Diagnostic Value of Coronary Artery Calcium Scoring in Low-Intermediate Risk Patients Evaluated in the Emergency Department for Acute Coronary Syndrome

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Early and accurate triage of patients with possible ischemic chest pain remains challenging in the emergency department because current risk stratification techniques have significant cost and limited availability. The aim of this study was to determine the diagnostic value of the coronary artery calcium score (CACS) for the detection of obstructive coronary artery disease (CAD) in low- to intermediate-risk patients evaluated in the emergency department for suspected acute coronary syndromes. A total of 225 patients presenting to the emergency department with acute chest pain and Thrombolysis In Myocardial Infarction (TIMI) scores <4 who underwent non-contrast- and contrast-enhanced coronary computed tomographic angiography were included. CACS was calculated from the non-contrast scan using the Agatston method. The prevalence of obstructive CAD (defined from the contrast scan as ≥50% maximal reduction in luminal diameter in any segment) was 9% and increased significantly with higher scores (p <0.01 for trend). CACS of 0 were observed in 133 patients (59%), of whom only 2 (1.5%) had obstructive CAD. The diagnostic accuracy of CACS to detect obstructive CAD was good, with an area under the receiver-operating characteristic curve of 0.88 and a negative predictive value of 99% for a CACS of 0. In a multivariate model, CACS was independently associated with obstructive CAD (odds ratio 7.01, p = 0.02) and provided additional diagnostic value over traditional CAD risk factors. In conclusion, CACS appears to be an effective initial tool for risk stratification of low- to intermediate-risk patients with possible acute coronary syndromes, on the basis of its high negative predictive value and additive diagnostic value.   © 2011 Elsevier Inc. All rights reserved. (Am J Cardiol 2011;107:17–23)

The coronary artery calcium score (CACS) has been proposed as an alternative approach for stratifying cardiovascular risk. In contrast to contrast-enhanced coronary computed tomographic angiography (CCTA), coronary artery calcium scoring has low radiation exposure, produces highly reproducible results, and requires no medication or contrast use and minimal patient cooperation. It has been shown that the presence of calcium is a quantifiable marker of atherosclerotic disease,[1] with good correlations with histologic, intracoronary ultrasound, and angiographic measures of plaque burden.[2,3] Moreover, CACS is an established predictor of cardiovascular events.[4] However, the role of CACS as part of the initial diagnostic evaluation of patients with suspected acute coronary syndromes (ACS) remains controversial.[5–10] The primary goal of this study was to determine the diagnostic utility of CACS in low- to intermediate-risk patients presenting to the emergency department (ED) with chest pain or angina-like symptoms, nondiagnostic electrocardiographic findings, and negative cardiac biomarkers.

Methods

From March 2007 to January 2009, all consecutive patients who were evaluated in the ED for suspected ACS with nondiagnostic electrocardiographic findings and negative initial cardiac troponin and subsequently underwent CCTA and coronary artery calcium scoring were retrospectively studied. Exclusion criteria included known significant coronary artery disease (CAD), defined as coronary artery stenosis ≥50% and/or previous coronary revascularization. Troponin I was considered negative when <0.5 ng/dl (the
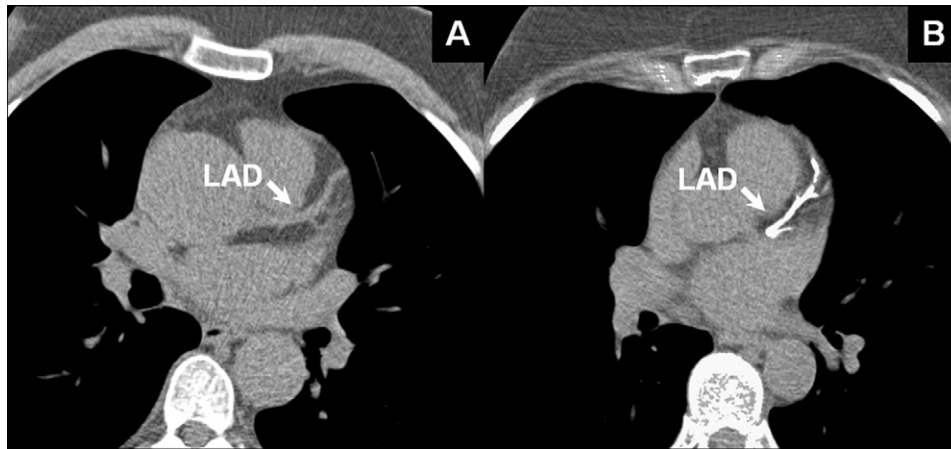
Figure 1. CACS reconstructed images in 2 different patients presenting with acute chest pain to the ED. *(A)* Absence of calcification in the proximal and mid left anterior descending coronary artery (LAD). *(B)* Heavy calcification in the same coronary segments is identified *(yellow)*.

upper limit of normal at our institution), and electrocardiographic findings were considered nondiagnostic in the absence of ST-segment elevation or depression ≥1 mm or T wave >4 mm in ≥2 contiguous leads. For the purpose of analysis, a modified Thrombolysis In Myocardial Infarction (TIMI) risk score[11] was retrospectively calculated. Because patients with positive troponin, diagnostic electrocardiographic findings for ischemia, and/or known significant CAD were excluded from the analysis, and the number of angina episodes was not consistently reported, a maximum score of 3 was possible on this modified scale. Pretest probability of CAD on the basis of American College of Cardiology and American Heart Association guidelines was also retrospectively calculated for further analysis.[12] The CAD risk factors were defined as follows: (1) diabetes mellitus as a history of ≥2 determinations of fasting blood glucose ≥126 mg/dl or taking insulin or oral antidiabetic drugs; (2) hypertension as a history of ≥2 determinations of systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or taking antihypertensive drugs; (3) smoking history, defined as current or previous tobacco use of 5 pack-years; (4) hypercholesterolemia as a history of total cholesterol ≥200 mg/dl and/or low-density lipoprotein ≥130 mg/dl or taking statins; and (5) positive family history when first-degree relatives had myocardial infarctions, coronary revascularization, or sudden death before the age of 55 years (men) and 65 years (women). The study was approved by the institutional review board of the Mount Sinai School of Medicine.

CCTA was performed using a 64-slice scanner (LightSpeed VCT, XT; GE Healthcare, Milwaukee, Wisconsin) with either retrospective or prospective electrocardiographic gating. All patients received sublingual nitroglycerin (0.4 mg) and β blockers (intravenous metoprolol 5 to 30 mg) if their heart rates were >60 beats/min, unless contraindications were present. After standard scouts in the supine position, a noncontrast scan was performed to assess coronary artery calcification. This consisted of a single inspiratory breath-hold craniocaudal acquisition covering from the carina to the inferior heart border. Prospectively triggered imaging was used, with a tube voltage and an effective current of 120 kVp and 200 mA, respectively. Subse-

quently, contrast-enhanced angiography was performed in which the contrast circulation time was determined with a timed bolus of 20 ml of contrast agent (Isovue 370; Schering AG, Berlin, Germany) or with the bolus-tracking technique with a threshold of 100 Hounsfield units in a region of interest in the ascending aorta. A 70- to 100-ml contrast bolus followed by 50 ml of saline was injected through a peripheral vein at 4 to 5 ml/s. For scanning, a detector collimation of 64×0.625 mm was used, with a gantry rotation of 330 ms, pitch of 0.16 to 0.25, tube voltage of 120 kVp, and tube current of 400 to 700 mA. Tube current modulation was used if applicable in the retrospective protocols.

Axial images were reconstructed with an image matrix of 512×512 pixels and slice thickness of 0.625 mm. A half-scan algorithm with a temporal resolution of approximately 165 ms was performed for retrospectively gated acquisitions, whereas a multisegment algorithm was used for heart rates >70 beats/min. Images were preferentially reconstructed in the mid-diastolic phase (65% to 85% of the cardiac cycle) for motion-free images of the coronary arteries. The CACS was calculated using the Agatston method, which is determined by calcified area and calcium score density.[1] Semiautomatic software (TeraRecon, San Mateo, California) displayed colored spots for calcium, defined as hyperattenuating lesions with ≥130 Hounsfield units with an area ≥1.0 mm², which were manually identified by the operator and automatically summed to obtain total calcium score (Figure 1). Patients were stratified according to CACS into 3 groups: normal (CACS = 0), low (CACS = 1 to 100), and high (CACS >100).[13] The results of CCTA were interpreted on a dedicated workstation (Aquarius; TeraRecon) by 2 experienced readers. Coronary assessment was performed on original axial sources images, thin-slice maximum-intensity projections, or multiplanar reformatted reconstructions. Significant or obstructive CAD was defined as ≥50% luminal diameter narrowing and considered moderate or severe when causing 50% to 70% or >70% stenosis, respectively.[14,15] Plaques causing <50% stenosis were considered nonsignificant disease. The presence of calcification per artery was also evaluated, as well as the composition of coronary plaques responsible for significant steno-

sis. Briefly, calcified plaque was defined as any lesion with attenuation >130 Hounsfield units and noncalcified plaque with attenuation below the contrast-enhanced coronary lumen and Hounsfield units >0.[16] Nondiagnostic results of CCTA were considered when any proximal or mid coronary segment was not evaluable because of motion artifacts, calcification, or low contrast-to-noise ratio.

Statistical analysis was performed with SPSS version 15.0 (SPSS, Inc., Chicago, Illinois). Continuous variables are expressed as mean ± SD or as median (range) depending on their distribution. Categorical variables are expressed as total number (percentage). The accuracy of CACS to detect significant CAD was assessed by the area under the receiver-operating characteristic curve. Sensitivity, specificity, and predictive values were calculated for a CACS of 0. Analysis of variance for trend and the Mantel-Haenszel test were performed to evaluate differential distribution of age, CAD risk factors, and significant CAD according to CACS severity. Multivariate analysis was used to identify independent predictors of significant CAD. Two logistic regression models were constructed; the first included age, gender, CAD risk factors, and chest pain characteristics, and the second model additionally included CACS. To evaluate the goodness of fit of the logistic regression models, the coefficient of determination (Nagelkerke's R^2) was calculated.[17] A p value <0.05 was considered statistically significant.

Results

From March 2007 to January 2009, 247 consecutive patients presenting to the ED with suspected ACS underwent CCTA. Of them, 22 patients did not have calcium score scans performed, because of histories of coronary revascularization or young age (<30 years). Therefore, the final cohort consisted of 225 patients. Study population characteristics are listed in Table 1. The prevalence of significant CAD was 9% and increased along with higher pretest probability and higher TIMI risk score (Figure 2). All patients with severe coronary stenosis on CCTA (n = 7) were referred for invasive coronary angiography and subsequent coronary revascularization. Patients with moderate stenosis were referred for invasive coronary angiography (n = 6), stress testing (n = 2), or clinical follow-up (n = 5), as determined by the attending physician in the ED in conjunction with the consulting cardiologist. Of a total of 13 patients referred for invasive coronary angiography, 2 had <50% coronary stenosis, and 11 had ≥1-vessel disease with >50% coronary stenosis. In 6 patients (3%), CCTA was considered a nondiagnostic test, and patients underwent nuclear stress testing or coronary angiography on the basis of the recommendation of the cardiology consult service. In these patients, the presence of significance was established on the basis of the subsequent test results. Mean radiation exposure for CACS scans was 0.8 ± 0.3 mSv and for CCTA was 8.5 ± 3.2 mSv.

The percentage of patients with CACS >0 was significantly higher in the presence of intermediate or high pretest probability compared to low pretest probability and gradually augmented with the modified TIMI risk

Table 1
Study population characteristics (n = 225)

Variable	Value
Age (years)	53 (32–89)
Men	102 (45%)
Race	
Hispanic	96 (43%)
African American	64 (28%)
Caucasian	49 (21%)
Asian American	16 (7%)
Cardiac risk factors*	
Hypertension	104 (46%)
Hypercholesterolemia	72 (32%)
Current or former smoker	69 (30%)
Diabetes mellitus	44 (20%)
Medical treatment	
Aspirin	41 (18%)
Statins	34 (15%)
Angiotensin-converting enzyme inhibitors	23 (10%)
Calcium channel antagonists	18 (8%)
Diuretics	14 (6%)
β blockers	10 (4%)
Symptoms	
Atypical chest pain	190 (84%)
Typical chest pain	35 (16%)
Acute dyspnea	39 (17%)
Chest discomfort and palpitations	10 (4%)
TIMI risk score	
0	134 (60%)
1	69 (31%)
2	18 (8%)
3	4 (2%)
Pretest probability of CAD	
Low	33 (15%)
Intermediate	172 (76%)
High	20 (9%)
Creatinine (mg/dl)	0.93 ± 0.21
CACS	0 (0–3,454)
Multidetector computed tomography	
Heart rate (beats/min)	67.2 ± 12.1
Systolic blood pressure (mm Hg)	135.1 ± 17.5
Diastolic blood pressure (mm Hg)	77.1 ± 13.2
Contrast agent (ml)	92.6 ± 23.8
Retrospective	197 (88%)
Metoprolol use	179 (79%)
Nitroglycerin use	213 (95%)

Data are expressed as median (range), mean ± SD, or number (percentage).

* Cardiac risk factors are defined in the "Methods" section.

score (Figure 3). Coronary artery calcification was found in the left anterior descending coronary artery in 85 patients (34%), the right coronary artery in 38 (17%), the left circumflex coronary artery in 36 (16%), and the left main coronary artery in 16 (7%). In the 133 patients (59%) with CACS of 0, 2 (1.5%) had significant CAD, 7 (5%) had nonsignificant CAD, and 124 (93%) had no evidence of CAD. One of the 2 patients with CACS of 0 and significant CAD had intermediate pretest probability and a TIMI score of 1 (a 48-year-old Hispanic man with multiple cardiac risk factors and atypical chest pain), and the other patient had high pretest probability and a TIMI score of 2 (a 75-year-old black woman without cardiac risk factors and typical chest
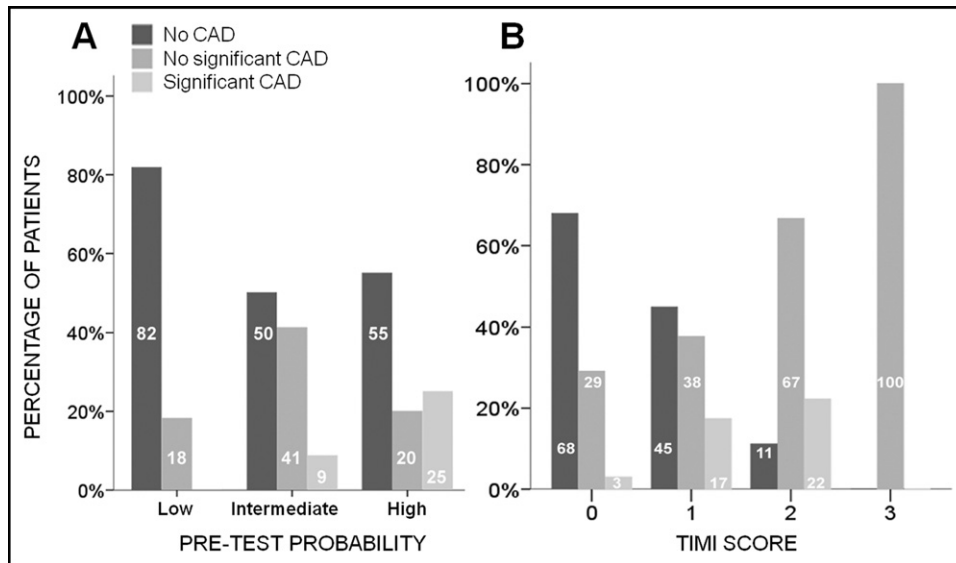
Figure 2. Prevalence of CAD across low, intermediate, and high pretest probability *(A)* and along the modified TIMI risk score *(B)* in patients evaluated for ACS.
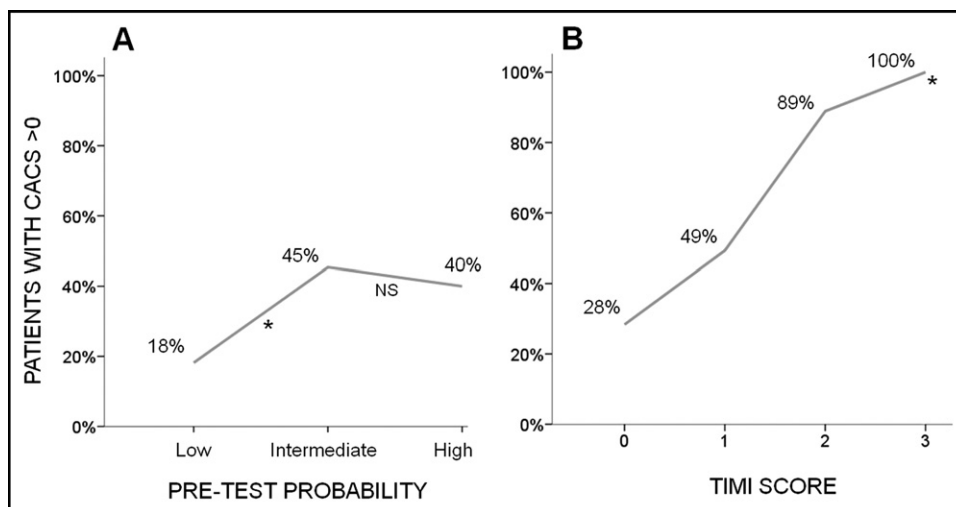

Figure 3. Percentage of patients with CACS >0 according to the pretest probability for CAD *(A)* and to the modified TIMI risk score *(B)*. *p <0.05 between low and intermediate pretest probability and for the trend across TIMI groups.

pain). In these cases, the stenosis was graded as moderate in severity, and subsequently, the patients underwent stress testing, which did not demonstrate inducible ischemia. Furthermore, no cardiovascular events were registered within 12 months after discharge.

The distribution of baseline characteristics, cardiac risk factors, and results of CCTA according to the severity of CACS is listed in Table 2. Age, male gender, hypercholesterolemia, diabetes, and previous aspirin use as well as the severity of CAD increased gradually among groups. Coronary plaques responsible for significant stenosis were predominately totally or partially calcified in composition. Of 34 significant stenoses found in our study population, 27 (80%) contained calcium, whereas 7 (20%) lesions were caused by noncalcified plaques. Noncalcified plaques causing significant stenosis occurred in patients with coronary calcification in other segments, and therefore, CACS was

positive, except in 2 cases. This finding suggests that is very rare to find obstructive noncalcified plaques in the setting of a CACS of 0.

The accuracy of CACS to detect significant CAD was good, with an area under the receiver-operating characteristic curve of 0.88 (95% confidence interval 0.78 to 0.96; Figure 4). In our study population, CACS had a negative predictive value of 99%, a positive predictive value of 20%, sensitivity of 91%, and specificity of 64%. The accuracy of CACS to detect significant CAD was higher in men compared to women (area 0.90 vs 0.83) as well as in younger (aged <65 years) patients compared to older (aged >65 years) patients (area 0.91 vs 0.74), but non–statistically significant differences were reached (p = 0.54 and p = 0.19, respectively). In the first multivariate model adjusted by CAD risk factors (age, male gender, hypertension, hypercholesterolemia, smoking history,

Table 2
Patients' characteristics according to the severity of coronary artery calcium score

Variable	CACS			p Value for Trend
	0 (n = 133)	1–100 (n = 61)	>100 (n = 31)	
Age (years)	51 ± 9	54 ± 9	66 ± 10	<0.01
Men	49 (37%)	35 (57%)	18 (58%)	0.01
Hypertension	57 (43%)	29 (48%)	18 (58%)	0.13
Hypercholesterolemia	24 (18%)	25 (41%)	23 (74%)	<0.01
Smokers	42 (32%)	17 (28%)	9 (29%)	0.66
Diabetes mellitus	13 (10%)	21 (34%)	10 (32%)	<0.01
Previous use of aspirin	14 (11%)	17 (28%)	10 (32%)	<0.01
Typical angina pectoris	22 (17%)	10 (17%)	3 (12%)	0.43
Significant CAD by CCTA	2 (1.5%)	6 (10%)	12 (39%)	<0.01
Moderate	2 (100%)	5 (83%)	6 (46%)	<0.01
Severe	0 (0%)	1 (17%)	6 (54%)	<0.01

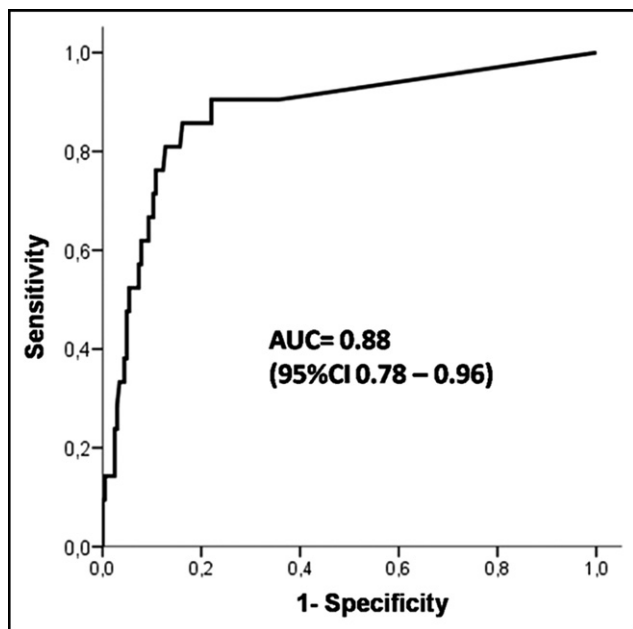Data are expressed as mean ± SD or number (percentage).

Figure 4. Receiver-operating characteristic curve for CACS to diagnose significant CAD assessed by contrast-enhanced CCTA. AUC = area under the curve; CI = confidence interval.

and diabetes) and typical chest pain, the independent variables associated with significant CAD were age (odds ratio [OR] 1.1, p = 0.01), smoking history (OR 4.2, p = 0.02) diabetes (OR 5.5, p <0.01), and typical chest pain (OR 4.2, p = 0.03). When CACS was included into the statistical model, age (OR 1.07, p = 0.01), smoking history (OR 3.78, p = 0.04), diabetes (OR 3.55, p = 0.049), and particularly CACS (OR 7.28, p = 0.02) were the independent predictors of significant CAD. The inclusion of CACS was demonstrated to improve the diagnostic accuracy of the model, resulting in an increase of Nagelkerke's R^2 from 0.32 to 0.38.

Discussion

The main finding of our study is that a CACS of 0 demonstrated a high negative predictive value to exclude significant CAD in low- to intermediate-risk patients presenting to the ED with acute chest pain and provided additional diagnostic value over CAD risk factors. The negative predictive value and the sensitivity of a CACS of 0 to exclude significant CAD in our study population were high (99% and 91%, respectively). Indeed, only 2 patients with absence of calcification had moderate lesions by CCTA, which allowed noninvasive management. However, the positive predictive value of CACS found in our cohort to diagnose significant CAD was 20%, suggesting that the clinical impact of a positive result is limited and may require further investigation. Although risk stratification scales based on pretest probability or TIMI scores are recognized useful tools in the evaluation of ED patients, as demonstrated in our study, CACS was found to provide independent and incremental diagnostic information. Additionally, a higher CACS was associated with a higher frequency of significant CAD.

There is still a discrepancy about the clinical utility of CACS in the evaluation of suspected ACS. Our findings are in line with those of previous studies demonstrating the usefulness of CACS in the acute setting. McLaughlin et al[8] evaluated 134 patients with acute chest pain and normal or nondiagnostic electrocardiographic results and concluded that patients with CACS of 0 could be safely discharged on the basis of the 98% negative predictive value demonstrated. Laudon et al[18] came to similar conclusions in a prospective observational study that included 105 patients with chest pain who underwent coronary artery calcium scoring, together with treadmill exercise test, coronary angiography, radionuclide stress test, and echocardiography. These investigators suggested that no further testing was needed when a CACS of 0 was found. Accordingly, Sarwar et al,[10] on the basis of a negative predictive value of 93% from a systematic review of 18 studies, argued that patients with negative CACS are highly unlikely to have CAD. When studying the relation between CACS and future cardiac events, Georgiou et al[6] observed a higher annual event rate in subjects with high CACS. Nabi et al[9] similarly reported excellent short-term outcomes for patients with acute chest pain and CACS of 0. Supporting this evidence, in the Rule Out Myocardial Infarction Using Computer Assisted Tomography (ROMICAT) study, only 1 of 197 patients with CACS of 0 had a cardiac event during 6-month follow-up.[16] In the opposite direction, Rubinshtein et al[14] found an incidence of significant CAD of 7% in a cohort of patients with CACS of 0 who were electively referred for CCTA. In another study that included 40 patients at high clinical risk for ACS, 5 of 13 patients (39%) with negative CACS had significant CAD, within an overall prevalence of significant CAD of 70%.[7] However, it is important to note that these studies were performed in clinical scenarios with remarkably high prevalence of significant CAD (56% to 70%), and subsequently, the negative predictive value afforded by CACS was lower.[19] In contrast, the prevalence of significant CAD was low (9%) in our investigation, which is

consistent with other published ED-based studies,[16] and all the patients had low to intermediate risk for ACS.

Although there are multiple diagnostic modalities available in the ED for risk stratification and early triage of patients with chest pain, all have significant limitations. Standard 12-lead electrocardiography lacks adequate sensitivity and negative predictive value to rule out any form of ACS.[20] Similarly, troponin has poor capacity to exclude myocardial ischemia or early manifestations of ACS.[21] Rest echocardiography can detect wall motion abnormalities and a reduced ejection fraction but its sensitivity to detect ACS is limited, and false-negative results are frequent.[22] The use of stress echocardiography improves negative and positive predictive value, but it requires highly experienced sonographers and physicians and as a result is not universally available, particularly off hours.[23] Exercise treadmill testing is a useful diagnostic tool for primary assessment of symptoms, but it is limited by a moderate predictive accuracy of approximately 70%.[24] Single photon-emission computed tomography shows an excellent sensitivity (>90%) and good specificity (67% to 78%) compared to coronary angiography[25] and sensitivity of 71%, specificity of 90%, positive predictive value of 38%, and negative predictive value of 97% in low-risk chest pain patients.[26] Additionally, perfusion imaging has been shown to have prognostic value and allows risk stratification for future events.[27] However, this technique is not ideal for initial ED evaluation of ACS for multiple reasons, including cost, time to perform the study, significant radiation exposure, specially trained personnel on site, and, as with other stress modalities, previous exclusion of acute infarction through serial enzyme measurements. More recently, a shortage of radiolabeled technetium compounds has resulted in increased use of thallium-201, further increasing patient radiation exposure. CCTA has similar accuracy to stress perfusion imaging but with shorter time to diagnosis and lower costs,[26] but contrast allergies, renal insufficiency, need for medication and physician expertise, and, moreover, patients' frequent inability to adequately cooperate limit its universal applicability. Additionally, there is still concern about unnecessary radiation exposure, particularly in younger patients. In comparison to these modalities, CACS also appears to provide valuable information for initial risk stratification of ED chest pain patients with several advantages. This noninvasive test has a high negative predictive value, similar to stress testing, without any clinical contraindication (such as atrial fibrillation, concurrent medications, patients' ability to exercise, or baseline wall motion or electrocardiographic abnormalities), need for iodinated contrast, or specific patient preparation. In addition, it is inexpensive, faster, simpler, and more available than other imaging techniques with minimal radiation dose.

The main limitation of the present study is that only a small proportion of patients underwent coronary angiography, and therefore the severity of CAD on CCTA was not confirmed by conventional angiography. Nevertheless, this is reflective of the current clinical management of patients, as the high concordance between CCTA and coronary angiography has been robustly demonstrated.[28] Another additional limitation is that using CCTA as the reference for defining significant CAD would have caused an overestimation of the actual prevalence of obstructive CAD. However, this prevalence in our study population is similar to that found in previous similar ED studies.[16] The absence of follow-up in all the patients precluded evaluation of the prognostic value of CACS results; however, this was not the objective of our study. Finally, because the information provided by predictive values is dependent on the prevalence of disease, our results may not be generalized to other institutions.

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