*Original Research Article*

# Sex Differences in Computed Tomographic Angiography in Patients with Low and Intermediate Pretest Probability of Coronary Artery Disease



## Abstract

**Background:** Multi-slice computed tomography (MSCT) coronary angiography has become one of the hot spots in cardiovascular imaging technology. Many of the sex-based research have shown that women have different pathogenesis, clinical presentation and complication related to coronary artery disease (CAD) as compared to the males. The aim of this study investigated the relationship between gender and coronary artery calcium (CAC) in patients with chest discomfort with low and intermediate pretest probability of CAD who underwent Coronary computed tomography angiography (CCTA) and referrals by gender for subsequent invasive coronary angiography and revascularization.

**Methods:** This prospective cohort study included 200 patients suspected to have coronary artery disease, negative or equivocal stress tests, with no prior known coronary artery disease (CAD), intermediate pretest probability for CAD according to the scoring method of (15-65 points), and Low likelihood for CAD (< 15 points). Patients were divided into two groups according to gender and were followed up. All patients underwent Full history taking, full clinical examination, routine laboratory investigation, resting and exercise ECG, echocardiography, CT coronary angiography and invasive Coronary angiography.

**Results:** Patients with mild calcium score level were significantly higher in no CAD group than CAD group ($p < 0.001$) and patients with high calcium score were significantly higher in CAD group than no CAD group ($p < 0.001$). In univariate regression analysis age, typical chest pain, obesity, coronary Ca score, and hyperlipidemia are independent predictors for CAD in females. In multivariate regression analysis, age, typical chest pain, hypertension, and coronary Ca score are predictors for CAD in males. Coronary calcium score is a good predicator for CAD (AUC =0.901, 95% CI =0.851-0.938, p value <0.001). At cut off value > 101, it has 70.97% sensitivity, 90.79% specificity, 92.6% PPV, and 65.7% NPV. Moreover, it is a good predicator for CAD in females (AUC =0.894, 95% CI =0.823 – 0.944, p value

<0.001). At cut off value > 101, it has 60.71% sensitivity, 91.67% specificity, 87.2% PPV, and 71.4% NPV.

**Conclusions:** In patients with chest discomfort with low and intermediate pretest probability of CAD who underwent CCTA and subsequent invasive coronary angiography and revascularization, female patients had lower age, hypertension, pretest probability score, calcium score, atypical angina, nonanginal chest pain and obstructive CAD but had higher BMI, typical angina than males' group. In females, coronary calcium score is a good predicator for CAD. When its level exceeds 100, it has 60.71% sensitivity and 91.67% specificity. In addition, it was found that in females typical chest pain and coronary Ca score are predictors for CAD and in males, age, typical chest pain, hypertension, and coronary Ca score are predictors for CAD.

**Keywords:** Sex Differences, Computed Tomographic Angiography, Pretest Probability, Coronary Artery Disease.



## Introduction:

Conventional coronary angiography has been considered the gold standard method for diagnoses of coronary artery lesions. However, coronary angiography is unlikely to be accepted in the absence of significant lesions and risk of complications due to its invasive features. Therefore, an alternative noninvasive procedure for determining coronary artery disease (CAD) is necessary [1].

In recent decades, multi-slice computed tomography (MSCT) coronary angiography has become one of the hot spots in cardiovascular imaging technology. This method has been applied for evaluating coronary artery stenosis, and was proposed as a potential alternative procedure for invasive coronary angiography [2].

Coronary CT angiography (CCTA) is unique in its ability to noninvasively visualize CAD and to accurately detect significant stenosis plus it is a quick and relatively simple procedure that can be performed within 10 to 20 minutes [3].

Several studies have demonstrated that coronary artery calcium (CAC) is a marker for atherosclerosis and hence for CAD [4]. Electrocardiogram-synchronized CCTA using fast scanners is a reliable method for estimating CAC. This is usually accomplished by summing all lesions using the Agatston Score [5].

Many of the sex-based research have shown that women have different pathogenesis, clinical presentation and complication related to CAD as compared to the males. Vaccarino et al have also provided new evidence, based on analysis of large databases, that there are differences between men and women in the natural history of CAD that are not related to age. More research-based evidence is needed to familiarize the physicians with these differences to set up the new guidelines for the women-based management of the heart diseases [6].

The aim of this study was to investigate the relationship between gender and CAC in patients with chest discomfort with low and intermediate pretest probability of coronary artery disease CAD who underwent CCTA and referrals by gender for subsequent invasive coronary angiography and revascularization.

## Patients and Methods:

This prospective cohort study included 200 patients who were evaluated at outpatient clinic cardiology department in Tanta university hospital suspected to have CAD, which were divided into, two groups: Males group (n=84) and females' group (n=116) then were followed up. The study was done after being approved from Tanta University ethical committee and informed written consent was obtained from all patients participating in the study.

Patients suspected to have CAD in the form of chest pain aged above 18 years old, negative or equivocal stress tests, no prior known coronary artery disease (CAD), intermediate pretest probability for CAD according to the scoring method of (15-65 points) (110), low likelihood for CAD (< 15 points) were included.

Clear evidence for ischemia in any stress test, high pretest likelihood (>65 points), arrhythmia, orthopnea, renal impairment (Creatinine level>1.5 mg/dl), contrast allergy, pregnancy, past history of PCI including stenting, past history of CABG, inability to hold breath for about 10 seconds, ACS one month before CT examination, any metallic implant (Pacemaker - ICD - Prosthetic Valve) were excluded.

**All patients in this study were subjected to the following:**

**Diagnosis of CAD by:**

**Full history taking** with emphasis on age, sex, history of risk factors for CAD as: [Diabetes Mellitus, hypertension, dyslipidemia, smoking and family history of CAD. Patient defined as having diabetes when he had previous history or current diagnosis of DM or on anti-diabetic drugs, according to American Diabetes Association the patient is diagnosed as diabetic if he has: HbA1C: 6.5 % or higher, Fasting blood glucose level: 126 mg/dl or higher, 2 hours post prandial blood glucose level: 200 mg/dl or higher [7].

**Systemic hypertension** was defined as systolic blood pressure of 140 mm Hg or more and/or diastolic blood pressure of 90 mm Hg or more measured on 3 separate occasions with or without treatment before admission [8]. **Dyslipidemia** is defined as serum total cholesterol level over 200 mg /dl or triglycerides more than 150 mg /dl or current treatment with lipid lowering medication [9]. **Smoking:** An adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes [10]. **Family history of CAD:** having first- or second-degree relatives with CAD (age >55 years). **Garrow Classification for obese patients** [11]**. Pretest probability for CAD** [12] according to the scoring method of (15-65 points) [13].

**Full clinical examination:** Vital signs (heart rate, blood pressure and respiratory rate). General examination with attention to height, weight, body mass index (BMI), patient look, decubitus, cyanosis, jaundice, with special attention to signs of heart failure. Local cardiac examination (abnormal pulsation, Heart sounds and murmurs).

**Resting 12 leads ECG:** Standard 12-lead ECG was obtained within 10 minutes of first medical contact (FMC) according to ESC guidelines 2017 including: (limb leads I, II, III, aVR, aVL, aVF, and Chest leads from V1to V6) for all patients on admission to the hospital [14]. Right pericardial leads (V3R, V4R, V5R, V6R) and posterior chest leads (V7 to V9) were done for some patients to detect posterior wall and right ventricular infarction [14].

**Routine laboratory investigation including** CKMB/Troponin, Lipid profile (total cholesterol, LDL, HDL and triglycerides), Urea/Creatinine level to ensure that the patient was fit for contrast material injection, and Complete blood count

**Exercise ECG:** Negative or equivocal stress tests patients are included in the study according to Bruce protocol.

**Echocardiography:** All studies were performed using (a GE vivid 7 Dimension Cardiac ultrasound phased array system) equipped with a 2.5 MHz variable frequency transducer. Standard views according to American Society of Echocardiography. It was used to assess the structure heart disease, presence of resting segmental wall motion and assessment of the ejection fraction.

Myocardial contractility/compliance, hemodynamic conditions (preload/afterload), the electrophysiology of the myocardium, the pericardium, and the function of other cardiac chambers/cardiac valves [15]. Global LV function can be assessed using changes in the LV dimensions and volumes between LV diastole and systole. The recommended calculations are as follows [16]: Fractional shortening (FS), Fractional area change (FAC), Ejection fraction (EF), Stroke volume (SV) and CO, Left ventricle dysfunction differs in males and females [16]

**CT coronary angiography examination:** 320 row CT scanner (Aquilion one system, Toshiba Medical Systems, Tokyo, Japan) was used to exam the studied patients.

**Multi-slice CT coronary angiography was done for all patients by these steps:**

1. **Instructions to the patients**

No food 3 or 4 hours before examination, no caffeine or smoking 12 hours before examination, encourage water intake, avoid exercise at the day of examination, avoid smoking, take all regular medications, take premedications for contrast allergy as needed, take premedications for renal protection as needed, Sildenafil should be avoided for 48 h before the scan and stop Metformin 48 h after the scan.

2. **Patient preparation:**

**Heart rate control:** In patients with a resting heart rate of 65 beats per minute or more before the scan, metoprolol was administered orally 50 mg one hour before the scan to achieve a target heart rate of less than or equal to 65 beats per minute. [87] Additional 50 mg of metoprolol was given after 60 minutes for patients with inadequate heart rate control. To those with contraindication to B-blockers we gave Ivabradine 5 mg orally one hour before the scan.87

a. **Intravenous access:** Intravenous access was obtained according to established protocols. While a 20-guage intravenous cannula may be adequate in most, in larger patients in whom rapid infusion rates are needed, an 18-guage cannula is required.

**At scanner room:** Patients were asked to lie supine on scanner table with arms raised above their heads. The patients should be positioned so that the heart lies in the focal point of the x rays (center of the gantry). Electrocardiogram (ECG) lead placement standards are also important and should not overly the heart so as to avoid streak artifact that may result. ECG tracings should be confirmed before the procedure by ensuring high amplitude of R wave. Breath holding test was performed to avoid respiratory motion artifacts. 5 mg sublingual Isosorbid dinitrates was given

3. **Contrast media injection:** Non-ionic contrast media **(Ultravist 370 mg *I*/mL; Bayer Health Care, Berlin, Germany)** was injected through IV line using a dual-head powered automatic injector. The patients received a 60-90 mL bolus of contrast medium at an infusion rate of 5 mL/sec, followed by 50 mL of saline solution. The scan was performed according to the bolus-tracking technique.

4. **CT scan protocol:** The first step in a CCTA examination was usually an anterior posterior scout topogram that allowed the technicians to accurately prescribe the scanned field of view (SFOV). The upper limit of the SFOV was just below the carina. The caudal limit of the sFOV should have been slightly below the diaphragm to include cardiac apex. The next step in the CCTA protocol was usually the non-contrasted scan for calcium scoring. Patients with calcium score more than 800 were excluded. Bolus tracking technique was used to detect the arrival of contrast material at descending aorta at mid heart level with trigger threshold set at 230 HU. Repetitive low dose monitoring examinations (120 KV, 50mAs, 0.5 second scanning time) were performed 10 seconds after contrast medium injection began. When the trigger threshold was reached, the scan started immediately after breath holding command.

**Image acquisition:** Acquisition parameters: 0.35 second gantry rotation time, variable mA according to patient body habitus (range: 100 135 Kv). Prospective ECG gating: was used with volume scanning method. Single heartbeat acquisition was routinely performed with heart rate below 65 bpm and the scan window was set at 70-80% of RR interval while 2 heartbeat acquisition was performed in patient with heart rate above 70 bpm. when heart rate between 65 and 70 bpm, the scanning window was set to 30-80% of RR interval to include end systolic phase. Images were reconstructed at a slice thickness of 0.5 mm and 0.5mm interval with smooth and sharp reconstruction kernels.

5. **Post processing:** The reconstructed images were transferred to **workstation (Vitrea Fx, vital images, USA)** to obtain multiplanar images in axial, sagittal and coronal planes. Also, maximum intensity projections, 3D Volume rendering technique and Curved Multiplanar Reconstruction were obtained.

6. **Image analysis**

   A. **Assessment of image quality:** The causes of impaired image quality were classified as blooming artifacts generated by large calcifications, motion artifacts related to noncompliance with breath holding, cardiac motion artifact related to sudden increase of heart rate, or impaired contrast to-noise ratio. Images were graded for overall image quality and motion artifact. The overall image quality was graded on a 4- point Likert scale: 1 = poor image quality, 2 = significantly reduced image quality, 3 = mildly reduced image quality and 4 = excellent image quality.

B. **Evaluation of coronary arteries:** An overview of the coronary artery anatomy and image quality is obtained by scrolling through the transverse image stack, thus providing a first impression of possible difficulties owing to the presence of calcifications and potential artifacts. During this overview, coronary anatomy needs to be assessed carefully for possible coronary artery anomalies. Thin-slab MIP images can be used for identification of lesions in the standard planes. The use of thin-slab MIP (with a slab thickness of 3–5 mm) provides a display of a longer portion of the vessel on a single image. Oblique MPR images parallel and orthogonal to the vessel centerline, including curved MPR images, should be used to assess all identified plaques in both planes. This is performed to assign a degree of stenosis to each plaque.

**CT analysis:** Reconstructed images are independently evaluated by two observers. Calcium score is evaluated [17]. All vessels were analyzed for stenosis or obstruction.

**7. Invasive Coronary angiography**

It was used as a reference standard at the same week of CCTA scan. The objective of the coronary artery evaluation is to convey clinically meaningful, consistent information about the presence, location, characterization and degree of atherosclerosis as well as to report on any coronary stenoses that are present. Coronary artery segments were evaluated using a Society of Cardiovascular CT model. Degrees of stenosis in invasive coronary angiography and CCTA were both divided into mild (<50%), moderate (50-69%), severe (70 99%), total occlusion (100%).

**The arterial access (Femoral approach):** Local anesthetic was introduced into an area 3 to 4 cm in diameter 3 to 4 cm below the inguinal ligament along the course of the femoral artery. An 18-gauge needle is introduced through the skin and tunnel into the lumen of the femoral artery. Once blood flows freely through the needle, a Teflon-coated guide wire is advanced into the lumen of the punctured vessel. Then a sheath with a side arm port is advanced over the wire into the vessel lumen, and the wire is removed.

**Left Coronary Imaging:** The left main artery should be approached in the 30-degree LAO projection and cannulated by JL4. A contrast injection in the left coronary cusp is a reasonable first step to define the ostium of the LM coronary artery. Left main coronary artery can be visualized mainly by AP view. Proximal part and mid-segment of LAD can be visualized clearly by AP cranial, RAO cranial and LAO cranial in patient with long left main but can be visualized by LAO caudal in patient with short left main artery. Distal LAD can be visualized clearly by AP caudal, LAO caudal and RAO caudal. AP caudal and RAO caudal views are the main views for visualization of LCx artery [18].

**Right coronary artery imaging:** The RCA should be approached in the 30-degree LAO projection. The JR4 is advanced to the aortic valve level and is slowly withdrawn approximately 2 cm while clockwise rotation is applied to rotate the catheter anteriorly to the right sinus of Valsalva. Then the catheter should sit in the RCA ostium. Usually, two or three views of the RCA are obtained. The LAO view is useful to evaluate the proximal and mid-RCA. The AP view with 30-degree cranial angulation is often the best for evaluating the RCA bifurcation and Ostia of the PDA and poster lateral branches. A shallow RAO view is useful to show the entire PDA. In the RAO view, the marginal branches point anteriorly, and the atrial branches point posterior; thus, this view is useful in differentiating atrial and marginal branches that may be overlapped in an LAO view. The lateral view may be useful to evaluate the mid-RCA and the Ostia of RV marginal branches [18].

**Angiographic evaluation of CAD severity:** All coronary angiography images were interpreted by an independent ICA reader blinded to all patient characteristics and CCTA results. The coronary angiography was qualitatively evaluated for coronary artery stenosis.

**Statistical analysis**

Statistical analysis was done by SPSS v27 (IBM©, Chicago, IL, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analysed by unpaired student t-test. Quantitative non-parametric data were presented as median and interquartile range (IQR) and were analysed by Mann Whitney-test. Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. Receiver Operating Characteristic curve (ROC-curve) analysis and univariate and multivariate analysis were performed. A two tailed P value < 0.05 was considered statistically significant.

## Results:

Baseline characteristics of the studied patients. Table 1

**Table (1): Baseline characteristics of the studied patients:**

| | | n (%) |
|---|---|---|
| **Sex** | **Male** | 84 (42.0%) |
| | **Female** | 116 (58.0%) |
| **Age (years)** | **Mean ± SD** | 47.0 ± 7.77 |
| | **Range** | 35 - 67 |
| **BMI (kg/m$^2$)** | **Mean ± SD** | 22.52 ± 3.17 |
| | **Range** | 17 – 27.9 |

BMI: body mass index

Age was significantly lower in females' group than males' group. BMI was significantly higher in females' group than males' group (P <0.05). Hypertension and smoking status were significantly lower in females' group than males' group. Obesity was significantly higher in females' group than males' group (P <0.05). DM, dyslipidemia, and family history of CAD were insignificantly different between both groups. Table 2

**Table (2): Age, BMI and risk factors in both groups:**

| | **Total (n =200)** | **Males (n = 84)** | **Females (n = 116)** | **P value** |
|---|---|---|---|---|
| **Age (years)** | 47.0 ± 7.77 | 49.81 ± 7.99 | 44.97 ± 6.97 | **<0.001*** |
| | 35 - 67 | 35 - 67 | 35 - 59 | |
| **BMI (kg/m$^2$)** | 22.52 ± 3.17 | 20.83 ± 2.71 | 23.74 ± 2.92 | **<0.001*** |
| | 17 – 27.9 | 17 - 25.5 | 18.7 - 27.9 | |
| **Risk factors** | | | | |
| **DM** | 28 (14%) | 12 (14.29%) | 16 (13.79%) | 1.000 |
| **Hypertension** | 116 (58%) | 60 (71.43%) | 56 (48.28%) | **0.001*** |
| **Dyslipidemia** | 88 (44%) | 36 (42.86%) | 52 (44.83%) | 0.885 |
| **Family history of CAD** | 112 (56%) | 48 (57.14%) | 64 (55.17%) | 0.781 |
| **Obesity** | 68 (34%) | 20 (23.81%) | 48 (41.38%) | **0.01*** |
| **Smoking status** | 32 (16%) | 29 (34.52%) | 3 (2.58%) | **<0.001*** |

BMI: body mass index, DM: Diabetes mellitus, CAD: Coronary artery disease, *: significant as p value ≤0.05.

Typical angina and atypical angina and were significantly higher in males' group than females' group (p =0.008, =0.003 respectively). Nonanginal chest pain was significantly higher in females' group than males' group ($p < 0.05$). Patients with low pretest probability score were significantly higher in females' group than males' group and patients with intermediate score were significantly higher in males' group than females' group ($p < 0.05$). Calcium score was significantly lower in females' group than males' group ($p < 0.05$). Table 3

**Table (3): Chest pain, pretest probability of coronary artery disease and Calcium score between both groups:**

| | | **Total (n =200)** | **Males (n = 84)** | **Females (n = 116)** | **P value** |
|---|---|---|---|---|---|
| **Chest pain** | **Typical angina** | 60 (30.0%) | 34 (40.48%) | 26 (22.41%) | **0.008*** |
| | **Atypical angina** | 76 (38.0%) | 42 (50.0%) | 34 (29.31%) | **0.003*** |
| | **Nonanginal chest pain** | 64 (32.0%) | 8 (9.52%) | 56 (48.28%) | **<0.001*** |
| **Pretest probability Score** | **Low** | 88 (44.0%) | 24 (28.57%) | 64 (55.17%) | **<0.001** |
| | **Intermediate** | 112 (56.0%) | 60 (71.43%) | 52 (44.83%) | **<0.001** |
| **Calcium score** | **Mean ± SD** | 173.38 ± 194.31 | 243.43 ± 212.78 | 122.6 ± 162.72 | **<0.001*** |
| | **Median (IQR)** | 93 (31-240) | 222 (54-290) | 68 (30.25-133) | |

*: significant as p value ≤0.05.

Number of patients with mild Calcium score was significantly higher in females' group than males' group, and number of patients with moderate or high calcium score was significantly higher in males' group than females' group ($p < 0.05$). Females without CAD was significantly higher than males ($p < 0.05$). Single vessel disease and non-significant disease were insignificantly different between males and females. All of patients with multivessel disease were males. Table 4

**Table (4): Calcium score categories and coronary angiography in both groups:**

| | | Total (n =200) | Males (n = 84) | Females (n = 116) | P value |
|---|---|---|---|---|---|
| **Calcium score** | **Mild** | 101 (50.5%) | 28 (33.33%) | 73 (62.93%) | **<0.001** |
| | **Moderate** | 69 (34.5%) | 37 (44.05%) | 32 (27.59%) | **<0.001** |
| | **High** | 30 (15%) | 19 (22.62%) | 11 (9.48%) | **<0.001** |
| **Coronary angiography** | **Absence of CAD** | 76 (38%) | 19 (22.62%) | 57 (49.14%) | **<0.001*** |

| | | | | | |
|---|---|---|---|---|---|
| | **Single-vessel disease** | 44 (22%) | 21 (25%) | 23 (19.83%) | 0.393 |
| | **Multivessel disease** | 20 (10%) | 20 (23.81%) | 0 | **<0.001*** |
| | **Nonsignificant disease** | 60 (30%) | 24 (28.57%) | 36 (31.03%) | 0.756 |

CAD: Coronary artery disease, *: significant as p value ≤0.05

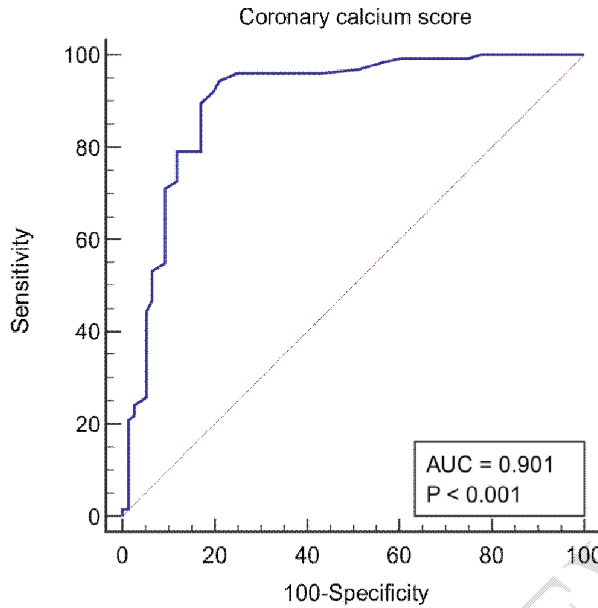
Patients with mild calcium score level were significantly higher in no CAD group than CAD group (p <0.001) and patients with high calcium score were significantly higher in CAD group than no CAD group (p <0.001). There was no significant difference in patients with moderate calcium score between no CAD and CAD groups. Table 5

**Table (5): Relation between calcium score and coronary angiography:**

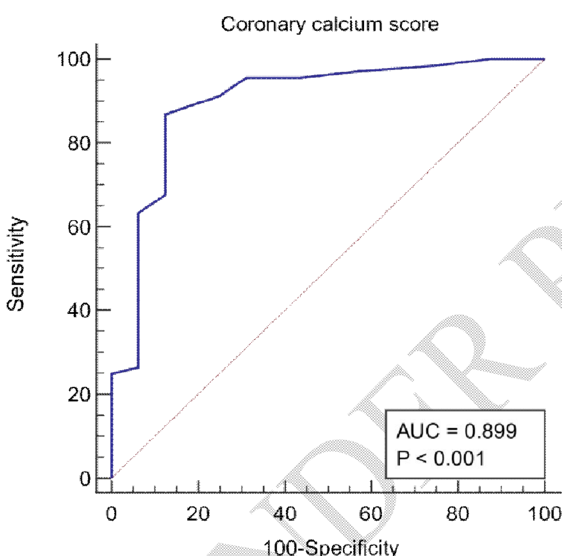
| | | **Absence of CAD (n =92)** | **CAD patients (n =108)** | P value |
|---|---|---|---|---|
| **Calcium score** | **Mild** | 62 | 39 | **<0.001*** |
| | **Moderate** | 27 | 42 | 0.180 |
| | **High** | 3 | 27 | **<0.001*** |

CAD: Coronary artery disease, *: significant as p value ≤0.05.

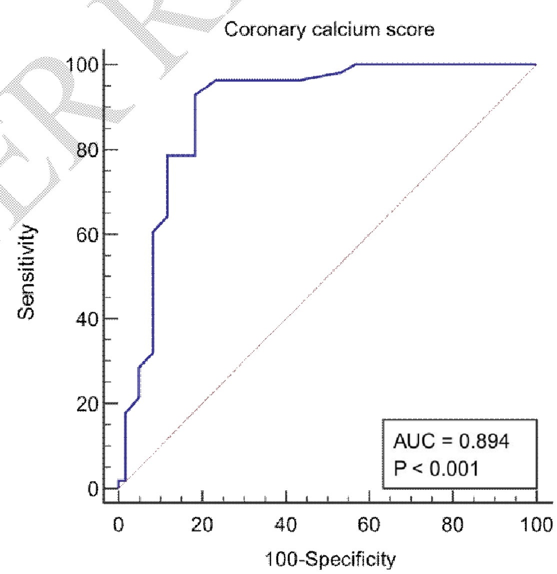
In all patients, coronary calcium score is a good predicator for CAD (AUC =0.901, 95% CI =0.851-0.938, p value <0.001). At cut off value > 101, it has 70.97% sensitivity, 90.79% specificity, 92.6% PPV, and 65.7% NPV. Coronary calcium score is a good predicator for CAD in males (AUC =0.899, 95% CI =0.814 – 0.954, p value <0.001). At cut off value > 166, it has 67.65% sensitivity, 87.5% specificity, 96.7% PPV, and 60.9% NPV. Coronary calcium score is a good predicator for CAD in females (AUC =0.894, 95% CI =0.823 – 0.944, p value <0.001). At cut off value > 101, it has 60.71% sensitivity, 91.67% specificity, 87.2% PPV, and 71.4% NPV. Figure 1




**(A)**




**(B)**




**(C)**

**Figure (1): ROC curve of coronary calcium score for prediction of CAD (A) in all patients, (B) in males and (C) in females.**



In univariate regression analysis, Age (OR: 1.95, 95% CI: 1.14 - 2.28), typical chest pain (OR: 5.21, 95% CI: 3.71 - 8.67), obesity (OR: 1.31, 95% CI: 1.79 – 2.53) hypertension (OR: 2.46, 95% CI: 1.78 - 3.12), hyperlipidemia (OR: 1.93, 95% CI: 1.81 – 2.73), and coronary Ca score (OR: 1.9, 95% CI: 1.63 – 2.25) are independent predictors for CAD in males, while atypical chest pain, family history of CAD, smoking, and diabetes mellites aren't.

In multivariate regression analysis, Age (OR: 2.01, 95% CI: 1.43 – 2.45), typical chest pain (OR: 3.74, 95% CI: 2.51 – 3.08), hypertension (OR: 1.24, 95% CI: 1.76 – 2.18), and coronary Ca score (OR: 2.49, 95% CI: 1.6 – 3.21) are predictors for CAD in males while hyperlipidemia and obesity aren't.

In univariate regression analysis, Age (OR:2.05, 95% CI: 1.33 – 3.17), typical chest pain (OR: 7.21, 95% CI: 5.64 – 9.22), hypertension (OR: 2.14, 95% CI: 1.36 – 3.38), hyperlipidemia (OR: 3.33, 95% CI: 2.02 – 5.47), smoking (OR: 1.59, 95% CI: 1.3 – 1.93), and coronary Ca score (OR: 1.7, 95% CI: 1.2 – 2.43) are independent predictors for CAD in males, while atypical chest pain, family history of CAD, obesity, and diabetes mellites aren't. In multivariate regression analysis, Age (OR:2.19, 95% CI: 1.75 – 2.62), typical chest pain (OR: 3.11, 95% CI: 2.78 – 3.29), hypertension (OR: 1.26, 95% CI: 1.04 – 1.54), and coronary Ca score (OR: 1.45, 95% CI: 2.4 – 2.98) are predictors for CAD in males while hyperlipidemia and smoking aren't.

In univariate regression analysis, Age (OR:1.86, 95% CI: 1.57 – 2.43), typical chest pain (OR: 3.53, 95% CI: 3.15 – 4.49), obesity (OR: 2.71, 95% CI: 1.85 – 3.41), coronary Ca score (OR: 1.92, 95% CI: 1.37 – 2.51), hyperlipidemia (OR: 3.33, 95% CI: 2.02 – 5.47) are independent predictors for CAD in females while atypical chest pain, family history of CAD, hypertension, diabetes mellites, and smoking are not. In multivariate regression analysis, typical chest pain (OR: 2.23, 95% CI: 3.15 – 4.59), and coronary Ca score (OR: 1.42, 95% CI: 1.19 – 2.41) are predictors for CAD in males while Age, obesity, and hyperlipidemia aren't. Table 6

**Table (6): Logistic regression of various variables for prediction of CAD in all patients:**

| | **Univariate** | **Multi-variate** |
|---|---|---|
| | **Odds ratio (95% CI)** | **Odds ratio (95% CI)** |
| **Age per year** | 1.95 (1.14 - 2.28) | 2.01 (1.43 – 2.45) |
| **Typical Chest pain** | 5.21 (3.71 - 8.67) | 3.74 (2.51 – 3.08) |
| **Atypical chest pain** | 0.98 (0.84 - 1.31) | --- |
| **Family history of CAD** | 1.47 (0.86-1.31) | --- |
| **Obesity** | 1.31 (1.79 – 2.53) | 1.24 (0.89 – 2.14) |
| **Coronary Ca score** | 1.9 (1.63 – 2.25) | 2.49 (1.6 – 3.21) |
| **Hypertension** | 2.46 (1.78 - 3.12) | 1.24 (1.76 – 2.18) |
| **Hyperlipidemia** | 1.93 (1.81 – 2.73) | 1.31 (0.74 – 1.21) |
| **Diabetes mellites** | 0.97 (0.76 – 1.42) | --- |
| **Smoking** | 1.41 (0.86 - 2.93) | --- |

| **Males** | | |
|---|---|---|
| **Age per year** | 2.05 (1.33 - 3.17) | 2.19 (1.75 – 2.62) |
| **Typical Chest pain** | 7.21 (5.64 - 9.22) | 3.11 (2.78 – 3.29) |
| **Atypical chest pain** | 1.51 (0.69 - 1.29) | --- |
| **Family history of CAD** | 1.47 (0.86-1.41) | --- |
| **Obesity** | 0.71 (0.85 – 1.24) | --- |
| **Coronary Ca score** | 1.7 (1.2 – 2.43) | 2.1 (1.7 – 2.43) |
| **Hypertension** | 2.14 (1.36 - 3.38) | 1.26 (1.04 – 1.54) |
| **Hyperlipidemia** | 2.71 (1.59 – 3.19) | 1.86 (0.92 – 1.37) |
| **Diabetes mellites** | 1.41 (0.92 - 2.61) | --- |
| **Smoking** | 1.59 (1.3 - 1.93) | 1.45 (0.87 – 1.11) |
| **Females** | | |
| **Age per year** | 1.86 (1.57 - 2.43) | 1.49 (0.71 – 1.51) |
| **Typical Chest pain** | 3.53 (3.41 - 5.28) | 2.23 (3.15 – 4.59) |
| **Atypical chest pain** | 1.93 (0.48 - 2.52) | --- |
| **Family history of CAD** | 1.1 (0.82-1.63) | --- |
| **Obesity** | 2.71 (1.85 – 3.41) | 1.45 (0.85 – 3.41) |
| **Coronary Ca score** | 1.92 (1.37 – 2.51) | 1.42 (1.19 – 2.41) |
| **Hypertension** | 1.14 (0.76 - 1.38) | --- |
| **Hyperlipidemia** | 3.33 (2.02 - 5.47) | 1.91 (0.84 – 1.26) |
| **Diabetes mellites** | 1.98 (0.41 - 2.61) | --- |
| **Smoking** | 1.13 (0.64 - 1.08) | --- |

## Discussion

Coronary artery disease (CAD) is the single most common cause of death in the developed world and western countries, responsible for about 1 in every 5 deaths [19].

In our present study, Pretest probability score was significantly lower in in females' group than males' group.

Our results were in line with Zhang et al**.** [20] who sought to determine whether the calculation of PTP differ by sex in symptomatic patients referred to coronary computed tomographic angiography (CCTA). The characteristics of 5777 men and women who underwent CCTA were compared. For each patient, PTP was calculated according to the updated Diamond–Forrester method (UDFM) and the Duke clinical score (DCS), respectively. The study concluded that women were more likely to be characterized as having a low PTP.

Moreover, ***Hemal et al. (2016)*** [21] confirmed our finding, as it was reported that, compared to men, all risk scores characterized women as lower risk, and providers were more likely to characterize women as having lower (<30%) pre-test probability for CAD than men (40.7% vs. 34.1%; p<0.001).

In our study, Calcium score was significantly lower in in females' group than males' group.

In consistence with our findings, Wong et al. [22] recruited 663 healthy subjects, aged 30 to 69 years, with no history of cardiovascular disease or diabetes were recruited from the general population. Subclinical coronary atherosclerosis was quantified via the coronary artery calcium score (CAC) with CAC of 0 indicating absence of calcified plaque, 1 to 10 minimal plaque, 11 to 100 mild plaque, and >100 moderate to severe plaque. The investigators found that the CAC score was significantly higher in men than women (43.1% vs 18.0%; P < 0.001).

Our findings reported that the number of patients with mild Calcium score was significantly higher in females' group than males' group, and number of patients with moderate or high calcium score was significantly higher in males' group than females' group.

Comparable to our results, in a recent retrospective cross-sectional study Saudi study carried by Al Helali et al. (2021) [23] with the target of studying the severity of CAC in relation to patient risk in a large sample of asymptomatic Saudi adult patients without pre-existing CAD referred to (64 multidetector spiral) computed tomography for standard indications. The results yielded higher extensive CAC (CCS > 400) in males (3.1%) compared with 1.6% in females. Further, the 90th percentile of CCS was 95.0 in males compared with 53.2 in females.

Similarly, in MESA prospective cohort study designed to investigate subclinical cardiovascular disease in a multiethnic cohort free of clinical cardiovascular disease. to examine the distribution of CAC on the basis of age, gender, and race/ethnicity in a cohort free of clinical cardiovascular disease and treated diabetes. The investigators observed men had higher calcium scores than women and almost two thirds of women (62%) had calcium scores of zero in the study sample, as opposed to 40% of men [24].

In our study, CAD was absent in 76 (38.0%) patients, females without CAD were significantly higher than males. Single vessel disease occurred in 44 (22.0%) patients, there was no significant difference between males and females. Multi vessel disease occurred in 20

(10%) patients, all of them were males. Non-significant disease occurred in 60 (30%) patients, there was no significant difference between males and females.

In agreement with our results, John et al. (2018) [25] study that included 208 consecutive patients hospitalized with CA who underwent resuscitation and subsequent coronary angiogram at an academic tertiary medical center. The primary outcome of interest was presence of obstructive CAD, defined as >1 coronary artery with >70% stenosis or >1 coronary bypass graft with >70% stenosis. It was detected that woman had a trend toward lower rates of obstructive coronary artery disease (CAD) and lower rates of multivessel CAD.

Further, Abbasi et al. (2012) [26] found that two-vessel disease and three-vessel disease were more prevalent amongst the men. However, they highlighted that the number of the involved coronary vessels differed significantly between the males and females ($P < 0.001$). Minimal CAD and single-vessel disease were reported more frequently in the females. This variance may be a result of the larger sample size recruited in the Iranian study, besides the ethnic consideration.

In the present study, coronary calcium score is a good predicator for CAD (AUC =0.901, 95% CI =0.851-0.938, p value <0.001). At cut off value > 101, it has 70.97% sensitivity, 90.79% specificity, 92.6% PPV, and 65.7% NPV. Moreover, it is a good predicator for CAD in females (AUC =0.894, 95% CI =0.823 – 0.944, p value <0.001). At cut off value > 101, it has 60.71% sensitivity, 91.67% specificity, 87.2% PPV, and 71.4% NPV.

Moreover, Choi et al. (2020) [27] included 2,658 patients to determine which stroke patients should undergo evaluation for asymptomatic CAD, and which screening tools are appropriate. They investigated the role of coronary artery calcium (CAC) score as a screening tool for asymptomatic but severe CAD in acute stroke patients. The results found that the sensitivity was 82.03 and the specificity was 48.50 of CAC score cut-off ≥100 for the predicting severe CAD by ROC curve analysis.

In line with our findings, Hanifehpour et al. (2016) [28] conducted a cross sectional study was carried out on a study population of 2527 consecutive stable patients with symptoms suggestive of CAD who were referred for coronary computed tomographic angiography (CCTA). They found that at the cutoff point of 100, they had high specificity (87%), sensitivity (79%), efficiency (84%), PPV (79%), and high NPV (87%) for excluding CAD risk.

Furthermore, in a recent published study, data obtained from 275 CTCA examinations were reviewed. CCS and Framingham risk estimates were compared to obtain the final results of CTCA to detect sensitivity and specificity of each one in detecting obstructive lesions. Patients were categorized as low, intermediate, moderately and high. Their findings found that CCS is a strong discriminator for obstructive CAD with 100% sensitivity and 89.2% specificity, PPV of 79.2%, and 100% NPV [29].

Our study demonstrated by using univariate regression analysis that age, typical chest pain, obesity, coronary Ca score, and hyperlipidemia are independent predictors for CAD in females while atypical chest pain, family history of CAD, hypertension, diabetes mellites, and smoking are not. In multivariate regression analysis, age, typical chest pain, hypertension, and coronary Ca score are predictors for CAD in males while hyperlipidemia and smoking aren't. In females, typical chest pain, and coronary Ca score are predictors for CAD while Age, obesity, and hyperlipidemia are not.

Similarly, Hemal et al. (2016) [21] reported by univariate analysis that age, BMI, and Framingham risk score were predictive of a positive test for CAD in women, while Framingham and Diamond and Forrester risk scores were predictive in men. Moreover, Wong et al. (2021) [22] noted that multivariable analysis revealed LDH was more significantly associated with CAC in women compared with men and generally significant associations of increasing age, male sex, higher blood pressure, increased glucose levels, and higher low-density lipoprotein cholesterol levels with the presence of any CAC.

However, Gheisari et al. (2020) [30] investigated the role of gender in the distribution of different risk factors in ischemic heart disease, so a cross-sectional study was carried out on more than one thousand (N = 1012) patients. The results documented, based on their logistic regression models, that diabetes mellitus, hypertension (HTN), and hyperlipidemia (HLP) had a strong correlation with IHD in their female population. Larger representative sample size and no exclusion of patients with high risk for IHD could explain this variability in results.

## Conclusions:

In patients with chest discomfort with low and intermediate pretest probability of CAD who underwent CCTA and subsequent invasive coronary angiography and revascularization, female patients had lower age, hypertension, pretest probability score, calcium score, atypical angina, nonanginal chest pain and obstructive CAD but had higher BMI, typical angina than males' group. DM, dyslipidemia, smoking status, family history, heart rate, and nonsignificant disease of CAD were insignificantly different between both sexes. In females, coronary calcium score is a good predicator for CAD. When its level exceeds 100, it has 60.71% sensitivity and 91.67% specificity. In addition, it was found that in females typical chest pain and coronary Ca score are predictors for CAD and in males, age, typical chest pain, hypertension, and coronary Ca score are predictors for CAD.

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