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Correlation Between Coronary Calcium Scoring and Duke's Treadmill Score in Patients with Normal Myocardial Perfusion Imaging SPECT

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Abstract: *Background*: Stress myocardial perfusion imaging (MPI) is a highly valuable test in the evaluation and risk stratification of ischemic heart disease. However, negative stress MPI does not exclude coronary atherosclerosis. The Coronary artery calcium (CAC) score is a validated simple test in the evaluation of coronary atherosclerosis. Our goal was to investigate the correlation between CAC score and Duke's treadmill score, as well as the prevalence of CAC in patients with negative MPI. *Methods*: A total of 926 consecutive Egyptian patients, aged 30 to 60 years without known CAD, underwent CAC score testing following normal MPI. *Results*: In the setting of normal MPI among Egyptian patients without known CAD, mean age 48±7 years, 325 (35%) patients had a positive CAC score, and 9% had high CAC>100. Out of CAC>0, 160 were low-risk DTS. Our study showed no correlation between CAC score and DTS (P value=0.5). Age (OR=1.119, P value=<.001 and 95% confidence interval (CI)=1.071 - 1.169), male gender (OR=2.795, P value=.001 and 95% (CI)=1.494 - 5.230), and statin therapy (OR=2.020, P value=.008 and 95% (CI)=1.199 - 3.404), were significant independent predictors of a high CAC score>100. *Conclusion*: In a large number of normal MPI Egyptian patients without known CAD, CAC prevalence was 35%, confirming the beneficial value of adding CAC score test to negative MPI for cardiovascular risk stratification and screening for subclinical CAD regardless of DTS. Higher CAC values and prevalence were associated with age and male gender.

Keywords: CAC Score, DTS, MPI

1. Introduction

The coronary artery calcification (CAC) score test is a simple anatomical test, relatively cheap, and does not require iodinated contrast agents. In conjunction with stress tests or myocardial perfusion imaging (MPI), the CAC score test improves the sensitivity and specificity of these functional tests. As well, it has great value for cardiovascular risk stratification and screening for subclinical CAD. When compared to the DTS and treadmill exercise tests alone, adding the CAC score enhanced identification of obstructive CAD. It has the potential to be a quick test for fine tuning risk stratification in non-diagnostic treadmill exercise tests [1].

Usually, those with borderline or equivocal stress tests are planned for further evaluation at another session either by MPI or other non-invasive tests. The CAC score does not require any prior preparation and has a rapid turnaround time. This fact will save time and cut the need for subsequent visits. Moreover, the calcium score also guides therapy for primary prevention. CAC greater than zero should trigger statin therapy and risk factor modification [2].

2. Methods

2.1. Study Population

This was a cross-sectional study from retrospectively collected data in an outpatient radiology Center, Alfa scan,

Cairo, Egypt. The study consisted of 926 consecutive patients, between the ages of 30 and 60 years, without known CAD and with no history of PCI or CABG, referred for a clinically indicated stress MPI study, between January 2018, and December 2019. All patients underwent CAC score testing offered in a complimentary fashion by a multislice computed tomography machine following a negative MPI study. All patient's data were extracted from medical records and electronic database. Age, hypertension, hypercholesterolemia, family history of CAD, diabetes, and smoking status (current, never, and former), were among the demographic and clinical data collected by one clinical coordinator. A systolic blood pressure of 140 mm Hg, a diastolic blood pressure of 90 mm Hg, and /or antihypertensive treatment were all considered hypertension. Patients using ant-diabetic medication self-reported diabetes mellitus (DM). Dyslipidemia was defined as total cholesterol ≥ 240 mg/dl or low-density lipoprotein (LDL) cholesterol ≥ 140 mg/dl and/or high triglyceride (TG) or lower high-density lipoprotein (HDL) cholesterol, or previous use of lipid-lowering medication. An informed consent was obtained from all subjects and the study was approved by the research ethics committee (REC) of Al Azhar university hospital, Car-med._0000074.

2.2. Myocardial Perfusion Imaging

Nine hundred and twenty-six patients underwent a symptom-limited treadmill exercise stress test according to the standard Bruce protocol [3]. Termination of the stress test was performed according to recommendations in the updated guidelines of exercise testing. All patients were subjected to same-day stress-only or two-day stress/rest MPI imaging following ASNC 2016 guidelines. A dual-head Philips Jetstream camera (Philips Healthcare, Milpitas, California) with low-energy, and high-resolution collimators was used to acquire all images. According to the standard protocols, all associated data and radionuclide images were processed. Using the standard 20-segment model, myocardial perfusion images were interpreted [4]. Each segment was semi-quantitatively assessed by at least two experienced nuclear cardiology experts, with 0 indicating normal uptake, 1, 2, and 3 indicating mild, moderate, and severe reductions in uptake, respectively, and 4 indicating no uptake. Summed stress, summed difference, and summed rest scores were calculated. High-risk markers were reported, including increased lung-to-heart ratio, transient left ventricular cavity dilatation, and abnormal regional and global wall motion abnormalities. A normal SPECT MPI study was defined as normal myocardial perfusion images (SSS<4 and SDS=0), no left ventricular dilatation and ejection fraction above 50%. All scans were reported by a board-certified nuclear cardiology expert.

2.3. CT Imaging Protocol & CAC Scoring

Using the Agatston scoring method, the CAC score was quantified and was confirmed when needed in OsiriX, Version 3.9 (Pixmeo, Switzerland) 64-bit image processing software [5]. CT scanning was performed on a Philips ICT 256 (Alfa scan, Cairo, Egypt). Coronary CT scans were performed with 2.5 cm slice thickness, 50% overlap, 120 kV, 50 to 100 mA, and 90 to 180 mAs tube current, automatically selected by Philips iDose Version V3. CAC scores>100 and ≥ 400 Agatston units were identified as high CAC scores, as they were significantly associated with an increased risk of mortality as well as the occurrence of major cardiac events (MACE) [6].

2.4. Treadmill Exercise

The Duke treadmill score (DTS) was calculated as follows: Duke treadmill score=maximum exercise time in minutes – 5×ST segment deviation in mm – 4×angina index. Angina index is expressed as 0=no angina, 1=non-limiting angina, and 2=exercise limiting angina. A Duke treadmill score ≥ 5 indicates low-risk for cardiovascular events. Moderate-risk DTS corresponds to values between 4 and -10. A score<–10 indicates high-risk for cardiovascular events [7].

2.5. Statistical Approach

SPSS version 17 (Softonic International, San Francisco, California) was used for statistical analysis. The differences between categorical variables and continuous variables were tested using χ^2 tests and unpaired t tests, respectively. An ANOVA test was used for inter-group comparison. Prediction analysis was done using logistic regression for identifying predictors of CAC>100. A P value of<0.05 was considered statistically significant.

3. Results

Table 1. *Baseline characteristics of the study population. N=926.*

Study population	N=926
Age (years ± SD)	48±7.4
Male sex, n (%)	599 (65%)
Hypertension, n (%)	423 (46%)
Dyslipidaemia, n (%)	537 (58%)
Diabetes mellitus, n (%)	233 (25%)
Smoking, n (%)	453 (49%)
Treadmill stress, n (%)	926 (100%)
Mean exercise duration (minutes)±SD	8.1±1.9
Coronary artery calcium score n (%)	926 (100%)
Obesity, n (%)	213 (25%)
Exercise chest pain, n (%)	166 (18%)
Mean Metabolic equivalents±SD	9.5±2.1
Abnormal exercise ST changes, n (%)	555 (60%)
History of chest pain, n (%)	619 (67%)

The demographic characteristics of the study population are presented in Table 1. Mean age was 48±7 years, with a range 30 to 60 years, 599 (65%) were males and 619 (67%) complained of chest pain during routine activity. Traditional risk factors of dyslipidemia, hypertension, tobacco use, and diabetes mellitus (DM) were (58%, 46%, 49%, and 25%, respectively). Patients with known CAD, and a history of PCI or CABG were excluded. Mean exercise duration (Bruce protocol) was 8.1±3.8 minutes with a range of 3.21 to 16.41 minutes. Out of 926 patients, 555 patients (60%) had an

abnormal exercise ECG and 166 (18%) complained of chest pain during exercise testing.

Out of 926 patients with normal MPI and without known CAD aged 30-60 years, 325 (35%) had a positive CAC score ranging from (1-1500) Agatston units, and 9% had a high CAC score>100. The highest CAC prevalence 213 (48%) was in the age group (50-60 years), while only 22 (15%) in the age group (30-39) (Figure 1). Across all age groups, men had higher calcium levels than women (amounts and prevalence). Moreover, the mean CAC score increased with age exponentially for both men and women, following a similar trend. Upon reaching age 50, the rate of rise was higher in women than in men, and CAC prevalence increased higher with age Figure 2.

Figure 3 Shows a positive linear correlation between CAC score and age.

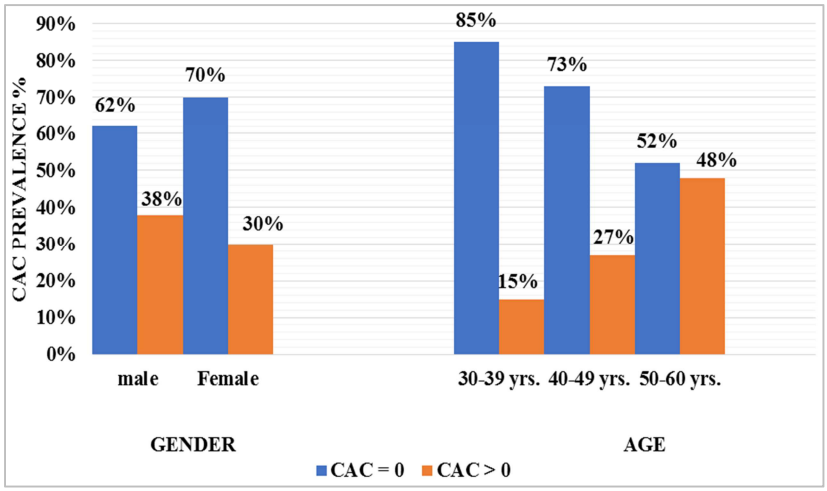

Figure 1. *Prevalence% of CAC across age groups and gender. Total=926.*

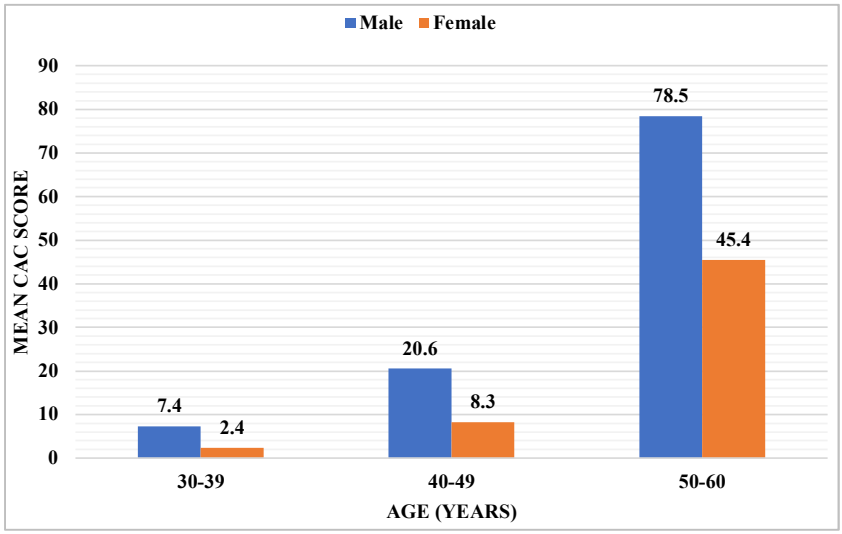

Figure 2. *Mean CAC score among men and women across all study age groups. Values are presented as means. P<.001 between CAC score and age.*

Table 2. *Baseline characteristics by CAC stages. Total=926.*

		CAC=0 (N=601)	CAC 1-10 (N=118)	CAC 11-99 (N=124)	CAC 100-399 (N=62)	CAC ≥400 (N=21)	P value
Gender, n, (%)	Male (N=599)	372, (62%)	75, (12.5%)	90, (15%)	48, (8%)	14, (2%)	.041
	Female (N=327)	229, (70%)	43, (13%)	34, (10%)	14, (4%)	7, (2%)	
Age, n, (%)	30-39 yrs. (N=146)	124, (85%)	11, (8%)	8, (5%)	3, (2%)	0	.000
	40-49 yrs. (N=335)	245, (73%)	41, (12%)	31, (9%)	16, (5%)	2, (.6%)	
	50-60 yrs. (N=445)	232, (52%)	66, (15%)	85, (19%)	43, (10%)	19, (4%)	
Dm, n, (%) (N=233)		126, (54%)	41, (18%)	41, (18%)	18, (8%)	7, (3%)	0.003
Hypertension, n, (%) (N=423)		246, (58%)	62, (15%)	64, (15%)	36, (8.5%)	15, (3.5%)	0.001
Dyslipidaemia, n, (%) (N=537)		318, (59%)	75, (14%)	81, (15%)	48, (9%)	15, (3%)	0.000
Smoking, n, (%) (N=453)		276, (61%)	69, (15%)	75, (16.5%)	28, (6%)	5, (1%)	0.046
Statin therapy, n, (%)	On statin (N=355)	200, (56%)	51, (14%)	56, (16%)	39, (11%)	9, (3%)	0.000
	Not on statin (N=526)	378, (72%)	62, (12%)	56, (11%)	20, (4%)	10, (2%)	

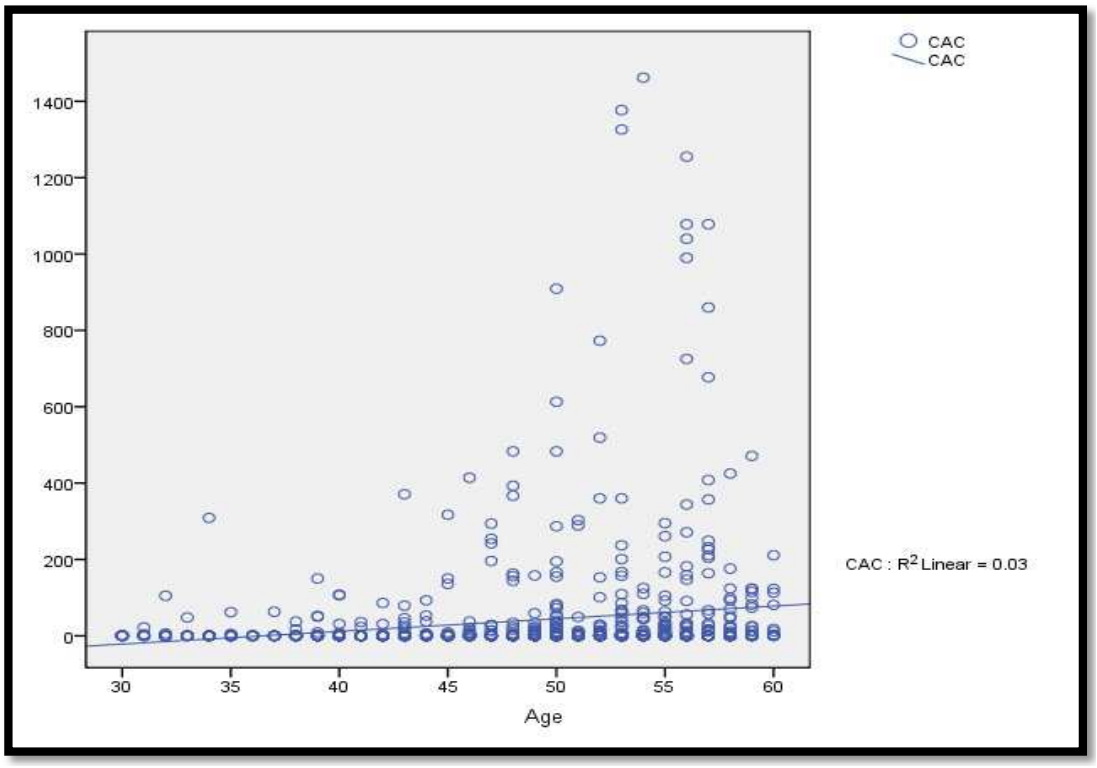

Figure 3. *Scatter plot of correlation between CAC score and age.*

Table 2 All traditional cardiovascular risk factors (hypertension, DM, dyslipidemia, and smoking) had a significant association with increasing CAC among negative MPI patients (P values=.001,.003,<.001,.046) respectively.

A multivariate logistic regression model was done to identify predictors of high CAC score>100 in negative MPI patients and showed that age (OR=1.119, P value=<.001 and 95% (CI)=1.071 - 1.169), male gender (OR=2.795, P value=.001 and 95% (CI)=1.494 - 5.230), and statin therapy (OR=2.020, P value=.008 and 95% (CI)=1.199 - 3.404) were significant independent predictors of a high CAC score>100 as shown in Table 3.

Figure 4 Statin therapy showed a significant association with increasing CAC, P value=<.001. Those without statin therapy were 526 (57%). Out of this group, 148 (28%) patients had a positive CAC score compared to 378 (72%) patients with a zero CAC score in the same group. On the other hand, those on statin therapy were 355 (38%) patients. Out of this group, 155 (44%) patients had a positive CAC score in comparison to 200 (56%) patients had a zero CAC score.

Out of 325 (35%) CAC scores>0, 160 were low-risk DTS, 163 were intermediate-risk DTS and 2 were high-risk DTS. The CAC score showed no statistically significant correlation with DTS among normal MPI study patients (P value=0.5) Figure 5.

Owing to the relatively low-risk nature of the study population, as all were normal stress MPI, 459 (49.6%) were low-risk DTS, 459 (49.6%) were intermediate-risk DTS, and 8 patients (0.8%) were high-risk DTS. All the high-risk DTS patients were women, aged 40-60 years and a mean CAC score of 3.5, mean exercise duration 5.35 minutes, baseline ECG changes were reported in all 8 patients and exercise chest pain was reported in 6 patients. In contrast, the majority of those with low-risk DTS were males, 359 (38.7%).

Table 3. *Predictors of high CAC score>100 in normal MPI patients.*

Variables	P-value	Odds ratio	95% confidence interval	
			Lower	Upper
Age	.000	1.119	1.071	1.169
Gender	.001	2.795	1.494	5.230
Hypertension	.641	1.300	.432	3.908
DM	.544	.701	.222	2.208
Dyslipidemia	.319	1.798	.567	5.697
Smoking	.330	.692	.330	1.451
Chest pain	.741	.920	.562	1.507
Exercise ejection fraction	.905	.998	.967	1.030
DTS	.529	.983	.931	1.037
Risk factors number	.934	1.043	.383	2.842
Exercise chest pain	.149	.574	.270	1.221
Statin therapy	.008	2.020	1.199	3.404

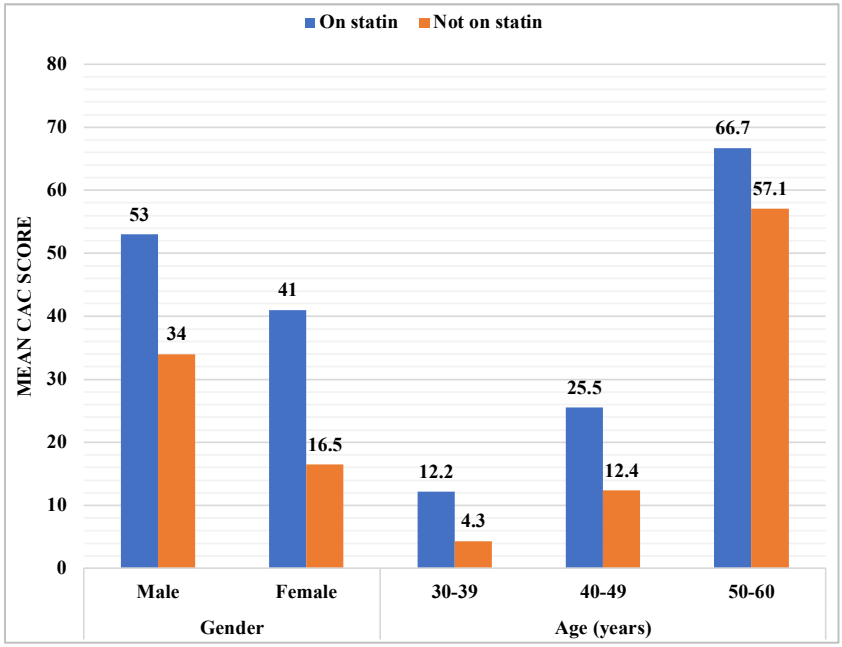

Figure 4. *Mean CAC score among men and women and across age stages in patients on statin and not receiving statin. Values are presented as means. P<.001 between CAC score and statin therapy.*

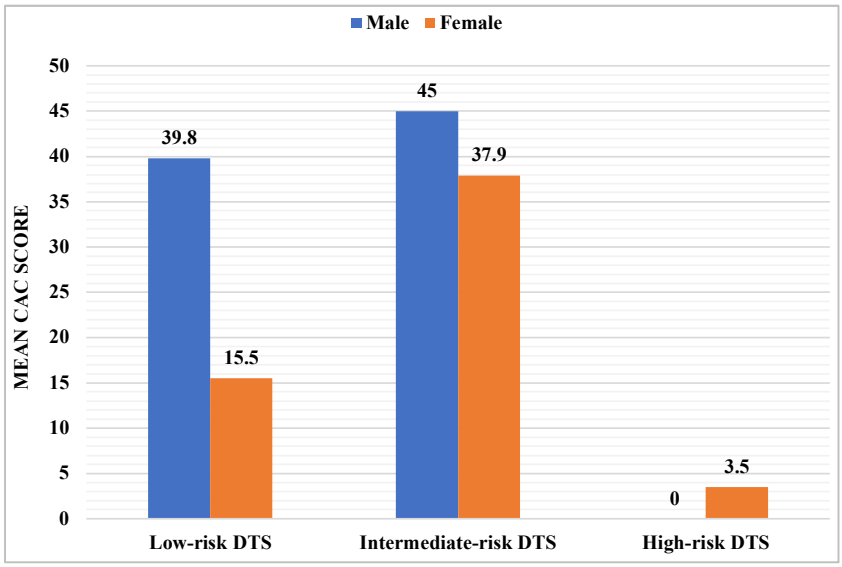

Figure 5. *Mean CAC score among men and women in each DTS risk category. P value=0.5 between CAC score and DTS.*

4. Discussion

The current study showed that among 926 patients with negative MPI and without known CAD aged 30-60 years, CAC prevalence was 35%. Also, (9%) had a high CAC score>100. Highest CAC prevalence was associated with age and male gender. Previous studies have shown that the prevalence of CAC among a small number of negative MPI Saudi subjects without known CAD was 114 (55%) [8]. While among asymptomatic individuals was 1053 (24%), 493 (27%) [9, 10] respectively.

The findings are consistent with the Multi-Ethnic Study of Atherosclerosis *(MESA*), which reported that male gender, hypertension, Dm, high body mass index, and age were associated with an increase in severity and incidence of coronary artery calcifications.

Age, male gender, and statin therapy were significant independent predictors of high CAC score (>100) in negative MPI Egyptian subjects without known CAD. *Sekine et al.* showed the same association in their study about CAC prevalence among asymptomatic Japanese subjects [10].

Allam et al. Pointed out the need for assessment of total body calcium, as subclinical atherosclerosis in extra coronary arterial beds sometimes predated coronary atherosclerosis in negative MPI patients without known CAD [11].

Various studies have shown the incremental prognostic and diagnostic value of adding CAC score test to MPI study for

cardiovascular risk stratification and subclinical CAD detection [12]. CAC positive/MPI positive patients have the highest mortality rate (12.5%), compared to 10.7% in CAC positive/MPI negative patients. On the other hand, patients with zero CAC/negative MPI have the lowest mortality rate (1.6%) [13]. A CAC score>0 should prompt a treatment strategy such as risk factor modification and statin therapy [14].

The current study showed that statin therapy is associated with increased coronary artery calcification (P value=<.001). Previous studies have shown the association between statin therapy and the increase in CAC score [15]. *AL Rifai et al.* reported that although statin therapy is linked with an increase in CAC, it does not affect the prognostic capability of coronary artery calcifications. Also, CAC is associated with incident atherosclerotic cardiovascular disease regardless of incidence or baseline statin use [16].

This study showed no correlation between DTS and CAC score (P value=0.5). The characteristic pattern of coronary calcification across different DTS risk categories is simply owing to the nature of the CAC score as an anatomical quantifiable risk stratification score, rather than being a representation of the clinical and exercise variables, which is the case in DTS.

All the high-risk DTS patients were women, and most low-risk DTS were men. This finding points to the weight of chest pain during stress tests in DTS calculation. Atypical chest pain among women during exercise is not uncommon, which may affect DTS accuracy in risk stratification among the female gender. Lower exercise capacity or inaccurate description of chest pain may explain this finding. *Paul et al.* reported that according to gender, clinical risk factors and exercise variables have different effect on overall mortality. Also, risk stratification is enhanced with a gender specific risk score, and patients at higher risk are easily identified [17]. DTS is not superior to exercise capacity alone, even though it can predict cardiovascular morbidity and mortality. Symptoms and ST segment changes during exercise stress test does not give supplemental prognostic information particularly in old women [18].

5. Study Limitations

The study had some limitations, including that it is a retrospective cross-sectional single-center study, with few numbers of patients with high-risk DTS. Also, MPI sensitivity for detecting ischemia is not 100%, so some patients may have had obstructive CAD.

6. Conclusion

In the setting of normal MPI among Egyptian patients without known CAD aged 30-60 years, CAC prevalence was 35% and 9% had a high CAC score>100. Higher CAC values and prevalence were associated with age and male gender. There was no clear correlation between CAC score and DTS. Age, male gender, and statin therapy were strong independent predictors of a high CAC score. The findings suggest the addition of CAC score test to negative MPI study for cardiovascular risk stratification and screening for subclinical CAD regardless of DTS.

Conflict of Interest

The authors declare that they have no competing interests.

Ethical Approval

The Research Ethics Committee at the Faculty of Medicine, Al-Azhar University, Cairo, Egypt, granted ethical approval for data collection Car-med._0000074.

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