



## Total cholesterol/high-density lipoprotein cholesterol and low-density lipoprotein cholesterol/high-density lipoprotein cholesterol as predictors of coronary artery calcification assessed by multidetector computed tomography coronary angiography

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### Original Article

#### Abstract

**BACKGROUND:** Coronary artery calcification (CAC) is an important marker of total burden of coronary atherosclerosis. Furthermore, it is a measure of subclinical atherosclerotic disease that correlates well with the cardiovascular risk. The aim of our study was to determine the role of the different lipid parameters in prediction of calcification in coronary arteries using multidetector computed tomography (MDCT).

**METHODS:** This study was conducted on 120 patients presenting to the clinic with typical or atypical chest pain or dyspnea on exertion, or equivocal stress test results along with standard cardiac risk factors; they all underwent computed tomography (CT) coronary angiography. A total calcium score was determined by summing individual lesion scores from each of our anatomic sites: left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA). The amount of calcium present in the coronary arteries was scored according to Agatston score, and patients were divided into 2 groups based on absence (group I) and presence (group II) of CAC. Clinical characteristics, lipid ratios, and a full blood count were calculated and compared between both groups.

**RESULTS:** Mean and standard deviation (SD) for age of group I was  $52.4 \pm 8.4$  years, while that of group II was  $53.7 \pm 7.9$  ( $P > 0.005$ ). Patients in group II had a higher total cholesterol (TC), low-density lipoprotein (LDL), TC/high-density lipoprotein cholesterol (HDL-C) and LDL/HDL-C ratio, and lower HDL levels. TC/HDL ratio and LDL/HDL ratio were found to be good predictors of calcium using a regression analysis model. Finally, at a cut-off value of  $\geq 3.108$ , LDL/HDL ratio showed a sensitivity of 58.8% and specificity of 84.6% in prediction of coronary calcium, while TC/HDL ratio  $\geq 4.742$  showed a sensitivity of 60.3% and specificity of 88.5%.

**CONCLUSION:** Amongst the different lipid parameters, TC/HDL-C and LDL/HDL ratio were found to be good predictors of presence of CAC in coronary arteries.

**Keywords:** Dyslipidemia; Atherosclerosis; Coronary Artery Disease

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#### Introduction

In the last few decades, the association between elevated lipid levels and cardiovascular disease (CVD) has been well-established. However, the extent to which components of blood lipids directly promote CVD or represent a biomarker of risk has been debated, especially for the triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C).<sup>1</sup> Several new markers have been introduced as alternative means to refine risk estimation beyond low-density lipoprotein cholesterol (LDL-C) from Friedewald's formula in the presence of CVD, such

as non-HDL-C, total cholesterol (TC)/HDL-C ratio, non-HDL-C/HDL-C, and the apolipoprotein B (apoB)/apolipoprotein A-I (apoA1) ratio.<sup>2</sup>

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A low level of HDL-C is a well-known strong and independent predictor of CVD.<sup>3</sup> Studies have also shown that increased levels of LDL-C play a role in the development and progression of atherosclerosis.<sup>4</sup> Moreover, previous studies reported that statin-induced changes in the ratio of LDL-C to HDL-C (LDL-C/HDL-C ratio) predicted atherosclerosis progression.<sup>5</sup> It is, therefore, important to observe not only HDL-C or LDL-C alone but also their ratios.

However, despite numerous studies highlighting the role of dyslipidemia in development and progression of atherosclerosis, little information is available regarding the predictive value of the LDL-C/HDL-C and TC/HDL-C ratio for prediction of coronary artery calcification (CAC).

Our aim was to study the relation between lipid profile including TC, TG, HDL-C, LDL-C, and the two deduced indices (TC/HDL-C and LDL-C/HDL-C) and the degree of calcification assessed using multidetector computed tomography (MDCT) in patients at low and intermediate risk.

## Materials and Methods

**Study population:** This was a case-control study held in Zagazig University hospitals, Zagazig, Egypt, between March 2019 and March 2020. All patients gave their written informed consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved

by institution's ethics committee of faculty of medicine, Zagazig University, Egypt. (reference number: 3364/10-7-2018) with waiver of individual consent.

Patient population is shown in figure 1. Of a group of 900 patients referred to our outpatient clinic 120 patients who had a 5%-90% pretest probability of coronary artery disease (CAD) were selected to undergo computed tomography (CT) coronary angiography. Patients included were those presenting to the clinic with typical or atypical chest pain or dyspnea on exertion, or equivocal stress test results along with standard cardiac risk factors.

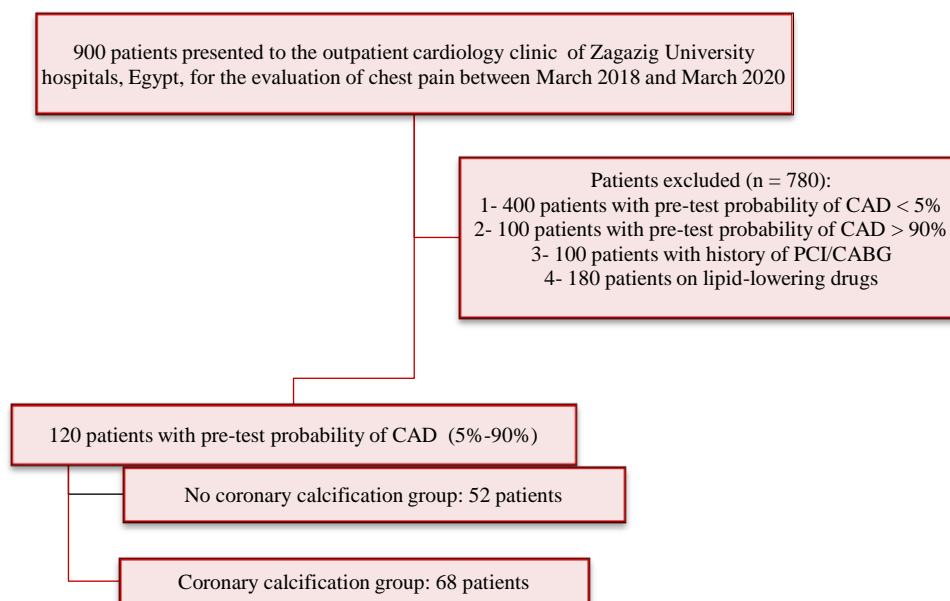
Patients with a pretest probability < 5% (n = 400) and those with a probability of > 90% (n = 100) were excluded. Furthermore, those with history of percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG) (n = 100) or on lipid-lowering drugs (n = 180) were excluded.

Patients were divided into 2 groups based on presence or absence of CAC:

Group I: No calcium according to Agatston score

Group II: Presence of mild moderate or severe calcification of coronaries

Clinical characteristics, lipid parameters, and laboratory test information of the study patients were collected. Lipid ratios were calculated and recorded. The definitions of hypertension (HTN), diabetes mellitus (DM), and dyslipidemia were reported in previous studies.<sup>6</sup>



**Figure 1.** Flowchart showing patient selection criteria (CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting)

Family history of premature coronary heart disease (CHD) was defined as CHD in first-degree male relatives  $\leq 55$  years of age or female relatives  $\leq 65$  years old. Waist circumference (WC) measurement was done using a tape; the correct place to measure the waist is horizontally halfway between the lowest rib and the top of the hipbone. This is roughly in line with the belly button.

**Laboratory results:** For all patients, complete blood counts (CBC) with automated differential counts were performed. CBC analysis was performed in samples anti-coagulated with ethylenediaminetetraacetic acid (EDTA) within 30 minutes after collection, using an automated cell counter (Sysmex KX21-N, Kobe, Japan). The neutrophil to lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count (ANC) by the absolute lymphocyte count (ALC); likewise, platelet-to-lymphocyte ratio (PLR) was calculated by dividing the absolute platelet count by ALC.

**Image acquisition and measurement of CAC:** All CT scans were performed on the Siemens Somatom Definition Flash which is a second generation dual-source 128-slice CT scanner. All images were acquired in cranio-caudal direction and electrocardiographic (ECG) gating. Prospective acquisition was done in all patients. The acquisitions were done in diastole over a single end-inspiratory breath-hold period (few seconds were required for whole breath-hold). Acquired images were constructed using B35 kernel; reconstruction increment was 3 mm resulting in a 50% overlap. ECG-triggered images were acquired at 80% of the R-R interval during an end-inspiratory breath-hold period.

**Measuring CAC:** All images were electronically transferred to one dedicated work station for evaluation (Leonardo, Siemens, Forchheim, Germany). CAC was defined as a hyperattenuating lesion  $> 130$  Hounsfield units (HU) with an area  $> 3$  pixels. Baseline CAC was quantified by calcium score which was calculated by multiplying the lesion area ( $\text{mm}^2$ ) by a density factor (between 1 and 4). A total calcium score was determined by summing individual lesion scores from each of our anatomic sites: left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA). The amount of calcium present in the coronary arteries was scored according to Agatston score; this was done by two experienced image analysts. Its calculation was based on the weighted density score given to the highest attenuation value (HU) multiplied by the area of the calcification speck (Density factor: 130-199 HU: 1, 200-299 HU:

2, 300-399 HU: 3, 400+ HU: 4).

**Statistical analysis:** All analyses were performed using the SPSS (version 20.0, IBM Corporation, Armonk, NY, USA) software package. Continuous variables were presented as mean and standard deviation (SD). Categorical variables were presented as number (percentages). All data were tested for normal distribution with the Kolmogorov-Smirnov test. Differences between frequencies (qualitative variables) and percentages in groups were compared by chi-square test and differences between parametric quantitative independent groups by t-test. P-value was set at  $< 0.05$  for significant results and  $< 0.001$  for highly significant results. Receiver operating characteristic (ROC) curve analysis was constructed at the most discriminating cut-off value aimed to document the predictive power of the lipid ratio for moderate calcium. A two-sided  $P < 0.05$  was considered statistically significant. The best cut-off values were expressed using the Youden index. The area under the ROC curve (AUC) also was calculated. We tried to avoid information bias through prospective collection of data, using standardized method for measurement of lipid profile. Wald test was used to assess the significance of each independent variable in a binary logistic regression model.<sup>7</sup>

## Results

In a total of 120 patients who underwent CT coronary angiography during the study period, 52 patients had no calcium (group I) and 68 had CAC (CAC score  $\geq 1$ ), based on Agatston score. Compared to group I, CAC group had higher frequency of  $> 50\%$  coronary lesions (57.4% vs. 21.2%,  $P < 0.001$ ).

Table 1 shows baseline characteristics of study groups and the mean lipid indices in both groups. Mean age of group I was  $52.4 \pm 8.4$  years, while that of group II was  $53.7 \pm 7.9$ . There was no significant difference between groups in all variables including age, gender, WC, body mass index (BMI), DM, HTN, smoking, and family history of premature CAD.

A comparison between lipid profiles of the two groups showed that group II had a significantly higher mean TC ( $P = 0.022$ ), LDL-C, TC/HDL ratio, and LDL/HDL ratio ( $P < 0.001$ ). Furthermore, they had significant lower HDL-C compared to patients in group I ( $P < 0.001$ ).

Binary logistic regression analysis for defining the independent variables associated with coronary calcification was shown in table 2.

**Table 1.** Basic characteristics of the study groups

	Group I* (n = 52)	Group II** (n = 68)	P
Age (year)	52.4 ± 8.4	53.7 ± 7.9	0.374
Gender			
Women	4 (7.7)	8 (11.8)	0.461
Men	48 (92.3)	60 (88.2)	
WC (cm)	99.9 ± 8.3	102.3 ± 6.5	0.074
BMI (kg/m <sup>2</sup> )	30.2 ± 1.1	30.3 ± 1.3	0.805
HTN	34 (65.4)	51 (75.0)	0.251
DM	26 (50.0)	32 (47.1)	0.749
Smoking	40 (76.9)	50 (73.5)	0.671
Positive family history	32 (61.5)	32 (47.1)	0.115
FBS (mg/dl)	106.7 ± 22.5	104.7 ± 15.1	0.566
HbA1C (%)	5.9 ± 0.7	6.0 ± 0.8	0.641
TC (mg/dl)	204.3 ± 21.7	215.8 ± 32.6	0.022
LDL (mg/dl)	126.8 ± 21.7	144.5 ± 23.9	< 0.001
HDL (mg/dl)	52.9 ± 16.3	45.1 ± 9.9	0.001
TG (mg/dl)	162.7 ± 71.1	183.4 ± 94.1	0.189
TC/HDL ratio	4.1 ± 0.8	5.0 ± 1.4	< 0.001
LDL/HDL ratio	2.5 ± 0.7	3.4 ± 0.9	< 0.001

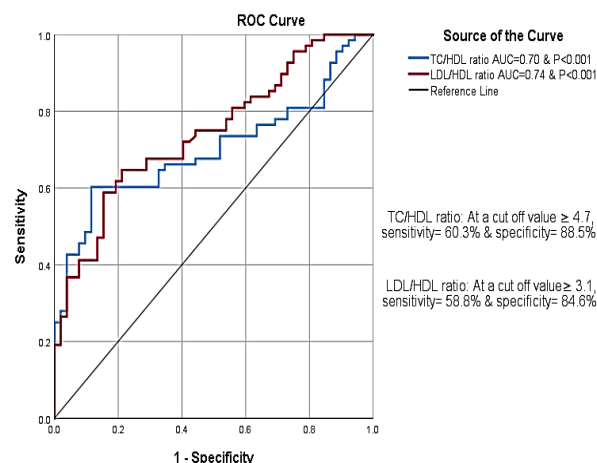
Data are presented as mean ± standard deviation (SD) or number and percentage

\*No coronary artery calcification (CAC) detected; \*\* CAC detected

WC: Waist circumference; BMI: Body mass index; HTN: Hypertension; DM: Diabetes mellitus; FBS: Fasting blood sugar; HbA1C: Hemoglobin A1C; TC: Total cholesterol; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride

LDL, TC/HDL, and LDL/HDL were all found to be significantly associated with CAC (P = 0.02, P = 0.005, and P < 0.001, respectively).

ROC curve analysis was performed for TC/HDL and LDL/HDL ratios for prediction of CAC (Figure 2). At a cut-off value of  $\geq 3.1$ , LDL-C/HDL-C ratio showed a sensitivity of 58.6%, specificity of 84.6%, and an AUC of 0.74, while TC/HDL-C ratio  $\geq 4.742$  showed a sensitivity of 60.3%, specificity of 88.5%, and an AUC of 0.7, in prediction of coronary calcium. Using the cut-off values deduced from the ROC, we performed binary logistic regression (crude and adjusted) shown in table 3 and found that TC/HDL  $\geq 4.742$  was significantly associated with calcification of coronaries [odds ratio (OR): 5.6, confidence interval (CI): 1.19-26.53, P = 0.029]. However, LDL/HDL was not significant at the deduced cut-off value (OR: 1.48, CI: 0.32-6.88, P = 0.612).



**Figure 2.** Receiver operating characteristic (ROC) curve showing sensitivity and specificity of different lipid indices in detection of coronary artery calcium (CAC) by multidetector computed tomography (MDCT)

**Table 2.** Binary logistic regression analysis of independent variables significantly associated with coronary calcification

Variables	B	SE	Wald	P	OR (95% CI)	Goodness-of-fit (Hosmer-Lemeshow)
TC	-0.030	0.04	0.620	0.430	0.97 (0.91-1.00)	P = 0.090
LDL	0.020	0.01	5.570	0.020*	1.20 (1.10-1.30)	
HDL	-0.001	0.04	0.002	0.970	0.99 (0.93-1.10)	
TC/HDL ratio	0.610	0.21	8.020	0.005*	1.80 (1.20-2.80)	
LDL/HDL ratio	1.200	0.29	18.300	< 0.001*	3.40 (1.90-6.00)	

\*Statistically significant

OR: Odds ratio; CI: Confidence interval; SE: Standard error; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TC: Total cholesterol



**Table 3.** Evaluation of the cut-off value for the lipid indices as predictors of coronary artery calcium (CAC) detected by multidetector computed tomography (MDCT) using binary logistic regression (crude and adjusted)

Adjusted variable*	Crude		Adjusted	
	OR (95% CI)	P	OR (95% CI)	P
TC/HDL $\geq$ 4.742	5.80 (1.60-21.50)	0.007*	5.60 (1.19-26.53)	0.029*
LDL/HDL $\geq$ 3.1	1.78 (0.48-6.60)	0.383	1.48 (0.32-6.88)	0.612

\*Adjusted for age, gender, smoking, diabetes mellitus (DM), hypertension (HTN), family history of coronary artery disease (CAD), body mass index (BMI)

OR: Odds ratio; CI: Confidence interval; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TC: Total cholesterol

## Discussion

This study was conducted on 120 patients with intermediate risk probability of CAD, who underwent MDCT coronary angiography. Patients with CAC detected using Agatston score were found to have higher TC, LDL-C, TC/HDL-C, and LDL/HDL-C ratio. They were also found to have significantly lower HDL-C levels.

A binary logistic regression analysis conducted on all the risk factors of CAC revealed LDL, TC/HDL ratio, and LDL/HDL ratio to be good predictors of CAC by MDCT. At a cut-off value of  $\geq 3.1$ , LDL-C/HDL-C ratio showed a sensitivity of 58.6% and specificity of 84.6%, while TC/HDL-C ratio  $\geq 4.742$  showed a sensitivity of 60.3% and specificity of 88.5% in prediction of coronary calcium. Using the cut-off values deduced, crude and adjusted logistic regression was done which revealed that TC/HDL  $\geq 4.742$  was significantly associated with calcification of coronaries. However, LDL/HDL was not significant at the deduced cut-off value.

In one retrospective study conducted by Hillerson et al. in 2020, detection of coronary calcification in chest CT was associated with increased risk of stroke and mortality in patients with atrial fibrillation (AF), independent of “congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category” (CHA2DS2-VASc) score.<sup>8</sup> In a study conducted by Matsumura et al. in 2020, 100 survivors of out-of-hospital cardiac arrest (OHCA) without ST-segment elevation with no obvious extra-cardiac cause underwent emergency CT and coronary artery angiography. Thirty survivors were diagnosed to have unstable coronary lesion. Sensitivity and specificity of CAC in identifying unstable coronary lesion were 87% and 60%, respectively. Multivariate logistic regression analysis revealed that CAC was an independent predictor of unstable coronary lesion (OR: 7.28, 95% CI:

2.00-26.56,  $P < 0.001$ ).<sup>9</sup>

From the technical point of view, coronary calcification is an established challenge during PCI.<sup>10</sup> In severe cases, calcification is considered an independent predictor of procedure complexity and complications.<sup>11</sup> LDL-C and non-HDL-C are reliable markers to assess the risk of coronary atherosclerosis.<sup>12</sup> Lipid profile association with CAC prevalence, incidence, and progression is a current point of interest, especially LDL-C, non-HDL-C, and apoB lipoproteins.<sup>13</sup>

Investigation of the association between dyslipidemia and CAC score could be helpful for risk stratification and prediction.

Current guidelines use the lipid profile for calculation of the ten-year risk of CVDs. However, they focus only on TC and LDL-C levels.<sup>14</sup> In the Framingham Study, TC levels between 150 and 300 mg/dl fell in the overlapping area between healthy individuals and patients with CAD.<sup>15</sup> Furthermore, normal LDL-C levels could not rule out the risk of CAD due to probability of presence of other atherogenic abnormalities including low HDL-C levels.<sup>16</sup> This could minimize the usefulness of using TC level or LDL-C level alone for calculating the patient risk.<sup>17</sup> Several studies demonstrated that TC/HDL-C ratio was a better predictor of CAD than isolated use of lipid profile parameters in prediction of CAD.<sup>16,18-21</sup> Furthermore, TC/HDL-C ratio has been linked to metabolic syndrome parameters including obesity and insulin resistance.<sup>16,18,22</sup>

In concordance with our findings, a study by Nair et al. in 2009 showed TC/HDL-C ratio  $\geq 4$  to be an independent predictor of obstructive CAD and proximal atherosclerotic plaque in patients who underwent MDCT. In this study, two-thirds of the atherosclerotic plaques were calcified.<sup>23</sup> Another study conducted in 2018 by Abd Alamir et al. showed that patients with normal lipid profile did not have coronary calcification. However, apart from hypertriglyceridemia, all parameters of

dyslipidemia were associated with multi-vessel coronary calcification as detected by MDCT.<sup>24</sup>

In terms of cardiovascular risk prediction, TG/HDL ratio was proposed as a potential predictor of cardiovascular risk in the research published in 2016 and 2019 by Gharipour et al., whose work was deduced from patients in the Isfahan Cohort Study, a 10-year follow-up of 5431 participants re-evaluated after 10 years using a standard protocol of medical interviews, physical examinations, and fasting blood measurements of TG/HDL-C. The TG/HDL-C ratio, at a threshold of 3.68, was used to screen for cardiovascular events among the study population. "High-risk" subjects were defined by the discrimination power of indices which were assessed using ROC analysis; the optimal cut-off point value for each index was then derived. They found that a threshold of TG/HDL  $\geq$  3.68 was the optimal cut-off point for predicting cardiovascular events in Iranian individuals.<sup>25</sup> In a retrospective study of 582 postmenopausal women conducted by Eun et al. in 2020, TG level (OR: 1.005, 95% CI: 1.002-1.008, P = 0.003) and waist-hip ratio (WHR) (OR: 1.103, 95% CI: 1.018-1.195, P = 0.017) were strongly associated with CAC.<sup>26</sup>

### Conclusion

LDL/HDL-C and TC/HDL-C ratios can be used as reliable predictors of calcification measured by MDCT. We believe that adding these ratios to the lipid profile of intermediate-risk patients will improve predictability of presence of CAC. We recommend that future multicenter studies test these ratios on a large sample of intermediate-risk patients.

**Limitations:** This was a single-center study that had a relatively small sample size. Larger multicenter studies are needed.

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### Conflict of Interests

Authors have no conflict of interests.

### Authors' Contribution

All three authors shared in all of the following:

(a) Conception, design, analysis, and interpretation of data

- (b) The drafting of the article and critical revision for its content  
(c) Final approval of the version to be published.

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