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Predictive ability of coronary computed tomography angiography parameters in patients suspected of obstructive coronary artery disease: a single-center cross-sectional study

A. ZLIBUT[1], R.I. ORZAN[1], D. FARAH[1], C. CIONCA[1,2], I.D. MURESAN[1], D. HORVAT[1], I.D. POPA[3], R. REVNIC[1,4], M. FLOREA[4], T. MOCAN[5], L. AGOSTON-COLDEA[1,6]

[1]Department of Internal Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[2]Department of Radiology, Hiperdia-Affidea Imaging Center, Cluj-Napoca, Romania
[3]Niculae Stancioiu Heart Institute, Cluj-Napoca, Romania
[4]Department of Family Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[5]Physiology Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[6]2nd Department of Internal Medicine, Emergency County Hospital, Cluj-Napoca, Romania

Abstract. – OBJECTIVE: Coronary computed tomography angiography (CCTA) is becoming increasingly useful for the diagnosis of coronary artery disease (CAD). Coronary calcium score (CCS), epicardial fat volume (EFV), and number of coronary plaques (NoP) add important information for the risk stratification and prognosis prediction of these patients. However, evidence about their ability to predict obstructive CAD is limited. We sought to evaluate the ability of CCTA parameters in predicting obstructive CAD.

PATIENTS AND METHODS: We conducted a cross-sectional, single-center study on patients at risk to develop CAD. CCS, EFV and NoP were determined by CCTA. CAD was defined as coronary stenosis > 50%. CCS was then ranked 5 severity groups: 0, 1-99, 100-399,400-999, and ≥1000. NoPs were classified in four categories: no plaques, 1-5, 6-10 and ≥10. Logistic regression analyses were performed, and statistical analysis was considered significant if $p<0.05$.

RESULTS: Off all 540 patients (55.8±11.1 years) who met the enrolment criteria, 98 had obstructive CAD. CCS, EFV and NoP were significantly associated with the presence of obstructive CAD ($p<0.0001$). The area under the receiver operating characteristics (ROC) analysis revealed significant cut-off values ($p<0.0001$) of CCS (70.3), EFV (40.8), NoP (4) for predicting obstructive CAD. Their association proved to have an AUC of 0.969, and a specificity of 95%. A scoring system based on regression coefficients which proved to have statistical significance for obstructive CAD as further constructed. It included EFV, CCS and left ventricular ejection fraction. This scoring system significantly predicted obstructive CAD for a cut-off value of 62.46, with a NPV of 96.3%.

CONCLUSIONS: The combined use of CCS, EFV and NoPs increases the predictive ability for obstructive CAD of each parameter used alone. These could be useful for developing a novel scoring system.

Key Words:
Obstructive coronary artery disease, Coronary computed tomography angiography, Coronary artery calcification score, Epicardial fat volume.

Abbreviations

AHT, arterial hypertension; AUC, area under the curve; BMI, body mass index; CAD, coronary artery disease; CCS, coronary calcium score; CCTA, coronary computed tomography angiography; DM, diabetes mellitus; EAT, epicardial adipose tissue; ECG, electrocardiogram; EFV, epicardial fat volume; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HU, Hounsfield Units; IQR, inter-quartile range; LDL-C, low-density lipoprotein cholesterol; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MACEs, major adverse cardiovascular events; NoPs, number of coronary plaques; NPV, negative predictive value; NYHA, New York Heart Association; PPV, positive predictive value; PTP, Pre-test probability; ROC, receiver operating characteristics; SCORE, Systematic Coronary Risk Evaluation; Se, sensitivity; Sp, specificity.

Corresponding Author: Radu Revnic, MD, Ph.D; e-mail: radu_revnic@yahoo.com

Introduction

In spite of current medical advances, coronary artery disease (CAD) still remains the main cause of death in Europe[1,2], while traditional cardiovascular risk scores have failed to accurately predict coronary events[3,4]. Therefore, the continuous development of non-invasive diagnosis tools which could overcome these flaws is imperative. These methods should better stratify patients at risk of CAD in order to increase diagnosis accuracy and to limit prediction biases.

Coronary computed tomography angiography (CCTA) is an advanced non-invasive cardiovascular imaging method that has become increasingly used for the diagnosis and risk assessment of patients with CAD, especially when it comes to obstructive CAD[2]. In the last decade, the role of several CCTA parameters has been demonstrated. Coronary calcium score (CCS) or Agatston score, and number of coronary plaques (NoPs) are two measurements that proved to have tremendous ability to predict coronary events, and, also, increasing evidence endorse their roles in excluding obstructive CAD[5,2]. The ability of CCS to predict major adverse cardiovascular events (MACEs) have been supported by published data[6-8]. Starting from this point, a number of algorithms based on CCS have been proposed, however they determined a divergent reclassification of risk in up to 30% of patients[8,9].

CCTA is able to identify coronary plaques, and to structurally characterize them. Studies[10,11] have shown that high-risk coronary plaques and, NoPs were significantly associated with the risk of both acute and chronic coronary syndromes. Nevertheless, the ability of NoPs to predict obstructive CAD has not yet been approached.

Epicardial adipose tissue (EAT) is responsible for various molecular mediators with proven roles in vascular inflammation and atherogenesis. These molecules are involved in the regulation of various cardiac functions and have important effect seven on the coronary arteries. Conversely, when dysfunctionalities of the EAT occur, the synthesis of these molecules is dysregulated, and, therefore, they become pro-atherogenic[12]. It has recently been shown that EAT was significantly associated with coronary events, despite traditional cardiovascular risk factors[13]. Additionally, EAT was even correlated with intra-stent restenosis at 9 and 15 months after percutaneous coronary intervention procedures[14]. Furthermore, it has latterly been shown that vascular inflammation may determine phenotypic changes in adjacent EAT and may lead to important dysfunctionalities[15]. CCTA is able to evaluate EAT by measuring the epicardial fat volume (EFV). Yerramasu et al[16] have shown that EFV was independently associated with the progression of CAD, but studies are only in their starting point.

In our study, we sought to evaluate the ability of CCTA parameters in predicting obstructive CAD.

Patients and Methods

Study Population

We conducted a single-center, cross-sectional study on 773 patients suspected of CAD, which were examined in the 2nd Department of Internal Medicine of the Cluj County Emergency Hospital, between June 2018 and April 2020. The inclusion criteria embedded any of the following: patients suspected of CAD with typical chest pain (constricting chest pain or in the neck/jaw/shoulder/arm, precipitated by exertion, brief discomfort, relieved at rest or at < 5 minutes) or atypical (two of typical's characteristics; digestive or respiratory manifestations) and/or dyspnea; abnormal stress-test; multiple cardiovascular risk factors[2]. Exclusion criteria were considered, as follows: 1) history of CAD, defined previous myocardial infarction, recent acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass graft; 2) patients with other cardiac diseases; 3) patients with renal failure; contrast allergy; 4) life expectancy less than one year. The current research has been approved by the Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca – decision number 435/15.10.2019. The study has been conducted in accordance with the Declaration of Helsinki. All patients signed a written consent form.

Medical History and Clinical Examination

The evaluation protocol of the patients included demographic data, medical history, physical examination, electrocardiogram, pre-test probability (PTP) based on Duke or updated Diamond-Forrester scores, laboratory tests, stress tests, echocardiogram and CCTA. Standardized questionnaires were used to obtain demographic, medical history and cardiovascular risk factors data, including active smoking. Arterial hypertension (AHT) was defined as a systolic blood pressure ≥140 mmHg and/or diastolic ≥90 mmHg,

or antihypertensive treatment. Diabetes mellitus (DM) was defined as a fasting plasma glucose level of over 126 mg/dL or use of antidiabetic therapy. Dyslipidemia was defined as the previous diagnosis of high levels of LDL-C of ≥140 mg/dL, fasting triglycerides of ≥150 mg/dL, or lipid-lowering medications. Body mass index (BMI) (kg/m^2) was calculated from measured height and weight. Cardiovascular risk was assessed by SCORE diagram, given personal history, exposure to toxicants and smoking status. Renal function was assessed by eGFR, and a value under 60 mL/min/1.73 m^2 was considered impaired.

The New York Heart Association (NYHA) functional class was used to assess the severity of dyspnoea. Both resting ECG and 24-hour ECG monitoring were performed at enrolment. A change in resting ECG was defined as ≥1mm ST depression in at least 2 contiguous leads.

Coronary Computed Tomography Angiography

CCTA was performed with a second generation single-source CT scanner (Siemens SOMATOM Definition Edge, Siemens Healthcare, Erlangen, Germany), in accordance with the current international guidelines[17]. Patients were instructed in breath-holding technique in order to minimize artifacts. The scan range was from the carina and down to 1 cm below the diaphragm, while the patients were continuously ECG monitored. Prospectively, ECG-triggered high-pitch spiral or sequential acquisitions were used to acquire the images. The acquisition parameters were as follows: collimation of 128x0.6 mm, slice thickness of 0.6 mm, gantry rotation time of 280 ms, tube voltage of 70-140 kv, tube current of 500-650 mAs/rotation, heart-rate adaptive pitch of 0.2-0.5, FOV adjusted for each patient size; image reconstructions using 1-1.5 mm cutting thickness and 0.5 mm interval. Dual-head power injector (SCT 210, Medrad, PA, USA) and the nonionic contrast medium (Omnipaque 350 mgI/ml, GE Healthcare, Princeton, New Jersey, 80 to 100 ml) followed by saline (50 to 80 ml), was injected into the antecubital vein, with a flow rate of 5 ml/s. Data acquisition was initiated with a delay of 5 seconds after the signal attenuation threshold. Prospective ECG triggering was used to scan 70 to 80% of the RR-interval, in patients with heart rate >65 bpm. Radiation dose was estimated using dose-length product from the dose report of the CT scanner and European Commission chest conversion factor 0.014 mSv (mGy x cm) 0.014 mSv mGy−1 cm−1 (effective dose (mSv) = total dose length product (mGycm) × 0.014 mSv mGy−1 cm−1)[18]. All examinations were performed by two level III-trained experts, with over 10-year experience in the field of advanced cardiovascular imaging, who were blinded to all clinical data. Disagreements between the two examiners were resolved by consensus reading.

Axial, coronal and sagittal planes were used for coronary reconstructions. All images were built using iterative image reconstruction algorithms. All segments ≥2 mm in diameter were identified and specifically analyzed by Coronary Artery Disease-Reporting and Data System[19]. Obstructive CAD was defined as a coronary stenosis >50%. The diameter of the vessel that normally appears seated proximal to the plate served as a reference for comparison.

Left ventricular (LV) ejection fraction (LVEF) was determined, as previously described, in short-axis slices in a remote workstation using a dedicated cardiac evaluation software Syngo. CT Cardiac Function (Siemens Healthineers, Erlangen, Germany). The endocardial contours were manually traced in short-axis views, from the base to the apex in both end-diastole and end-systole. The papillary muscles were considered to be part of the LV cavity. LV end-diastolic (LVEDV) and end-systolic volumes (LVESV) were calculated using the same software. Afterwards, LVEF was determined by the subtraction of LVESV from LVEDV and dividing it afterwards by LVEDV[20].

Non-contrast-enhanced scans were performed at 3 mm slices and prospective ECG-triggered technique was acquired to quantify CCS and EFV. CCS was semi-automatically quantified using Syngo Calcium Scoring (Siemens Healthineers, Erlangen, Germany). The Agatston algorithm was used to quantify CCS, which was considered to be significant when at least 4 contiguous pixels with a density ≥130 HU with a surface area of over 1mm^2 were identified[21]. EFV was measured from the pericardium fat volume slices within 15 mm above and 30 mm below the left main coronary artery. This region was selected because it includes the pericardium fat located around the proximity of the coronary arteries. A cursor pointer was used to manually trace the pericardial contour with 0.75-mm-thick reconstructed axial slices[22]. The pericardium contour was extrapolated by using a specialized software (Syngo Volume, Siemens Medical Solutions) for the non-traced slices and rechecked by the operator. EFV analysis software was used to discern fat from other tissues, using a

threshold of -30 to -190 HU. Coronary atherosclerotic plaques were quantified and characterized using the previously published methods[23].

Statistical Analysis

Descriptive data is reported as numbers (%) for dichotomized variables, as mean ± standard deviation (SD) for normally distributed characteristics or median, and IQR for non-normally distributed. The Chi-square test was used to compare variables among groups. Non-normally distributed variables were log-transformed before the analyses were performed. CCS was ranked, as previously recommended, into four groups: 0, 1-99 (mild), 100-399 (moderate), 400-999 (extensive) and ≥1000 (very extensive)[21], whereas, based on NoPs, the subjects were classified in four groups, such as no plaques, 1-5, 6-10 and ≥10. Spearman's coefficient was used to assess the correlations between CCTA parameters and clinical factors. Unadjusted and multivariable adjusted model 1 (age, gender, typical-angina, ST-T changes, AHT, dyslipidemia, DM, smoking, and obesity), model 2 (model 1+CCS), model 3 (model 1+NoP), model 4 (model 1+EFV) and model 5 (age, gender, typical angina, ST-T changes, CCS, NoP, EFV) were used. Receiver-operating curves (ROC) were used to compare the discriminatory performance of models using CCS, EFV and NoP for the prediction of obstructive CAD by area under the curve (AUC). The levels of significance and reliability of the main indices of determination: sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV). Further, we constructed a risk scoring system based on the logistic regression model, with B coefficients of significant predictors. Its efficacy was evaluated using ROC curves. The results were considered statistically significant if $p<0.05$. SPSS Software package (Chicago, IL, USA) and MedCalc 19.2.1 were used.

Results

Baseline Characteristics and CCTA Measurements

540 patients (55.8±11.1 years; 52.03% female) met the enrolment criteria (Figure 1), and 18.14% of them were diagnosed with obstructive CAD. Baseline characteristics are presented in Table I. 52.2% presented with atypical angina, 33.5% with non-specific chest pain, 33.1% with dyspnoea, whereas only 14.2% had typical angina. Age, male gender, smoking, typical angina, and dyslipidemia were more frequent in those with obstructive CAD ($p<0.001$; $p<0.01$).

All CCTA parameters were impaired in those with obstructive CAD (for all, $p<0.001$). Patients with obstructive CAD had significantly increased coronary calcium burden, with more of them being in the moderate, extensive and very extensive groups of CCS ($p<0.001$). In those with intermediate CCS burden (intermediate calcium score groups), there was a considerable heterogeneity between CCS and NoPs (Figure 2), while those with CCS>400 had NoPs over 10. The distribution of NoPs according to CCS is presented in Table II.

Regarding the agreements of LVEF, EFV and CCS, the intra-observer and inter-observer reproducibility indexes were excellent (Table III).

ROC Curve Analysis for Assessing the Ability of CCTA to Predict Obstructive CAD

Overall, CCS was significantly associated with number of coronary arteries involved. The ROC analyses of the CCTA parameters are presented in Figure 3, and all of them reached statistical significance. Therefore, for the prediction of obstructive CAD, the cut-off values were: <61% for LVEF [AUC = 0.700; Se 69% (95% CI: 59.3-78.3); Sp 66% (95% CI: 62.1-71.1); NPV 90.8% (95% CI: 87.1-93.7)], 40.8 ml/m^2 for EFV [AUC = 0.816; Se 69% (95% CI: 59.3-78.3); Sp 86% (95% CI: 82.9-89.5); NPV 92.7% (95% CI: 89.8-95.0)], 70.3 for CCS [AUC = 0.927; Se 90% (95% CI: 83.3-95.7); Sp 89% (95% CI: 85.6-91.7); NPV 97.8% (95% CI: 95.8-99.0)], and 4 for NoP [AUC = 0.928; Se 88% (95% CI: 79.6-93.5); Sp 90% (95% CI: 86.9-92.7); NPV 97.1% (95% CI: 94.9-98.5)]. The combined use of CCS, EFV and NoP significantly increased the prediction of obstructive CAD beyond each parameter used alone and provided an AUC of 0.969 with a 95% Sp.

Univariate and Multivariate Logistic Regression for CCTA to Predict Obstructive CAD

The results of univariate and multivariate logistic regression are presented in Table IV. Model 1 retained all candidate predictors with traditional cardiovascular risk factors and provided a significant prediction for obstructive CAD ($p<0.001$). The addition of CCS, EFV and NoP significantly decreased the effects of AHT and obesity. In models 2 and 3, the predictive ability for obstructive CAD was significantly improved by CCS and

Table I. Baseline characteristics of patients in study.

		All patients n=540	CAD- n=442	CAD+ n=98	*p*-value
Demographics characteristics					
-Age, years		55.8 (11.1)	55.0 (11.1)	59.6 (10.6)	<0.001
-Male gender, n (%)		259 (47.9)	191 (43.2)	68 (69.4)	<0.001
-Body-mass index, kg/m^2		28.9 (5.9)	28.9 (6.1)	28.7 (5.1)	NS
-Systolic blood pressure, mmHg		138.2 (20.6)	138.0 (21.0)	139.1 (18.9)	NS
-Diastolic blood pressure, mmHg		82.4 (12.3)	82.7 (12.5)	80.9 (11.4)	NS
CAD risk factors, n (%)					
-Hypertension, n (%)		355 (65.7)	287 (64.9)	68 (69.3)	NS
-Diabetes mellitus, n (%)		80 (14.8)	62 (14.0)	18 (18.4)	NS
-Dyslipidemia, n (%)		299 (55.3)	236 (53.4)	63 (64.2)	0.01
-Smoking, n (%)		208 (38.5)	164 (37.1)	44 (44.9)	<0.01
-Obesity		210 (38.9)	176 (39.8)	34 (34.7)	NS
Symptoms, n (%)					
-Typical angina		77 (14.2)	60 (13.6)	17 (17.3)	<0.01
-Atypical angina		282 (52.2)	235 (53.1)	47 (47.9)	NS
-Non-specific chest pain		181 (33.5)	147 (33.2)	34 (34.7)	NS
-Dyspnea		179 (33.1)	144 (32.5)	35 (35.7)	NS
Electrocardiogram, n (%)					
-ST-T change		194 (35.9)	160 (36.2)	34 (34.7)	NS
-Left bundle branch block		28 (5.2)	23 (5.2)	5 (5.2)	NS
-Right bundle branch block		28 (5.2)	24 (5.4)	4 (4.1)	NS
Biomarker levels, mediane, IQR					
-Fasting plasma glucose, mg/dl		101 (59-379)	100 (59-310)	101 (75-379)	NS
-LDL-Cholesterol, mg/dl		142 (65-273)	136 (72-205)	156 (65-273)	<0.001
-HDL-Cholesterol, mg/dl		43 (13-122)	44 (21-122)	40 (13-87)	<0.01
-Triglyceridemia, mg/dl		152 (34-986)	153 (34-604)	149 (37-986)	NS
-eGFR, ml/min/1.73 m^2		86.9 (65.9-124.2)	88.5 (70.9-124.2)	83.8 (65.9-119.2)	NS
Medications, n (%)					
-Beta-blockers		402 (74.4)	328 (74.2)	74 (75.5)	NS
-ACEIs or ARBs		346 (64.1)	286 (64.7)	60 (61.2)	NS
-Calcium channel blockers		115 (21.3)	89 (20.1)	26 (26.5)	<0.01
-Statins		309 (57.2)	255 (57.7)	54 (55.1)	NS
-Antiplatelet therapy		293 (54.2)	235 (53.1)	38 (30.6)	<0.001
-Diuretics		222 (41.1)	177 (40.0)	45 (45.9)	NS
Coronary Computer Tomographic Angiography					
-CCS, median (25th–75th)		144.8 (0-920.9)	33.7 (0-320.8)	645.2 (191.8-1890.8)	<0.001
-Group CCS	0	278 (51.5)	278 (62.9)	0 (0)	<0.001
	1-99	132 (24.4)	122 (27.6)	10 (10.2)	<0.001
	100-399	60 (11.1)	35 (7.9)	25 (25.6)	<0.001
	400-999	49 (9.1)	7 (1.6)	42 (42.8)	<0.001
	>1000	21 (3.9)	0 (0)	21 (21.4)	<0.001
-NoP	0	280 (51.9)	279 (63.1)	1 (1.1)	
-LVEDV indexed, mL/m^2		75.0 (15.2)	74.6 (15.1)	76.2 (15.6)	NS
-LVESV indexed, mL/m^2		26.9 (9.3)	26.8 (9.4)	27.3 (8.8)	NS
-LVM indexed, g/m^2		57.7 (11.7)	57.3 (11.4)	59.4 (13.1)	NS
-LVEF, %		63.6 (7.5)	64.5 (7.4)	59.9 (6.8)	<0.001
-EFV indexed, ml/m^2		33.7 (11.3)	31.4 (9.8)	44.6 (11.5)	<0.001

Abbreviations: n, number of patients; IQR, interquartile range; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; CAD, coronary artery disease; CCS, coronary calcium score; EFV, epicardial fat volume; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; NoP, number of calcified plaques. Data are reported as mean (standard deviation) or median (IQR) or n (%).

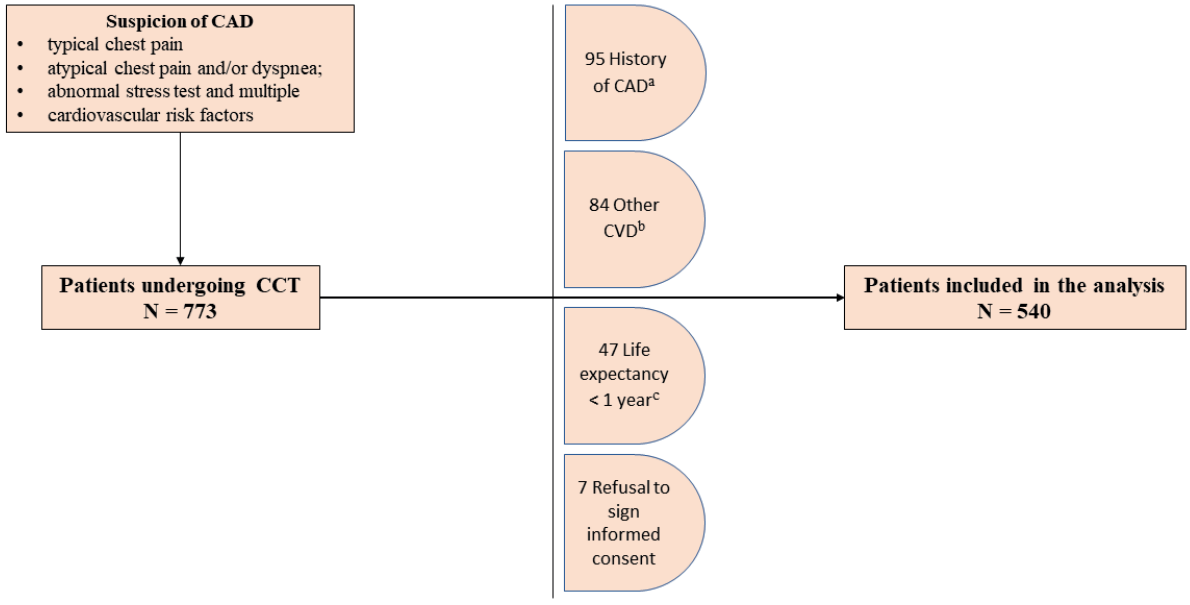
Table II. The number and distribution of calcified coronary plaques in different CCS groups.

CCS		1-100	101-400	401-1000	>1000
NoP					
0	Reference	-	-	-	-
1-5		1.287 (1.673-2.875)	2.065 (1.876-2.345)	2.267 (2.012-6.356)	3.791 (3.567-7.388)
6-10		2.060 (1.127-3.289)	3.427 (1.879-6.250)	5.167 (2.319-11.513)	6.783 (4.461-10.311)
>10		6.138 (2.281-12.327)	7.234 (3.991-13.563)	9.167 (3.872-15.673)	10.730 (6.184-18.620)

NoP, respectively (p<0.0001; p<0.001). Moreover, EFV decreased the effects of AHT, obesity and even dyslipidemia (p<0.01). Furthermore, the replacement of traditional cardiovascular risk factors with all three CCS, EVF and NoP (Model 5), provided a significant predictive power for obstructive CAD.

Predictive Scoring System for Obstructive CAD

Based on multivariate logistic regression, we constructed a model that included CCS, EFV and, traditional cardiovascular risk factors (AHT, DM, smoking, dyslipidemia). The constructed model was validated by a significant statistical value (chi square=395.348, p=0.0001). Therefore, the significant predictors proved to be CCS (p=0.0001), EFV (p=0.0001), and LVEF (p=0.004). Based on regression coefficients, we have constructed a scoring system based on the aforementioned parameters (SCORECV=0.91*EFV+0.006*CCS - 0.08*LVEF). The score ranged between a minimum of 4.76 and a maximum of 115.3 and revealed obstructive/non-obstructive CAD significant between-group significance (48.9 *vs.* 77.5,



[a]coronary artery bypass graft, percutaneous coronary intervention, myocardial infarction and suspicion of recent acute coronary syndrome
[b]atrial fibrillation and other arrhythmias, severe valvulopathies or prosthetic valve, implantable cardiac device
[c]patients with a life expectancy of less than one year due to other terminal illnesses
CAD, coronary artery disease; CCT, coronary computed tomography; CVD, cardiovascular disease;

Figure 1. Study design chart.

Table III. Reproducibility inter and intra-observer agreement of ct measurements.

Parameter	Coefficient Kappa	95% Confidence Interval	Standard Error
Inter-observer			
- LVEF	0.91	0.872 to 0.941	0.026
- EFV indexed	0.97	0.909 to 0.989	0.012
- CCS	0.96	0.933 to 0.978	0.006
Intra-observer			
- LVEF	0.98	0.977 to 0.992	0.009
- EFV indexed	0.98	0.967 to 0.991	0.004
- CCS	0.99	0.973 to 0.998	0.003

Abbreviations: LVEF, left ventricular ejection fraction; EFV, epicardial fat volume; CCS, coronary calcium score.

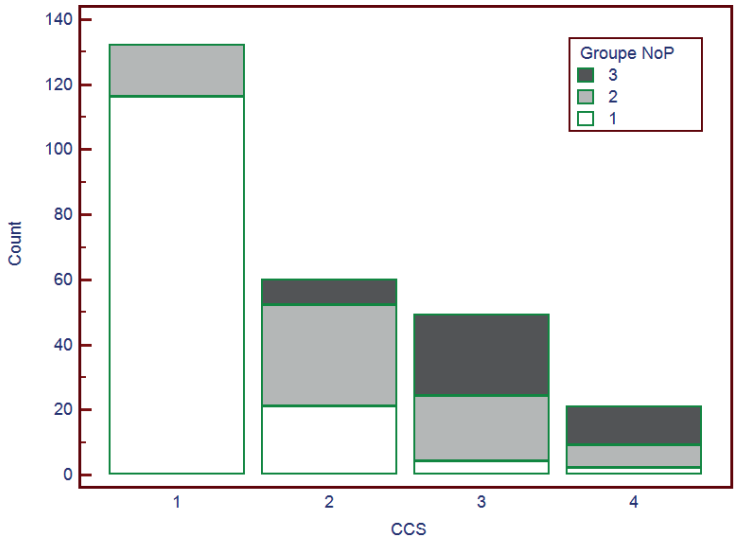


Figure 2. Coronary calcium score according to the number of calcified plaques. Group 1 means a CCS between 1-99, Group 2 means a CCS between 100-399, Group 3 means a CCS between 400-999 and Group 4 means a CCS between ≥1000.

p=0.0001). The ROC analysis of SCORECV provided an AUC of 0.893 (p<0.0001), with an optimal cut-off value of 62.46 for obstructive CAD and is presented in Figure 4. For the mentioned cut-off values, SCORECV has presented only 85.7% Se (95% CI: 77.2-92.0%), but quite high Sp of 82.5% (95% CI: 78.7-86.0%) and NPV 96.3% (95%CI: 93.9-98%) for the prediction of obstructive CAD.

Discussions

Our current study was conducted on a well-defined cohort of patients suspected of CAD in which we evaluated the incremental ability of CCS, EFV and NoPs to identify obstructive CAD, beyond traditional cardiovascular risk scores. Furthermore, we have also shown that their combined use might be able to increase the predictive

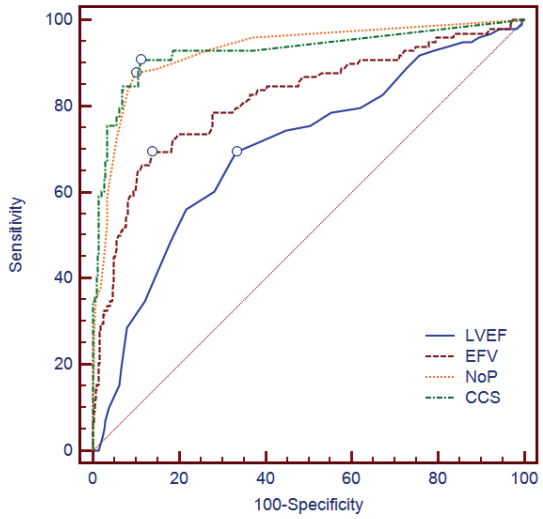


Figure 3. The area under the receiver operator curves of CCTA parameters. Abbreviations: CCS, coronary calcium score; EFV, epicardial fat volume; LVEF, left ventricular ejection fraction; NoP, number of calcified plaques.

Table IV. Logistic Regression Analysis for Predictor of Obstructive CAD.

Univariate		Multivariate				
		Model 1	Model 2	Model 3	Model 4	Model 5
Age	1.040 (1.018-1.063)	1.044 (1.021-1.067)	1.019 (0.981-1.053)	1.023 (1.020-1.065)	1.035 (1.008-1.064)	0.976 (0.933-1.021)
Male gender	0.335 (0.210-0.536)	0.331 (0.198-0.511)	0.317 (0.147-0.681)	0.366 (0.175-0.765)	0.289 (0.161-0.520)	0.271 (0.105-0.697)
Typical Angina	1.339 (1.040-2.424)	1.652 (1.033-2.216)	1.835 (1.214-2.781)	1.782 (1.293-3.434)	1.823 (1.562-2.378)	1.937 (1.239-3.768)
ST-T change	1.187 (1.051-1.387)	1.169 (1.019-1.899)	1.267 (1.012-1.982)	1.852 (1.192-2.882)	1.134 (1.090-1.626)	1.974 (1.039-3.747)
Smoking	1.205 (0.992-1.462)	1.046 (0.842-1.299)	1.113 (0.622-1.398)	1.146 (0.675-1.598)	1.423 (0.994-2.036)	-
Diabetes mellitus	1.379 (0.774-2.756)	1.150 (0.616-2.144)	1.237 (0.967-2.349)	1.089 (1.013-1.715)	1.606 (0.830-3.105)	-
Dyslipidemia	1.571 (0.998-2.472)	1.293 (0.783-2.134)	1.094 (0.489-2.456)	1.305 (0.597-2.872)	NS	-
Arterial Hypertension	1.224 (0.763-1.962)	0.890 (0.518-1.532)	NS	NS	NS	-
Obesity	1.213 (0.912-1.614)	1.664 (0.863-1.576)	NS	NS	NS	-
CCS	1.008 (1.006-1.009)	-	1.009 (1.007-1.011)	-	-	1.001 (1.003-1.008)
NoP	1.597 (1.466-1.774)	-	-	1.660 (1.501-1.836)	-	1.379 (1.195-1.593)
EFV indexed	1.137 (1.106-1.16)	-	-	-	1.151 (1.114-1.185)	1.185 (1.125-1.248)
p-value						
Hosmer-Lemeshow		$p<0.001$	$p<0.0001$	$p<0.001$	$p<0.01$	$p<0.0001$

Abbreviations: CAD, coronary artery disease; CCS, coronary calcium score; EFV, epicardial fat volume; NoP, number of calcified plaques. Data are odds ratio (95% CI). Model 1 = age + sex + typical angina + ST-T changes + arterial hypertension + dyslipidemia + smoking + obesity + diabetes mellitus; Model 2 = Model 1 + CCS; Model 3 = Model 1 + NoP; Model 4 = Model 1 + EFV indexed; Model 5 = age + sex + typical angina + ST-T changes + CCS + NoP + EFV indexed

power of each parameter used alone. Therefore, we endorse the importance of creating new predictive models based on CCTA parameters, with respect to the simple PTP scores (age, gender, chest pain and ST-T changes). To our knowledge, this is the first study to evaluate the predictive ability of combined CCS, EFV and NoP, and, also to create a predictive scoring system based on these CCTA parameters.

In patients with intermediate PTP, their diagnosis ability of obstructive CAD is limited, while for those with low PTP, both EDACS and HEART had highly efficient ability to identify CAD and to predict MACEs[24]. Therefore, in subjects with intermediate PTP, since traditional scores are lacking, current guidelines recommend CCTA as a primary diagnosis tool[25]. van Rosendael et al[26] created an algorithm based on the degree of coronary artery stenosis and plaque composition, which was able to improve the prediction of MACEs. Moreover, Blaha et al[27] proposed the use of the diffusivity index with CCS to improve this prediction. Additionally, CCTA was also useful to detect obstructive left main coronary artery disease, coronary anomalies, and intra-stent restenosis[28]. In the current study, the CCTA measure-

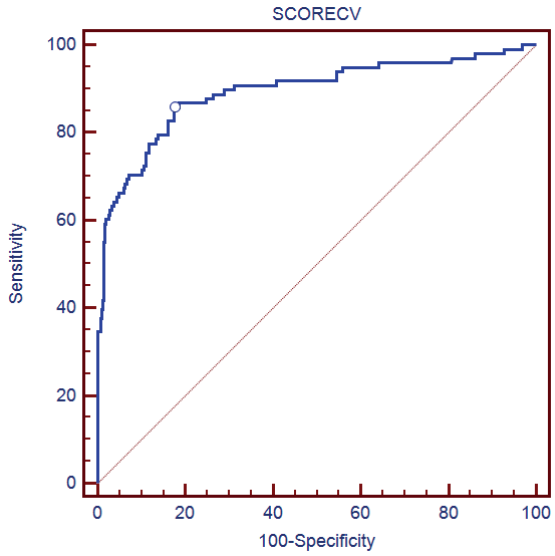


Figure 4. The area under the receiver operator curves for prediction scoring system SCORECV.

ments had an excellent intra and inter-observer reproducibility.

Coronary calcium burden is described as an ectopic bone production triggered by inflammatory and metabolic factors[29]. Being objective, reproducible, and robust, numerous studies render the use of CCS in patients with CAD in terms of screening, risk assessment, and therapy guidance[30,31]. CCS was able to improve risk discrimination and net correct reclassification in younger subjects[30,32]. In addition, Mlynarksa et al[33] identified a positive correlation between CCS and MACEs. Likewise, in the study of Detrano et al[34] patients with a CCS of over 300 had a 9.67-fold increased risk to have obstructive CAD and also to develop MACEs. Similarly, in our study, those with obstructive CAD had increased CCS, EFV and NoP. Nevertheless, in association with demographic parameters, CCS alone did not increase the prediction ability for obstructive CAD[35], whereas in patients with intermediate to high PTP, it was unable to ensure proper discrimination between obstructive and non-obstructive CAD[36]. Interestingly, in our study, for a cut-off value of 70.3, CCS identified obstructive CAD with an exceptional AUC of 0.927 and a NPV of 97.8%, regardless of traditional cardiovascular risk factors.

Arnson et al[37] have shown that higher NoPs were positively associated with all-cause mortality, and also the addition of low and medium CCS to them, significantly increased mortality prediction. In our study, NoPs were significantly increased in those with obstructive CAD and positively associated with CCS, especially for a cut-off value of 4 with an excellent NPV of 97.1%.

Emerging data suggest that EFV could provide increased efficacy for the prediction of obstructive CAD. Petrini et al[38] have found that there was a significant association between EFV and CAD, while Yuan et al[39] have shown that EFV might become an independent predictor of high risk thin-cap coronary atheroma. Furthermore, it has been shown that epicardial fat was independently associated with the progression of CAD[16], and, also with the occurrence of coronary events[13], and intrastent restenosis[14]. Moreover, it has been suggested that EFV might become a useful predictor for obstructive CAD[40], even in those with atypical chest pain[41]. Nonetheless, the incremental value of EFV for predicting CAD has not yet been approached. In our study, EFV was significantly higher in subjects with obstructive CAD. Furthermore, for a threshold of 40.8 mL/m^2, it proved an important predictive ability for obstructive CAD, with an AUC of 0.816, with a high NPV of 92.7%.

In our current study, we tested the incremental value of combined CCS, EFV and NoPs for the prediction of obstructive CAD and we identified an AUC of 0.969 with a Sp of 82.5% and a NPV of 96.3%. Our findings suggest that the addition of EFV and NoP to CCS significantly improved the discriminatory ability of each parameter used alone (model 1 *vs.* model 3; model 1 vs model 4). Additionally, when CCS is assessed by CCTA, it can automatically evaluate both EFV and NoPs, without any supplemental radiation exposure. Similarly, Zhou et al[22] demonstrated that EFV was able to improve the prediction of obstructive CAD, beyond CCS used alone. Moreover, the addition of all three CCS, EFV and NoPs to the simplest PTP consisted of age, gender, symptoms and ST changes allowed us to construct the fifth predictive model. Based on it, we found a very high predictive ability for obstructive CAD, in spite of traditional cardiovascular risk factors. Therefore, the validation of the combined use of all three CCTA parameters in patients suspected of CAD in larger cohorts could be imperative, because it could stand as a promising premise in modern cardiology.

In order to evaluate the clinical adaptability of these CCTA parameters, we tested them against traditional cardiovascular risk factors, and we were able to elaborate a novel risk scoring sys-

tem, SCORECV, for the prediction of obstructive. Even though it has an acceptable sensitivity, for a cut-off value of 62.46, SCORECV provided a high NPV of 96.3%. However, large cohort studies are required to establish its clinical usefulness.

Study Limitations

Firstly, the absence of invasive coronary angiography to correctly establishing CAD and differentiate between obstructive and non-obstructive CAD, chiefly in patients with increased calcium burden to related artifacts [42]. Secondly, the study was cross-sectional, therefore the follow-up is lacking. Thirdly, it has been emphasized the value of combined use of CCTA with functional testing in order to avoid unnecessary diagnostic testing[43]. Fourth, these generated models should not be used in primary prevention of asymptomatic individuals without further investigations.

Conclusions

The combined use of CCS, EFV and NoP has the ability to increase the predictability of obstructive CAD, beyond each parameter used alone. The novel developed risk scoring system proved a significant capacity to identify the presence of obstructive CAD.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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