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Coronary artery anomalies in patients with zero calcium score: A new evidence supports the 2016-NICE guidance

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ABSTRACT

Background: Currently, guidelines from around the world endorse measurement of coronary artery calcium (CAC) to improve clinical risk prediction in appropriately selected asymptomatic and stable symptomatic individuals. A CAC score of zero may discourage from further testing as coronary computed tomography angiography (CCTA). We investigate the presence of malignant coronary artery anomalies (CAA)s among stable symptomatic patients with zero CAC.

Methods: A total of 281 individuals' information was obtained. These individuals had low to intermediate pre-test probability of coronary artery disease, complained of stable typical or atypical chest pain, were not known to have CAD, and had CAC scan score of zero. After investigating the CCTA, Angelini's classification system for CAA was utilized in adapted form to determine the presence, the class and type of the CAA.

Results: The CAAs were detected in 16 (5.7 %) patients on CCTA, 15 (8.1 %) of them were below 45 years. The mean age for patients with CAAs was 31.8. According to Angelini classification system, most of the detected CAAs were malignant such as the origination of the coronary artery from the opposite sinus with arterial course between the aortic and pulmonary trunks and the intramural muscular bridge course.

Conclusion: It is preferable to perform CCTA in young patients with cardiac symptoms, especially in Asian and Middle Eastern countries even of the CAC score is zero.

1. Introduction

Over the past two decades, non-contrast cardiac computed tomography has become an established diagnostic tool in clinical practice [1,2]. The main purpose of these coronary calcium scans is to obtain the coronary artery calcium (CAC) score, which is associated with a graded and greater risk of future coronary artery disease (CAD), heart failure and mortality [3,4]. On the other hand, a negative or zero CAC score indicates a mid- to long- term risk of coronary events that is close to zero [5]. Currently, guidelines from around the world endorse measurement of CAC to improve clinical risk prediction in appropriately selected asymptomatic individuals [6,7]. Also, according to many previous guidelines and practice of some institutions, in stable symptomatic patients with low-to-intermediate pre-test probability of obstructive CAD which applied to the vast majority of patients being referred for advanced imaging procedures, a CAC score of zero would generally signify no need for further testing as coronary computed tomography angiography (CCTA) or invasive coronary angiography (ICA) [8–10].

Coronary artery disease is one of the leading causes of morbidity and mortality worldwide. Among these, coronary artery anomalies (CAAs), although less prevalent, are a potential source of malignant arrhythmias, ischemia and myocardial dysfunction [11]. In young individuals, CAAs are the second most common cause of sudden cardiac death (in 17 % of deaths) and are generally triggered by vigorous physical exercise [12]. Although most of these anomalies are inherently

Abbreviations: CAA, coronary artery anomalies; CAC, coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; ICA, invasive coronary angiography

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benign, some are associated with myocardial ischemia, angina, acute coronary events, arrhythmias, and sudden cardiac death [13–15]. In this article, we evaluate the presence of malignant CAAs among stable symptomatic patients with zero CAC who; according to some guidelines and institutions; may not be offered angiography especially in young age group.

2. Material and methods

This study was conducted at a tertiary medical educational institute. After obtaining the Institutional Review Board approval, we retrospectively identified and retrieved data on individuals who underwent CAC scan with zero score from January 2016 to March 2018. The following information were obtained: standard demographic information (age, sex), clinical presentation, CCTA images, and follow up information.

Only patients presented with low to intermediate pre-test probability of CAD, with stable typical or atypical chest pain, without history of CAD, and with CAC scan of zero were included. A total of 281 individuals' information was obtained. These individuals referred from our cardiology outpatient clinics and they offered CAC scan and CCTA as a cases of low-to-intermediate pre-test probability stable angina patients. The CAC score for all individuals was zero.

After investigating the CCTA, modified Angelini's classification system for CAA was utilized to determine the class and type of the CAA if present in these individuals. The classed are summarized in the Supplementary Table.

The CAC scores were measured by computed tomography of the coronary arteries. Multi-detector computed tomography was performed and multi-slice computed tomography scanner was used. After lying supine on the tomography table, the electrocardiographic monitoring electrodes were placed to synchronize image capture and heart rate observation during the examination. The acquisition is prospective in synchrony with the electrocardiogram at a predetermined moment in the R-R interval, usually in the mid/late diastole without intravenous contrast administration. The effective dose of radiation is usually less than 1.5 mSv. The operator recorded an average of 136 cardiac image slices, which also included the coronary arteries. Axial chest images were captured in a window from the aortic root to the apex of the heart. Forty contiguous transverse images 2.5–3.0 mm thick were captured at the moment of diastole, with a 15-second inspiratory pause. The test was performed without the use of medications or contrasts and without specific preparation. The CAC score was obtained from calcification fragments measured using the calcification index; age correction was performed, and the results were classified according to degree of calcification according to the Calcium volume scoring method: for a CAC score of zero there was no calcification. Calcification is identified as areas of hyper-attenuation of at least 1 mm2-with > 130 Hounsfied units or ≥3 adjacent pixels. After that, contrast material was injected to demonstrate the coronary arteries for any obstructive CAD. All the CAC scan and CCTA images were studied and reviewed by two expert radiologists (one of them was with 29 years of experience and the other one with 7 years of experience) independently and they were blinded about the identifying data for the individuals.

All individuals were stable symptomatic, were low to intermediate risk based on the pre-test probability for CAD and were not known to have CAD. As a general protocol in our institution, the intermediate and low risk individuals with stable symptoms are offered CAC scan followed by CCTA.

Data were entered into a spreadsheet. Statistical analyses were performed using IBM SPSS Statistics Software (v.21), 2012. Data were presented as frequency distributions for categorical variables and mean ± standard error of the mean for continuous variables. Data was tested at a significance level of 0.05 %. Pearson $\chi 2$ test was used to investigate the significance of association between categorical variables, while student's *t*-test was applied to examine the significance level for continuous normally distributed variables. The $P < 0.05$ is the significant relationship between variables.

Table 1
Individuals characteristics and Results.

General Frequency		
Sex, n (%)	**Number**	**Percent %**
Male	130	46.3
Female	151	53.7
Age Groups	**Number**	**Percent %**
Young	185	65.8
Elder	96	34.2
CAA	**Number**	**Percent %**
Yes	16	5.7

Distribution CAA within age groups	Young, N (% within young patients)	Elder, N (% within elderly patients)	*P*-value
Presence of CAA	15 (8.1 %)	1 (1.0 %)	0.005

Sex differences for the presence of CAA	Male	Female	*P*-value
Presence of CAA	10 (7.7 %)	6 (4.0 %)	NS

Abbreviation: CAA: Coronary artery anomaly; NS: not significant.

3. Results

The study included 281 individuals (130 males and 151 females). Young patients below the age of 45 years were 185 individuals The CAAs were detected in 16 (5.7 %) patients on CCTA, 15 (8.1 %) of them were below 45 years. The mean age for patients with CAAs was 31.8. The sex did not reveal any difference for the presence of CAAs. The presence of CAA was significantly higher in young patients comparing to elder ($p < 0.05$). All patients with CAAs presented with chest pain especially with exercise. Two of them had family history of sudden death at young ages (Table 1).

According to Angelini classification system, these CAAs were as follow: three cases of left coronary artery originating from right sinus with arterial course between the aortic and pulmonary trunks Fig. 1, four cases of right coronary artery originating from left sinus with arterial course between aortic and pulmonary trunk Fig. 2, three cases of left anterior descending artery originating from right sinus with arterial course between the aortic and pulmonary trunks Fig. 3, and four cases of intramural muscular bridge course of the left anterior descending Fig. 4. Moreover, one case of double right coronary artery and one case of dominant left coronary artery (in the elder patient) were detected.

Of those 16 patients, 4 of them underwent revascularization treatment. Another three individuals lost their follow up. The remaining individuals of class 3 did not receive surgical treatment with only close follow up.

4. Discussion

To best of our knowledge, this is the first study that reveal the presence of significant number of malignant CAA in young patient who presented with stable cardiac symptoms and the result of CAC score was zero. This guide us to the importance of managing and investigating these patients with CCTA.

CAC is indicated by calcium deposits in the coronary artery wall. Calcification is a component of atherosclerosis and CAD [16,17]. There is a strong relationship between the amount of CAC and coronary plaques [18]. Moreover, it has been demonstrated that CAC scan can be used to predict risk of CAD in both symptomatic and asymptomatic patients [6–10]. The CAC score is a well-established test for risk stratifying asymptomatic patients, is an independent predictor of long-term prognosis, and performs better than many other risk-stratifying tools.

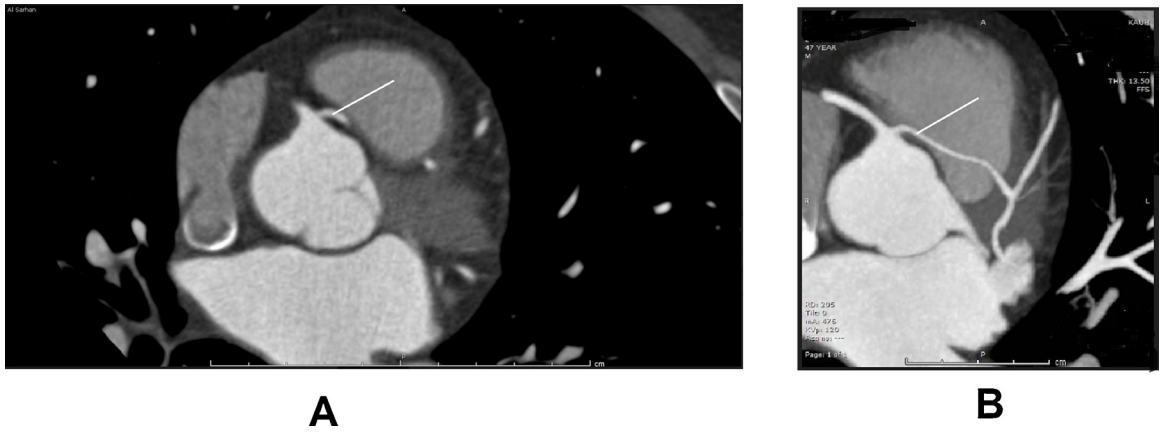

Fig. 1. CCTA axial view shows the left coronary artery originate from right sinus (A) and take it course in acute angle between the aorta and pulmonary trunk (B). The left coronary artery is indicated by the white arrow.

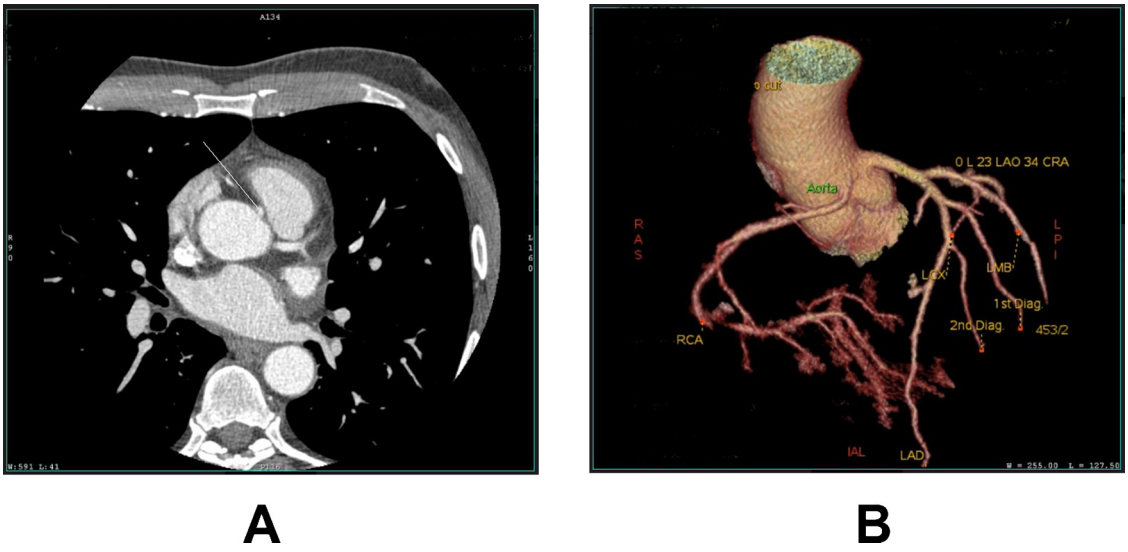

Fig. 2. (A) Two-dimensional CCTA axial view indicating the malignant course of the right coronary artery which arises from the left coronary sinus, passing between the pulmonary trunk and ascending aorta. The artery is indicated by arrow. (B) Three-dimensional CCTA demonstrates the origin of right artery from left sinus.

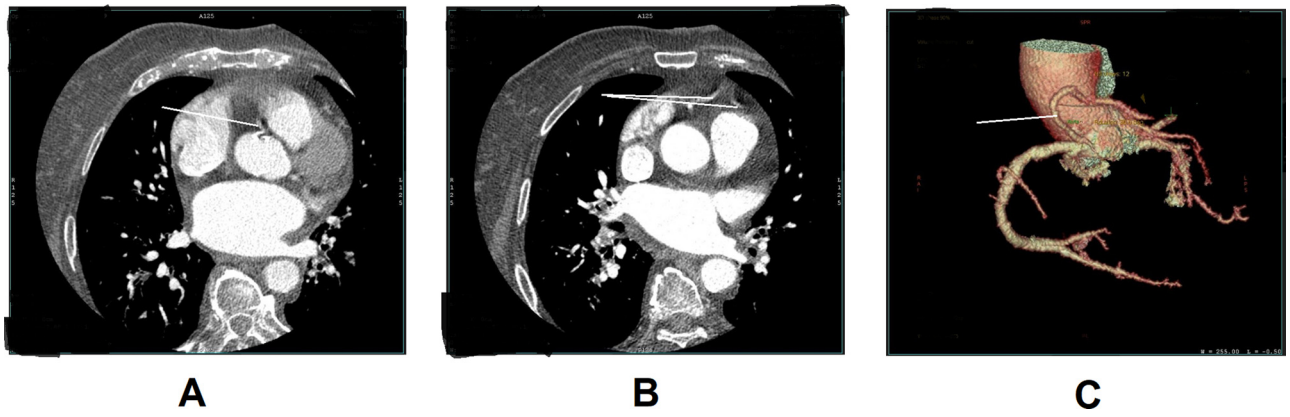

Fig. 3. Two-dimensional CCTA axial view (A, B) demonstrates the origin of left anterior descending artery (A) from the right sinus and its long and malignant course (B). (C) Three-dimensional CCTA for the left anterior descending artery originating from right sinus. The left anterior descending artery is indicated by arrow.

According to the most recent American Heart Association and American College of Cardiology Foundation guidelines, CAC score has class IIA and IIB recommendations for assessing risk in intermediate- and low- to intermediate-risk asymptomatic patients, respectively [19–21]. In addition, the presence of CAC among individuals aged between 32 and 46 years was associated with increased risk of fatal and nonfatal CAD during 12.5 years of follow-up. A CAC score of 100 or more was associated with early death [22].

For symptomatic patients with stable symptoms, Sarwar et al., 2007 ACC/AHA expert consensus statement and recent National Institute for

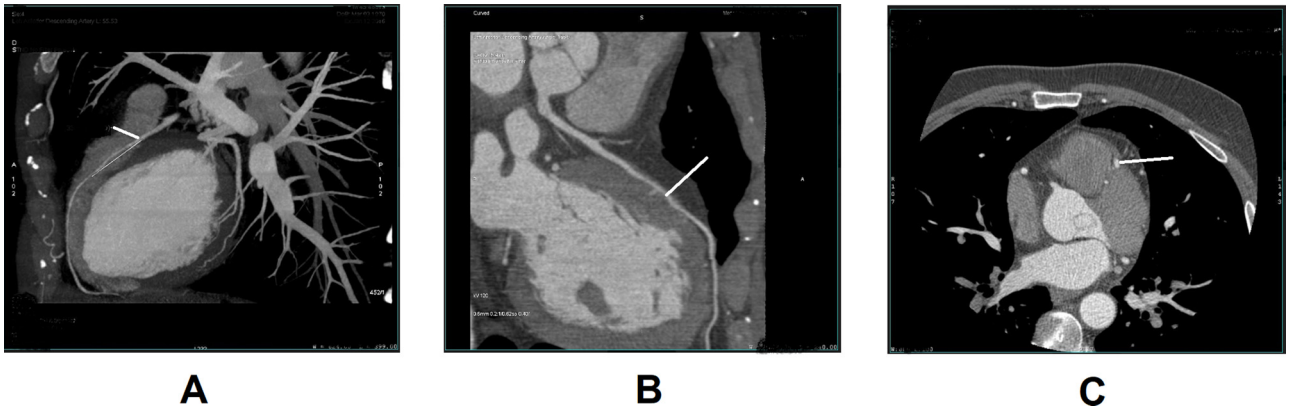

Fig. 4. (A, B) CCTA sagittal view for the of left anterior descending artery through its malignant intramural course "muscular bridging". (C) CCTA axial view for bridging of the left anterior descending artery. The left anterior descending artery is indicated by arrow.

Health and 2010 National Institute for Health and Care Excellence (NICE) guidelines stated that the use of CAC testing for low-risk, stable symptomatic patients, where CAC testing is used as a filter for further cardiovascular testing in a binary fashion (CAC present or absent). Specifically, patients without CAC (CAC = 0) avoid further cardiovascular testing (CAD ruled out) and those with any CAC (CAC > 0) receive additional testing, such as CCTA or ICA [8–10]. However, Villines et al. concluded that in symptomatic patients with a CAC score of 0, obstructive CAD is possible and is associated with increased cardiovascular events. CAC scoring did not add incremental prognostic information to CCTA [23]. Subsequently NICE updated their guidelines in 2016 and recommended the use of CCTA as the first-line investigation for patients with stable angina and no prior CAD, irrespective of pre-test probability, with second-line functional imaging if required [24]. Ruckel and Gulat, and Rozanski and Berman pointed out that this issue requires prospective evaluation to assess its potential impact on patients' clinical outcomes [25,26]. This study supports the new NICE guidance and emphasize on the importance of prospective evaluation based on serious observation of significant number of young patients with CAA who had a CAC = 0.

Most CAA have no clinical significance, although a minority have been documented to have increased risk of myocardial infarction and ischemia, congestive heart failure and sudden cardiac death. CAA are the second leading cause of sudden cardiac death in the young exceeded only by hypertrophic cardiomyopathy [27]. Those with the highest risk include individuals with an anomalous coronary artery originating from the opposite sinus [28]. This risk increases to that CAA which take an inter-arterial course between the aorta and pulmonary artery, and this has been documented in both anomalous origins of the right coronary artery from the left coronary sinus and in anomalous origins of the left coronary artery from the right coronary sinus [29–31]. Other anatomical features which are associated with high risk include intra-mural course "muscular bridging", slit-like orifice and angulated take-off which are all thought to contribute to myocardial ischemia [32]. In this study, we report significant number of CCAs most of them harbor lethal potential.

Alkhulaifi et al. reported that Asian and Middle Eastern population have a relatively higher incidence of malignant CAA, with passage of the major aberrant trunk between the two great vessels [33]. This could be explained by higher relative marriage in these countries which facilitates the transmission of any genetic or genetic-related disorder.

Our study is not without limitation, first, it is a retrospective single center study, further multicenter prospective studies are recommended. Many of patients were lost follow up. In addition, as expected, most patients were young individuals because the included individuals were with low- to intermediate- pre-test probability.

5. Conclusion

It is preferable to perform CCTA in young patients with cardiac symptoms, especially in Asian and Middle Eastern countries even if the CAC score is zero. These data support the implantation of the new NICE guidelines. Moreover, it is important to consider the CAAs as causative factor for chest pain in young. In the debate between the protagonists and antagonists to use CAC scanning as a gatekeeper for further testing among chest pain patients with a low-intermediate likelihood of CAD, the presence of significant number of malignant CAA among young individuals rises the necessity for prospective evaluation study. It is worth to consider the CAA in these future prospective studies.

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Ethics and patient consent

Written informed consent was obtained from the patients for publication. Institutional approval was obtained from the Institutional Review Board at Jordan University of Science and Technology. This study was conducted in accordance with the Declaration of Helsinki.

DData availability

The datasets generated and analyzed during the current study are available from the corresponding author.

Declaration of Competing Interest

There are no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejro.2019.12.005.

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