The significance of coronary artery calcium score as a predictor of coronary artery stenosis in individuals referred for CT angiography

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Abstract

Introduction: Cardiovascular diseases, including coronary artery disease (CAD), are among the most common causes of death in the elderly population. Recent studies have found that coronary artery calcium score (CACS) is a strong independent predictor of CAD. Here we aimed to investigate the association between CACS and demographic, clinical, laboratory, and CT angiographic findings in patients with suspected CAD.

Methods: From June 2008 to August 2018, we retrospectively reviewed 219 consecutive patients suspected with CAD who were referred for CT angiography in Rajaie Cardiovascular, Medical, and Research Center. Medical records were reviewed, and relevant demographic, clinical, laboratory and imaging were collected.

Results: A total of 219 patients with an average age of 62.64±12.39 were included. Twelve patients (5.5%) had normal coronary angiography, and 50.2% had mild CAD. An obstructive CAD was found in 97 patients (44.3%). The median CACS was 76.4 (IQR, 13.0-289.1). The frequency of obstructive CAD was 28.1% in the CACS <100 group, and 67.0% in CACS >100 group (P<0.001). On multiple logistic regression analysis, age (OR=1.04 [1.01-1.07], P=0.006), CACS (OR= 4.31 [2.33-7.98], P<0.001), and neutrophil to lymphocyte ratio (NLR) (OR = 0.82 [0.68-0.98], P=0.027) were independent predictors of obstructive CAD.

Conclusion: We found a direct association between higher CACS and obstructive patterns in coronary CT angiography. Our findings indicate that the possibility of the presence of obstructive CAD was higher among symptomatic patients with older age, lower NLR, and CACS >100.

Introduction

Cardiovascular diseases, including coronary artery disease (CAD), are among the most common causes of death in the elderly population. According to the World Health Organization (WHO), cardiovascular diseases take nearly 18 million lives annually.1 The lifetime risk of developing CAD is estimated to be 49 percent in men and 32 percent in women.2 Therefore, identifying people at risk and early diagnosis is important.

Older age, male gender, hypertension, diabetes, dyslipidemia, obesity, smoking, and low physical activity are among the most established risk factors for cardiovascular diseases.3,4 Recent studies have found that coronary artery calcium (CAC) is a strong independent predictor of CAD.5,6 Calcification of the coronary arteries has an important role in the pathophysiology of atherosclerosis. CAC can be easily measured by noninvasive imaging methods, including electron-beam tomography (EBT) or multidetector computed tomography (CT).7 CAC score (CACS) measured by noncontrast cardiac CT scan is a low-radiation and relatively cheap test that provide a quantitative assessment of the overall coronary atherosclerotic burden.8 Growing evidence suggests that CACS is a useful test for risk stratification of both symptomatic and asymptomatic individuals.9-13 Higher CACSSs has been shown to be associated with a higher risk of major cardiovascular events and all-cause mortality.14,15 Several studies have claimed that there are some associations between CACS and cardiac risk factors.16-18 However, there were great inconsistencies between the reported results. Here we aimed to investigate the association between CACS and demographic, clinical, laboratory, and CT angiographic findings in patients with suspected CAD. We also evaluated the predictive value of
CACS beyond traditional cardiovascular risk factors for obstructive CAD.

Materials and Methods
From June 2008 to August 2018, we retrospectively reviewed 219 consecutive patients suspected with CAD who were referred for CT angiography in Rajaie Cardiovascular, Medical, and Research Center, affiliated to Iran University of Medical Sciences. Inclusion criteria included all adult patients with stable angina candidate for CT angiography. Patients with a prior history of CVDs, chronic kidney disease, significant liver dysfunction were excluded. Also, who had history of previous percutaneous coronary intervention or coronary artery bypass grafting were excluded. The patient with suspicious or confirmed acute coronary syndrome excluded. Patients’ demographic, clinical, and laboratory findings were obtained from data bank.

Computed tomography scanning protocol
Coronary CT angiography was performed with 192-slice CT scanner (SOMATOM FORCE, Forchheim, Germany). In all patients, a non-contrast enhanced scan (120-kV tube voltage and 3-mm slice thickness) to calculate the total CACS was performed prior to CCTA (120-kV tube voltage, 0.75-mm slice thickness, 0.3 or 0.4-mm reconstruction increment). A 50-60-ml contrast (IOHEXOLE: Omnipaque 350 mgI/mL, GE HealthCare Inc, USA), followed by a 20-ml saline solution chaser, was injected at 3.5–5.5 mL/s. Nitroglycerine sublingually was administered immediately before contrast injection. The Agatston scoring method was used to measure the CACS.19 The total CACS was categorized as low (0–100) and high (>100). Coronary CT angiography scans were evaluated by experienced radiologists, blinded to the CACS results. Obstructive CAD was defined as ≥50% luminal narrowing of C1 coronary segment on CCTA.

Statistical analysis
Statistical analyses were performed using the Statistical Package of Social Science version 25. Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables are presented as absolute numbers and percentages. The independent samples t test or chi-square test was used to compare variables between the groups. Multivariate logistic regression analysis was performed to identify independent risk factors of obstructive CAD. A two-sided P<0.05 was considered statistically significant.

Results
A total of 219 patients were studied. Patients’ demographic, clinical, and laboratory findings are summarized in Table 1 and Table 2. The mean EF was 44.39±12.48. Twelve patients (5.5%) had normal coronary angiography, and nearly half of the participants had mild CAD. An obstructive CAD was found in 97 patients (44.3%).

| Table 1. Patients’ characteristics |
|-----------------------------------|
| Characteristics                  |       |
| Age, years [mean±SD]             | 62.6±12.4 |
| Male, n (%)                      | 121 (55.3) |
| Risk factors, n (%)              |       |
| Diabetes                         | 60 (27.4) |
| Dyslipidemia                     | 93 (42.5) |
| Hypertension                     | 120 (54.8) |
| Smoking*                         | 51 (65.4) |
| Positive family history          | 44 (20.1) |
| Chief complaint, n (%)           |       |
| Chest pain                       | 132 (60.3) |
| Dyspnea                          | 105 (47.9) |
| SBP, mm Hg [mean±SD]             | 127.7±17.9 |
| DBP, mm Hg [mean±SD]             | 78.2±12.4 |
| Ejection fraction [mean±SD]      | 44.4±12.5 |
| CCTA, n (%)                      |       |
| Normal                           | 12 (5.5) |
| Mild CAD                         | 110 (50.2) |
| 1-vessel disease                 | 44 (20.1) |
| 2-vessel disease                 | 28 (12.8) |
| 3-vessel disease                 | 25 (11.4) |
| CACS, n (%)                      |       |
| 0-100                            | 128 (58.4) |
| 100-300                          | 39 (17.8) |
| >300                             | 52 (23.7) |

CACS, coronary artery calcium score; CAD, coronary artery disease; CCTA, coronary computed tomographic angiography; SD, standard deviation

* Data were available from 78 patients.

| Table 2. Laboratory findings |
|-----------------------------|
| Test                        |     |
| Hemoglobin (g/dL)           | 13.4±1.8 |
| White blood cells (/mm³)     | 7403.2±2571.0 |
| Neutrophil (%)              | 65.3±11.3 |
| Lymphocyte (%)              | 24.6±10.6 |
| Platelets (/mm³)             | 193.2±55.0 |
| Platelet-to-lymphocyte ratio| 134.3±74.0 |
| Neutrophil-to-lymphocyte ratio| 3.5±2.2 |
| Triglyceride (mg/dL)         | 144.6±86.2 |
| Cholesterol (mg/dL)          | 153.4±40.5 |
| LDL (mg/dL)                  | 88.8±31.0 |
| HDL (mg/dL)                  | 39.7±10.1 |
| Fasting blood glucose (mg/dL)| 120.1±40.9 |
| BUN (mg/dL)                  | 21.3±15.6 |
| Creatinine (mg/dL)           | 1.1±0.6  |
| ESR                          | 18.2±14.5 |
| HsCRP* (mg/L)                | 11.0±17.9 |

BUN: blood urea nitrogen; HsCRP: high-sensitivity C-reactive protein; ESR: erythrocyte sedimentation rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

*Data were available from 65 patients.
Other important CT angiographic findings were positive remodeling in nine patients (4.1%), napkin ring sign in four patients and low-density plaque in three patients. The median CACS was 76.4 (IQR, 13.0-289.1).

Patients’ characteristics are compared across the CACS groups in Table 3. Patients with higher CACSs were significantly older than patients with CACS<100 (P <0.001). The frequency of obstructive CAD was 28.1% in the CACS< 100 group, and 67.0% in CACS>100 group (P <0.001).

We also compared the characteristics of patients with and without obstructive CAD (Table 4). Patients with obstructive CAD were significantly older than patients with normal angiography or mild CAD (P =0.001). Patients with obstructive CAD had significantly lower neutrophil to lymphocyte ratio (NLR) values compared to the other group (P =0.005).

On multiple logistic regression analysis, age, CACS, and NLR were independent predictors of obstructive CAD (Table 5). Older age and lower NLR values were associated with a higher probability of obstructive CAD. Patients with CACS>100 had a 4.31-fold greater risk of obstructive CAD.

Discussion

In the present study, we evaluated the association between CACS and demographic, clinical, laboratory, and CT angiographic findings of patients suspected with CAD. In the univariate analyses, we found that patients with greater CACSs (>100) were older and the frequency of obstructive CAD was higher among them. When we compared the characteristics of patients with and without obstructive CAD in CT angiography, we realized that patients with obstructive CAD were older and had lower NLR values. Finally, we found that older age, lower NLR, and CACS>100 are independent significant predictors of the presence of obstructive CAD in CT angiography.

Previous studies have shown that increased CACS is significantly associated with increased cardiovascular risk factors and more severe coronary artery stenosis.20-22 Ho et al,20 reported that patients with higher CACS were older and the prevalence of male gender, hypertension, and significant CT angiographic stenosis were higher among them. Likewise, Ueda et al,21 noticed that greater CACSs in patients with suspected CAD was significantly associated with older age, male gender, and presence of hypertension, diabetes, and hypercholesterolemia. The also realized that the prevalence of obstructive CAD increased with the CACS. Similar to these studies, we found that the prevalence of obstructive CAD was greater in patients with CACS>100 compared with those with lower CAC levels (67.0% vs 28.1%). CACS>100 was associated with a 4.31-fold increased risk of obstructive CAD.

Older age was another independent risk factor for obstructive CAD in this study. We also found that the mean age of patients with increased CACS was significantly higher than patients with lower CACSs. This finding is in line with earlier studies which reported a direct association between age and CAC.23 Unlike the abovementioned studies, we did not find any significant association between CACS and male gender, diabetes, dyslipidemia, hypertension, and smoking.20-22 Variation in study design, CACS cut-off points, sample size, and analytic approaches could explain these inconsistencies.

Inflammation plays a pivotal role in the pathophysiology of atherosclerosis.24 Some earlier studies have shown that higher levels of inflammatory markers, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and inflammatory cytokines such as interleukin 1 (IL-1), IL-6, IL-10, monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor-alpha (TNF-α) may predict poor cardiovascular prognosis.24-26 In the present study, we found no significant association between ESR or CRP and CACS. Also, we realized that none of these markers significantly correlate with CACS in this study.

Table 3. Clinical characteristics according to CACS groups

|        | CACS <100 (n=128) | CACS >100 (n=91) | P     |
|--------|-------------------|------------------|-------|
| Age, years [mean±SD] | 60.1±12.6        | 66.2±11.3        | <0.001|
| Male, n (%)         | 65 (50.8)         | 56 (61.5)        | 0.130 |
| Diabetes, n (%)     | 34 (26.6)         | 26 (28.6)        | 0.760 |
| Dyslipidemia, n (%) | 52 (40.6)         | 41 (45.1)        | 0.579 |
| Hypertension, n (%) | 70 (54.7)         | 50 (54.9)        | 1.000 |
| Smoking, n (%)      | 33 (67.3)         | 18 (62.1)        | 0.806 |
| Positive family history, n (%) | 29 (22.7) | 15 (16.5) | 0.306 |
| Chest pain, n (%)   | 76 (59.4)         | 65 (61.5)        | 0.781 |
| Dyspnea             | 61 (47.7)         | 44 (48.4)        | 1.000 |
| LVEF [mean±SD]      | 44.2±13.3         | 44.6±11.1        | 0.815 |
| Obstructive CAD     | 36 (28.1)         | 61 (67.0)        | <0.001|
| Remodeling          | 8 (6.3)           | 1 (1.1)          | 0.084 |
| Hemoglobin (g/dL)   | 13.5±1.9          | 13.3±1.8         | 0.655 |
| WBC (/mm³)          | 7594.1±2639.7     | 7134.3±2460.4    | 0.193 |
| Neutrophil (%)      | 66.5±11.8         | 63.7±10.4        | 0.070 |
| Lymphocyte (%)      | 24.2±10.6         | 25.2±10.6        | 0.511 |
| Platelets (/mm³)    | 197.3±60.3        | 187.4±64.1       | 0.189 |
| PLR                 | 134.1±71.0        | 134.5±73.5       | 0.970 |
| NLR                 | 3.6±2.2           | 3.3±2.2          | 0.355 |
| Triglyceride (mg/dL)| 145±88.3          | 143±83.8         | 0.871 |
| Cholesterol (mg/dL)| 150±63.8          | 157±34±35        | 0.235 |
| LDL (mg/dL)         | 88.0±29.2         | 89.5±33.4        | 0.668 |
| HDL (mg/dL)         | 38.9±10.3         | 40.8±9.8         | 0.169 |
| FBS (mg/dL)         | 120.2±43.8        | 119.8±32.9       | 0.954 |
| BUN (mg/dL)         | 20.4±11.3         | 22.4±19.8        | 0.397 |
| Creatinine (mg/d)   | 1.1±0.7           | 1.0±0.3          | 0.492 |
| ESR                 | 17.8±15.0         | 18.8±13.9        | 0.622 |
| hsCRP (mg/L)        | 8.4±7.4           | 9.4±8.4          | 0.618 |

ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; HsCRP, high sensitivity C reactive protein; FBS, fasting blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; WBC, white blood cells.
Elevated NLR values were
16 (16.5)
0.066
21 (67.7)
0.806
195.0±50.9
88.0±30.6
26.0±9.1
7558.7±2588.7
1.1±0.9
0.093
0.027
0.754
30 (63.8)
0.180
0.308
0.398
0.686
0.810
P
43 (44.3)
0.658
70 (57.4)
0.891
24
17.5±14.3
1.0±0.2
0.162
0.316
27-29
19.2±14.8
0.678
62 (63.9)
153.3±40.8
39.5±9.3
124.4±57.2
21.8±19.4
13.3±1.8
0.006
66 (54.1)
0.945
45 (46.4)
0.75 (0.41-1-40)
<0.001
0.221
142.1±84.5
0.335
7207.5±2548.4
63 (51.6)
58 (59.8)
0.274
Diabetes, n (%) 37 (30.3) 23 (23.7) 0.290
Dyslipidemia, n (%) 50 (41.0) 43 (44.3) 0.680
Hypertension, n (%) 66 (54.1) 54 (55.7) 0.891
Smoking, n (%) 30 (63.8) 21 (67.7) 0.810
Positive family history, n (%) 28 (23.0) 16 (16.5) 0.308
Chief complaint, n (%) Chest pain 70 (57.4) 62 (63.9) 0.335
Dyspnea 60 (49.2) 45 (46.4) 0.686
LVEF [mean±SD] 44.8±11.7 44.0±13.1 0.467
Hemoglobin (g/dL) 13.3±1.8 13.5±1.8 0.467
WBC ([mm³]) 7207.5±2548.4 7558.7±2588.7 0.316
Neutrophil (%) 63.8±9.6 66.6±12.4 0.074
Lymphocyte (%) 26.0±9.1 23.5±11.5 0.093
Platelets ([mm³]) 195.0±50.9 191.7±58.2 0.658
PLR 124.4±57.2 142.1±84.5 0.066
NLR 3.0±1.8 3.8±2.4 0.005
Triglyceride (mg/dL) 139.5±72.9 148.7±95.6 0.433
Cholesterol (mg/dL) 153.6±40.3 153.3±40.8 0.945
LDL (mg/dL) 80.0±30.6 89.3±31.4 0.754
HDL (mg/dL) 39.5±9.3 39.9±10.7 0.806
FBS (mg/dL) 114.4±29.0 124.3±47.6 0.162
BUN (mg/dL) 20.5±8.1 21.8±19.4 0.574
Creatinine (mg/d) 1.1±0.9 1.0±0.2 0.180
ESR 19.2±14.8 17.5±14.3 0.398
HsCRP (mg/L) 10.1±8.6 7.7±6.9 0.221

Table 4. Clinical characteristics according to stenosis status

|                  | Obstructive CAD + (n=97) | Obstructive CAD - (n=122) | P     |
|------------------|--------------------------|---------------------------|-------|
| Age, years [mean±SD] | 65.7±11.4               | 60.2±12.6                | 0.001 |
| Male, n (%)       | 63 (51.6)                | 58 (59.8)                | 0.274 |
| Diabetes, n (%)   | 37 (30.3)                | 23 (23.7)                | 0.290 |
| Dyslipidemia, n (%)| 50 (41.0)                | 43 (44.3)                | 0.680 |
| Hypertension, n (%)| 66 (54.1)                | 54 (55.7)                | 0.891 |
| Smoking, n (%)    | 30 (63.8)                | 21 (67.7)                | 0.810 |
| Positive family history, n (%) | 28 (23.0) | 16 (16.5) | 0.308 |
| Chest pain (%)    | 70 (57.4)                | 62 (63.9)                | 0.335 |
| Dyspnea (%)       | 60 (49.2)                | 45 (46.4)                | 0.686 |
| LVEF [mean±SD]    | 44.8±11.7                | 44.0±13.1                | 0.467 |
| Hemoglobin (g/dL) | 13.3±1.8                 | 13.5±1.8                 | 0.467 |
| WBC ([mm³])       | 7207.5±2548.4            | 7558.7±2588.7            | 0.316 |
| Neutrophil (%)    | 63.8±9.6                 | 66.6±12.4                | 0.074 |
| Lymphocyte (%)    | 26.0±9.1                 | 23.5±11.5                | 0.093 |
| Platelets ([mm³]) | 195.0±50.9               | 191.7±58.2               | 0.658 |
| PLR               | 124.4±57.2               | 142.1±84.5               | 0.066 |
| NLR               | 3.0±1.8                  | 3.8±2.4                  | 0.005 |
| Triglyceride (mg/dL) | 139.5±72.9            | 148.7±95.6               | 0.433 |
| Cholesterol (mg/dL) | 153.6±40.3             | 153.3±40.8               | 0.945 |
| LDL (mg/dL)       | 80.0±30.6                | 89.3±31.4                | 0.754 |
| HDL (mg/dL)       | 39.5±9.3                 | 39.9±10.7                | 0.806 |
| FBS (mg/dL)       | 114.4±29.0               | 124.3±47.6               | 0.162 |
| BUN (mg/dL)       | 20.5±8.1                 | 21.8±19.4                | 0.574 |
| Creatinine (mg/d) | 1.1±0.9                  | 1.0±0.2                  | 0.180 |
| ESR               | 19.2±14.8                | 17.5±14.3                | 0.398 |
| HsCRP (mg/L)      | 10.1±8.6                 | 7.7±6.9                  | 0.221 |

ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; HsCRP, high sensitivity C reactive protein; FBS, fasting blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; WBC, white blood cells.

Table 5. Independent predictors of obstructive CAD

|                  | OR (95% CI) | P     |
|------------------|-------------|-------|
| Age              | 1.04 (1.01-1.07) | 0.006 |
| Male sex         | 0.75 (0.41-1.40) | 0.371 |
| CACS>100         | 4.31 (2.33-7.98) | <0.001 |
| NLR              | 0.82 (0.68-0.98) | 0.027 |
| PLR              | 1.00 (0.99-1.00) | 0.678 |

CACS, coronary artery calcium score; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

In conclusion, we found a direct association between higher CACS and obstructive patterns in coronary CT angiography. Our findings indicate that the possibility of the presence of obstructive CAD was higher among symptomatic patients with older age, lower NLR, and CACS>100.

Competing interests
None declared.

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Ethical approval
The protocol of this study was reviewed and approved by the Institutional Review Board and the Ethics Committee of Iran University of Medical Sciences (the ethical code No. IR.IUMS.FMD.REC1396.9411171011). An informed consent form was signed by all subjects prior to inclusion.

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References
1. Mendis S, Puska P, Norrving B (Eds.). Global atlas on cardiovascular disease prevention and control. World Health Organization; 2011.
2. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime...
risk of developing coronary heart disease. **Lancet** 1999;353(9147):89-92. doi:10.1016/S0140-6736(98)0279-9

3. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. **Lancet** 2004;364(9438):937-952. doi:10.1016/S0140-6736(04)17018-9

4. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. **JAMA** 2003;290(7):891-897. doi:10.1001/jama.290.7.891

5. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups. **N Engl J Med** 2008;358(13):1336-1345. doi:10.1056/NEJMoa0802100

6. Elias-Smale SE, Proenca RV, Koller MT, Kavousi M, van Rooij FJ, Hunink MG, et al. Coronary calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. **J Am Coll Cardiol** 2010;56(17):1407-1414. doi:10.1016/j.jacc.2010.06.029

7. Vliegenthart R, Oudkerk M, Hofman A, Oei HH, van Dijk W, van Rooij FJ, et al. Coronary calcium scoring improves cardiovascular risk prediction in the elderly. **Circulation** 2005;112(4):572-577. doi:10.1161/CIRCULATIONAHA.104.489916

8. Tota-Maharaj R, Blaha MJ, McEvoy JW, Blumenthal RS, Muse ED, Budoff MJ, et al. Coronary calcium for the prediction of mortality in young adults <45 years old and elderly adults >75 years old. **Eur Heart J** 2012;33(23):2955-2962. doi:10.1093/eurheartj/ehs230

9. Mao SS, Pal RS, McKay CR, Gao YG, Gopal A, Ahmadi N, et al. Comparison of coronary artery calcium scores between electron beam computed tomography and 64-multidetector computed tomographic scanner. **J Comput Assist Tomogr** 2009;33(2):175-178. doi:10.1097/RCT.0b013e31817579ee

10. Madaj P, Budoff MJ. Risk stratification of non-contrast CT beyond the coronary calcium scan. **J Cardiovasc Comput Tomogr** 2012;6(5):301-307. doi:10.1016/j.jcct.2012.02.008

11. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. **J Am Coll Cardiol** 2007;49(18):1860-1870. doi:10.1016/j.jacc.2006.10.001

12. Lo-Kioeng-Shioe MS, Vavere AL, Arbab-Zadeh A, Schuijf JD, Rochitte CE, Chen MY, et al. Coronary Calcium Characteristics as Predictors of Major Adverse Cardiac Events in Symptomatic Patients: Insights From the CORE 320 Multinational Study. **J Am Heart Assoc** 2019;8(6):e007201. doi:10.1161/JAHA.117.007201

13. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/ AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. **J Am Coll Cardiol** 2007;49(3):378-402. doi:10.1016/j.jacc.2006.10.001

14. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. **J Am Coll Cardiol** 2005;46(1):158-165. doi:10.1016/j.jacc.2005.02.088

15. Shemesh J, Morag-Koren N, Goldbourt U, Grossman E, Tenenbaum A, Fisman EZ, et al. Coronary calcium by spiral computed tomography predicts cardiovascular events in high-risk hypertensive patients. **J Hypertens** 2004;22(3):605-610. doi:10.1097/00004872-200403000-00024

16. Valdes AM, Wolfe ML, Tate HC, Gefter W, Rut A, Rader DJ. Association of traditional risk factors with coronary calcification in persons with a family history of premature coronary heart disease: the study of the inherited risk of coronary atherosclerosis. **J Investig Med** 2001;49(4):353-361. doi:10.2310/6650.2001.33901

17. Nasir K, Budoff MJ, Wong ND, Scheuner M, Herrington D, Arnett DK, et al. Family history of premature coronary heart disease and coronary artery calcification: Multi-Ethnic Study of Atherosclerosis (MESA). **Circulation** 2007;116(6):619-626. doi:10.1161/01.atherosclerosis.2013.11.042

18. Hoff JA, Daviglus ML, Chomka EV, Krainik AJ, Sevrucko A, Kondos GT. Conventional coronary artery disease risk factors and coronary artery calcium detected by electron beam tomography in 30,908 healthy individuals. **Ann Epidemiol** 2003;13(3):163-169. doi:10.1016/s1047-2797(02)00277-6

19. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. **J Am Coll Cardiol** 1990;15(4):827. doi:10.1016/0735-1097(90)90282-t

20. Ho JS, Fitzgerald SJ, Stolius LL, Wade WA, Reinhardt DB, Barlow CE, et al. Relation of a coronary artery calcium score higher than 400 to coronary stenoses detected using multidetector computed tomography and to traditional cardiovascular risk factors. **Am J Cardiol** 2008;101(10):1444-1447. doi:10.1016/j.amjcard.2008.01.022

21. Rosen BD, Fernandes V, McClelland RL, Carr JJ, Detrano R, Bluemke DA, et al. Relationship between baseline coronary calcium score and demonstration of coronary artery stenoses during follow-up MESA (Multi-Ethnic Study of Atherosclerosis). **JACC Cardiovasc Imaging** 2009;2(10):1175-1183. doi:10.1016/j.jcmg.2009.06.014

22. Ueda H, Harimoto K, Tomoyama S, Tamaru H, Miyawaki M, Mitsusada N, et al. Relation of cardiovascular risk factors and angina status to obstructive coronary artery disease according to categorical coronary artery calcium score. **Heart Vessels** 2012;27(2):128-134. doi:10.1007/s00380-011-0128-2

23. Shaw LJ, Raggi P, Berman DS, Callister TQ. Coronary artery calcium as a measure of biologic age. **Atherosclerosis** 2006;188(1):112-119. doi:10.1016/j.atherosclerosis.2005.10.010

24. Hansson GK, Robertson AK, Soderberg-Naucler C. Inflammation and atherosclerosis. **Annu Rev Pathol** 2006;1:297-329. doi:10.1146/annurev.pathol.1.110304.100100

25. Ross R. Atherosclerosis--an inflammatory disease.
26. Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, et al. Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition [Health ABC] Study). Am J Cardiol 2003;92(5):522-528. doi:10.1016/S0002-9149(03)00718-5

27. Jenny NS, Brown ER, Detrano R, Folsom AR, Saad MF, Shea S, et al. Associations of inflammatory markers with coronary artery calcification: Results from the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 2010;209(1):226-229. doi:10.1016/j.atherosclerosis.2009.08.037

28. Reilly MP, Wolfe ML, Localio AR, Rader DJ. C-reactive protein and coronary artery calcification: The Study of Inherited Risk of Coronary Atherosclerosis (SIRCA). Arterioscler Thromb Vasc Biol 2003;23(10):1851-1856. doi:10.1161/01.ATV.0000092327.60858.4A

29. Hamirani YS, Pandey S, Rivera JJ, Ndumele C, Budoff MJ, Blumenthal RS, et al. Markers of inflammation and coronary artery calcification: A systematic review. Atherosclerosis 2008;201(1):1-7. doi:10.1016/j.atherosclerosis.2008.04.045

30. Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther 2013;11(1):55-59. doi:10.1586/14779072.2016.1154788

31. Park BJ, Shim JY, Lee HR, Lee JH, Jung DH, Kim HB, et al. Relationship of neutrophil-lymphocyte ratio with arterial stiffness and coronary calcium score. Clin Chim Acta 2011;412(11-12):925-929. doi:10.1016/j.cca.2011.01.021

32. Nam SH, Kang SG, Song SW. The Neutrophil-Lymphocyte Ratio Is Associated with Coronary Artery Calcification in Asymptomatic Korean Males: A Cross-Sectional Study. Biomed Res Int 2017;2017:1989417. doi:10.1155/2017/1989417