129	4.9	697	26.7	
Yes	197	127	64.5	14	7.1	56	28.4	0.321
Alcohol								
No	2723	1851	68	137	5	735	27	
Yes	82	58	70.7	6	7.3	18	22	0.436
Total	2805	1909	68.1	143	5.1	753	26.8	

*By Fisher's exact test. The other p values were calculated by Chi-square test.

https://doi.org/10.15218/zjms.2022.007

In multiple logistic regression, older ages, male sex, diabetes, and hypertension were independent significant predictors of the positive findings, whether obstructive or non-obstructive lesions (Table 4).

Discussion

Results showed that non-calcified plaques caused non-significant stenosis (<50%) in 26.8% of the patients with zero CAC score and significant stenosis (>50%) in only 5.1% of these patients, while 68.1% were normal. These results are consistent with previous studies that reported the presence of non-calcified plaques in patients with a zero CAC score at varying frequencies in the literature. These rates were reported to be 12% by Sosnowski et al.,[9] and 20% by Ergün et al.[10] However, Gabriel et al.[11] reported a rate of 9.3%. These different rates may have resulted from the differences in the characteristics of the patient populations that were included in the studies.

It is important to determine which patients with zero CAC score are at risk for CAD and which CTCA results will provide beneficial information regarding this risk. Varying results were obtained in studies that examined whether patients were symptomatic or asymptomatic. In a study by Mittal et al.,[12] patients with stable symptoms and a zero-calcium score have an extremely low prevalence of obstructive CAD and an excellent prognosis over the medium to long-term. However, Ergün et al.[10] did not find a correlation between symptoms and obstructive and non-obstructive lesions.

In our study, although the number of asymptomatic patients was low (only 15 patients were included), no obstructive plaques were recorded among this group. While among symptomatic patients, only around 5% of them had obstructive plaques, and we found that there is no strong correlation between symptoms and obstructive plaques.

Results regarding the detection of conventional cardiovascular risk factors for patients with a zero CAC score and whether it is beneficial in estimating the presence of atherosclerotic plaque using CTCA were variable.

Table 4 Logistic regression analysis between positive finding (obstructive or non-obstructive) as a dependent variable with several covariates

Covariates	B	*P* value	OR	95% CI for OR	
				Lower	Upper
Age (years)		< 0.001			
< 35 (reference)					
35-44	1.172	< 0.001	3.229	1.977	5.273
45-54	2.203	< 0.001	9.054	5.592	14.662
55-64	2.836	< 0.001	17.047	10.430	27.862
65-74	2.661	< 0.001	14.305	8.076	25.339
≥ 75	3.324	< 0.001	27.772	10.241	75.315
Male sex	0.654	< 0.001	1.923	1.597	2.316
Diabetes &/or hypertension		< 0.001			
None (reference)					
Hypertension	0.266	0.008	1.305	1.073	1.586
Diabetes	0.779	< 0.001	2.179	1.432	3.315
Both	0.593	< 0.001	1.809	1.348	2.429
Constant	-3.191	< 0.001	0.041		

https://doi.org/10.15218/zjms.2022.007

Overall results of this study showed that the male gender, smoking, increasing age, diabetes, and hypertension were significant risk factors for the presence of non-calcified plaques using CTCA in patients with zero CAC score based on the multivariate logistic regression analysis.

These findings were in agreement with Uretsky et al.[13] who reported that the male gender, age, and smoking were risk factors. In contrast, Ueda et al.[14] reported that diabetes and hypercholesterolemia were risk factors. Interestingly, Ergün et al.[10] reported that age and diabetes were risk factors for both genders. However, dyslipidemia was a risk factor for male patients only, and family history was a risk factor for female patients alone.

In this study, obstructive plaques were most frequently involving LAD artery (81.2%), followed by RCA (26.5%), then LCX artery in (11.18%) of cases. The pattern of obstructive plaques was as follows: a single vessel was involved in 83.91% of cases, two vessels were involved in 13.2% of cases, while three vessel disease affected only 2.7% of patients with obstructive plaques. This finding is consistent with other observations regarding the tendency of plaques to occur more frequently in the LAD and indicates that this tendency was similar among the plaques that were detected in patients with a zero CAC score.[15,16]

It is important to state that this study has a few limitations. Firstly, most of the patients' ethnic backgrounds whose images were used for analysis were similar. Secondly, the gold standard intravascular ultrasound of invasive coronary angiography was not performed to detect the obstructive non calcified coronary plaques. Thirdly, the studied population was not followed up to examine the outcomes. This could identify the clinical importance of diagnosing non-calcified plaques in patients with zero CAC score. Fourthly, Radiation exposure from CTCA is a matter of concern even though CTCA is recommended for some patients who score zero for CAC. The mean radiation exposure of CTCA is estimated to be high.[17] To minimize this dose and reserve the image quality, different techniques are used, such as the appropriate reduction of tube voltage or tube current, prospective electrocardiogram-gated scanning, and iterative reconstruction techniques.[18,19] Additionally, further developments that could significantly reduce the radiation dose are promising. This includes CT hardware developments, such as wider coverage scanners, faster gantry rotation speeds, and higher pitch scanning.[19]

Conclusion

The frequency of non-calcified plaques detected by CTCA examination in patients with zero CAC score is too high to be ignored. The absence of calcium in coronary arteries does not necessarily rule out coronary artery atherosclerosis. The early detection of non-calcified plaques is important because these plaques are unstable and tend to rupture but are responsive to medical treatment. Patients with zero CAC score and cardiovascular risk factors need to be evaluated by additional tests to detect non-calcified plaques. CTCA can detect coronary atherosclerosis noninvasively and highly accurate; therefore, it can be used as a preferred imaging method for detecting non-calcified plaques.

Funding

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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