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Keywords:	coronary artery disease, coronary CT angiography, CAD-RADS, cardiovascular risk factors

Cardiovascular risk factors as predictors of coronary artery disease assessed using CAD-RADS classification: a cross-sectional study in Romanian population

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Abstract

Objectives: The aim of this study was to evaluate the association between cardiovascular risk factors and CAD-RADS score. CAD-RADS is a new, standardized method to assess coronary artery disease (CAD) using coronary computed tomography angiography (CCTA).

Design: A cross-sectional observational, patient-based cohort study.

Setting: Referred imaging centre for coronary artery disease in Transylvania, Romania.

Participants: We retrospectively reviewed 674 patients who underwent CCTA between January 2017 and August 2018. The exclusion criteria included: previously known CAD, defined as prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery (n=91), cardiac CT for other than evaluation of possible CAD (n=85), significant arrhythmias compromising imaging quality (n=23). Finally, 475 patients fulfilled the inclusion criteria.

Methods: Demographical, clinical and CCTA characteristics of the patients were obtained. Coronary artery disease was evaluated using CAD-RADS score. Obstructive CAD was defined as ≥50% stenosis of ≥1 coronary segment on CCTA.

Results: We evaluated the association between risk factors and CAD-RADS score in univariate and multivariate analysis. On univariate analysis, male gender, age, hypertension, dyslipidemia, smoking, diabetes mellitus, typical angina and coronary artery calcium score (CACS) were positively associated with a higher CAD-RADS score. For the multivariate analysis, we divided the patients into 2 groups according to the CAD-RADS system: group 1: CAD-RADS score between 0-2 (stenosis <50%) and group 2: CAD-RADS score≥3 (stenosis ≥50%). Male sex, age>60 years, dyslipidemia, hypertension and typical angina remained major predictors of obstructive CAD. We developed 2 prediction models for CAD-RADS score≥3: a clinical model and one including also CACS. The clinical model had a good discriminative power (AUC=0.83, p<0.0001). After adding CACS, the prediction performance has been improved (AUC= 0.93, p<0.0001).

Conclusion: This study demonstrated that there is a significant association between multiple cardiovascular risk factors and a higher coronary atherosclerotic burden assessed using CAD-RADS system.

Keywords: coronary artery disease; coronary CT angiography; CAD-RADS; cardiovascular risk factors

Article Summary

Strengths and limitations of this study

- This is the first study to evaluate the association of cardiovascular risk factors and coronary artery disease assessed using coronary CT angiography in Romania.
- We quantified the coronary artery stenosis using the CAD-RADS classification, the newest, standardized method for reporting CAD.
- The patients were recruited from a single centre; therefore, the study population was relatively small.
- Another limitation is the design of the study: a cross-sectional, retrospective one.

Introduction

Coronary artery disease (CAD) is one of the major causes of morbidity and mortality worldwide. Despite the fact that CAD mortality rates have declined since 1980s, it still accounts for approximately one-third of all deaths of individuals aged over 35 years old(1,2).

It is well-known that atherosclerosis is the underlying cause of cardiovascular diseases and multiple risk factors augment the atherosclerotic process. These risk factors include non-modifiable ones such as age and sex and modifiable risk factors such as hypertension, dyslipidemia, obesity, diabetes mellitus and smoking (3-7). Studies suggest that the majority of patients with CAD have at least one modifiable risk factor and their presence has an impactful role in the progression of CAD (8,9).

Prognostic assessment is very important in the management of the patients with CAD. Therefore, many risk-scoring systems have been developed such as Framingham and SCORE, which are based on the presence of various traditional cardiovascular risk factors (10,11).

Moreover, with the recent advancements made in medical technology, coronary CT angiography (CCTA) has rapidly evolved into one of the most highly accurate methods for diagnosis and evaluation of CAD. It is an unique non-invasive test which can provide direct and accurate visualization of the coronary vessel lumen, being able to quantify the presence and extent of coronary stenosis and to assess the characteristics of coronary atherosclerotic plaques (12).

CCTA has been included in the latest ESC guideline on the management of stable artery disease, being categorized as class II LOE C recommendation. CCTA should be used for risk stratification in patients with stable CAD who are in the lower range of intermediate pre-test probability. Also, it can be considered for patients who are unable to exercise or to perform a stress test or for subjects with inconclusive functional test results (13).

In recent years, many studies have been conducted to evaluate the short and long-term prognostic importance of CCTA. They demonstrate the fact that measurements of both stenosis severity and

plaque features provide powerful prognostic information superior to traditional cardiovascular risk factors (14-18).

In 2016, the Society of Cardiovascular Computed Tomography published the CAD-RADS grading system, which is a standardized reporting method of CCTA results. This is meant to facilitate communication of the results along with suggestions for consecutive management of the patients. The grading system ranges from 0 to 5, where CAD-RADS 0 score means complete absence of stenosis and CAD-RADS 5 represents total occlusion of at least 1 coronary segment (19).

The aim of this study is to evaluate the association between traditional cardiovascular risk factors and coronary artery disease evaluated using the CAD-RADS score.

Methods

Study population

We retrospectively reviewed 674 consecutive patients who underwent CCTA between January 2017 and August 2018 in our institution. The indications for CCTA were: atypical angina, typical angina with an inconclusive stress test, patients with intermediate/high-risk for major cardiac events. The exclusion criteria included: previously known CAD, defined as prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery (n=91), cardiac CT for other than evaluation of possible CAD (n=85), significant arrhythmias compromising imaging quality (n=23). Beside these exclusion criteria, patients with renal failure, documented contrast allergy or pregnant women did not perform the CT examination. Finally, 475 subjects fulfilled the inclusion criteria.

Scan protocol

All CCTA scans were performed with a 64-sliced multi-detector CT (Sensation 64, Siemens, Forchheim, Germany). The scanning parameters were: slices/collimation 64/0.6 mm, tube voltage 120 kv, 850 mAs, gantry rotation time 330 ms, pitch 0.2, effective slice thickness 0.75 mm and reconstruction increment 0.4 mm. Patients with a heart-rate > 70 bpm received premedication with oral beta-blockers 1 hour prior the examination. Short-acting nitroglycerine sublingual spray was administered to all patients for coronary vasodilatation.

First, a non-contrast enhanced scan was performed in order to assess the coronary artery calcium score (CACS). This scan was followed by the coronary computed tomography angiography (CCTA) to evaluate the coronary artery lumen and to characterize the atherosclerotic plaques. A bolus of 80 ml of iodinated contrast medium was administered intravenously at 5 ml/sec, followed by 40 ml of saline injected at the same rate. After the acquisition, the images were transferred to a dedicated workstation for post-processing, which included multiplanar

reconstructions (MPR), maximum intensity projections (MIP) and volume rendering images (VRT).

Coronary artery analysis

All CCTA images were assessed by an experienced radiologist who was blinded to the study (LE.P.). CACS was calculated using a semi-automatically software, according to the Agatston method. Plaque composition was classified as: calcified, non-calcified or mixed, with coronary calcified plaque being defined as any structure with a density ≥130 HU.

Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. We evaluated only the coronary segments with a diameter greater than 1.5 mm.

Every patient receieved a final CAD-RADS score based on the extent of coronary stenosis (Figure 1). CAD-RADS score of 0 was assigned if there was total absence of coronary plaques or stenosis. Minimal coronary stenosis between 1-24% was considered CAD-RADS 1. CAD-RADS score 2 was given when there was a mild stenosis between 25-49%. CAD-RADS score of 3 corresponded to a moderate stenosis between 50-69%. CAD-RADS score of 4 was assigned if there was a single coronary stenosis between 70-99% or if the left main artery was depicted with a stenosis of more than 50%. Also, CAD-RADS score of 4 was given in the situation of 3-vessel obstructive disease, when there were stenosis of more than 70% involving all the three coronary arteries (left anterior descending artery, circumflex artery and right coronary artery). If total occlusion was identified in at least one coronary segment, a CAD-RADS score of 5 was assigned.

Obstructive CAD was defined as ≥ 50% stenosis of ≥1 coronary segments on CCTA.

Cardiovascular risk factors

Prior to CCTA, a detailed medical history with the risk factors was obtained from all patients. Hypertension was defined as blood pressure ≥ 140/90 mm Hg or treatment with antihypertensive medications. Dyslipidemia was defined as a total cholesterol level ≥ 220 mg/dl or treatment with lipid-lowering medications. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dl or the use of insulin or oral antidiabetic agents. Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2. Self-reported smoking status was obtained by a query regarding both current and previous smoking history. Classification of symptoms (typical angina, atypical angina, non-anginal pain) was judged by cardiologists in patient interviews conducted prior to the CT examination.

Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables with normal distribution were expressed as means ± standard deviation, those with non-normal distribution as median with interquartile range. Normality was tested with the Kolmogorov-Smirnov test.

Differences between CAD-RADS groups were evaluated using one-way analysis of variance (ANOVA) for continuous variables and $\chi 2$ test for categorical variables. . Whenever the distribution of continuous data was not normal, non-parametric Kruskal-Wallis test was used for comparison. A Bonferroni correction for multiple (9) comparisons was used; statistical significance was accepted with a p value of 0.005 (0.05/9).

Cardiovascular risk factors that showed a significant association with the CAD-RADS score were included in multivariate regression analysis in order to evaluate their simultaneous influence. Through multiple regression analysis, independent predictors for obstructive CAD (CAD-RADS score ≥ 3) were identified.

Two prediction models for CAD-RADS score ≥ 3 were developed using area under the operating characteristic curve (AUC) analysis. When appropriate, a 95% confidence interval (CI) was calculated.

For all comparisons, a p value of <0.05 was considered statistically significant. The statistical analysis was performed using commercially available software (MedCalc for Windows, version 14.8, MedCalc Software, Ostend, Belgium).

Results

Demographic and Clinical Data

The clinical and angiographic characteristics of our study population are shown in Table 1. Among the 475 patients included in this study, the mean age was 57.8±13.2 years and the majority of them were females: 54.4%. There was a high prevalence of both hypertensive (74.5%) and dyslipidemic (64.2%) patients. The percentage of diabetic subjects was relatively small, with only 19.3% individuals having this condition. The majority of the patients included in this study were symptomatic, 72.6 % presenting with either typical or atypical angina.

When we classified the patients according to the CAD-RADS score, 177 of them had CAD-RADS score=0, 99 patients had CAD-RADS score=1 while 80 subjects CAD-RADS score=2. A percentage of 14.1% of people included in this study were diagnosed with CAD-RADS 3 score. Finally, 9.3% patients had severe stenosis, with a CAD-RADS score of 4 and 5 subjects had total occlusion of a coronary segment (CAD-RADS score=5).

CAD-RADS score and multiple cardiovascular risk factors

Using the cardiovascular risk factors mentioned above, we tested if there is any association regarding their presence and the severity of coronary artery disease (Table 2).

Our results show that a CAD-RADS score of 0 was more frequent in younger patients, with a mean age of 48.8 ± 12.1 years in this subgroup, while patients older than 60-years old were more likely to develop coronary atherosclerotic plaques and more significant coronary stenosis.

Regarding the gender, subjects with higher CAD-RADS score were more frequently males. More than 55% of the patients who were diagnosed with CAD-RADS score ≥ 2 were males, while the majority of the female patients (69.3%) received a CAD-RADS score of 0 or 1.

Our findings indicated a positive association between systolic hypertension and CAD-RADS score, with over 90% of the subjects with moderate/severe stenosis (CAD-RADS ≥ 3) being hypertensive. Moreover, based on our results, patients with CAD-RADS scores ≥ 3 had a greater frequency of dyslipidemia, with more than 85% patients in these categories being also dyslipidemic.

Furthermore, the proportion of smokers was larger among patients identified with higher CAD-RADS scores: over two-third of the patients who received a CAD-RADS score ≥ 2 admitted the use of cigarettes. On the other hand, in the CAD-RADS groups of 0 and 1, the percentage of the smokers was less than 50%.

Regarding the association between diabetes mellitus and CAD-RADS score, our results show increasing percents of diabetic individuals proportional with higher CAD-RADS scores: from 9% diabetic patients in CAD-RADS 0 group to 50% diabetic subjects in CAD-RADS 5 group. However, the percentage of obese subjects did not differ significantly among different CAD-RADS groups.

The percentage of symptomatic patients was higher among the subjects with greater atherosclerotic burden, with more than 65% people diagnosed with CAD-RADS score ≥ 3 presenting with typical angina.

Finally, the severity of coronary artery stenosis increased significantly with CACS.

Multivariate analysis

According to the multivariate analysis, male sex, age ≥ 60 years, hypertension, dyslipidemia and typical angina remained major predictors of obstructive CAD defined as CAD-RADS score ≥ 3(Table 3). Males had almost 4 times higher oddsof developing significant coronary stenosis. The odds ratio for coronary stenosis ≥ 50% was approximately 2-fold greater in individuals over 60-years old. Our results showed that having dyslipidemia significantly increased the odds of moderate/severe coronary stenosis by more than 3 times. Hypertension was correlated with increased odds of having CAD-RADS score ≥ 3 by approximately 3times.Last but not least, our findings revealed that the odds ratio for significant coronary stenosis was more than 5-fold greater for patients who accused typical angina.

We developed a clinical prediction model for CAD-RADS score ≥ 3 in which we included all the risk factors that proved to be statistically significant in the multivariate analysis. This model had a good discriminative power (AUC=0.83, p<0.0001, 95% CI: 0.797- 0.866). Furthermore, we developed a second prediction model, adding an imaging factor: CACS to the clinical model.

This model proved improved the prediction performance (AUC= 0.93, p<0.0001, 95% CI: 0.902 to 0.950). The ROC curves of these two models are shown in Figure 2.

Discussion

CAD-RADS is a new CT angiography classification system dating since 2016 and there are only a few studies published in the area of cardiac imaging using the CAD-RADS score. CAD-RADS score is a standardized reporting system for CAD in patients with suspected or known coronary artery disease (19), a system of communication between radiologists and clinicians, to provide a basis for further investigation, diagnosis, management and treatment planning of the patients with coronary artery stenosis. It was demonstrated that using CAD-RADS classification system reduces the human error substantially and improves data integrity (20). Other similar standardized reporting systems were introduced in other fields in medical imaging (breast, prostate, liver or lung) and studies have verified their ability of standardizing patient management (21). To the best of our knowledge, our study is the first one to evaluate the association between multiple cardiovascular risk factors and coronary artery stenosis assessed using CAD-RADS score in a Romanian population.

There are some well known risk factors associated with the development of coronary artery disease and with an increased risk of acute coronary syndrome: male gender, hypertension, diabetes mellitus, hypercholesterolemia, family history, smoking (22). The correlation between cardiovascular risk factors and cardiovascular events was first demonstrated by the Framingham study through an epidemiological approach (23). Afterwards, the association between the presence, the extent, and severity of CAD and cardiovascular risk factors was demonstrated.

Our results are similar to those described in other studies from different countries regarding the association between traditional risk factors and coronary artery disease, coronary artery stenosis or the calcium scoring assessed using Agatston score.

The INTERHEART study (24) shows that the cumulative effect of risk factors increased the risk of CAD, especially of myocardial infarction worldwide, in both sexes and all ages in all region of the world; they accounted for 53% of the population attributable risks of acute myocardial infarction (24). They reported nine risk factors for most of the risks of myocardial infarction: abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables and alcohol, and regular physical activity (24). Collectively, these factors accounted for 90% of the population attributable risks in men and 94% in women (24).

Our research reports that male sex, age over 60 years, hypertension, dyslipidemia and typical angina are the major predictors of obstructive CAD defined as CAD-RADS score ≥ 3. A positive association between coronary artery burden estimated through CAD-RADS 0-5 score and diabetes mellitus and smoking was established. These risk factors were found with high values in

the majority of studies (22, 24-28). Cumulative effect of major risk factors increased the prevalence of CAD.

In our study, the most important cardiovascular risk factor with a high prevalence (74.5%) was hypertension, with over 85% of our subjects having moderate/severe stenosis with CAD-RADS score ≥ 3. Hypertension was reported as an important factor for CAD (54.4%) by Al-Mukhtar et al (26). Mirza et al reported that the most prevalent risk factor for CAD was obesity (86%), followed by smoking (62%) and hypertension (24%) (27). Konishi et al have found that the pericardial fat is more highly associated with early development of CAD than simple anthropometric measures of abdominal obesity (28). Pericardial fat volume was reported as a indicator of abdominal fat, and not waist circumference, and it was associated independently and significantly with the presence of coronary plaques (28). In our study, obesity was defined as body mass index (BMI) ≥ 30 kg/m^2. The prevalence of obesity in our group was of 42.3%. We did not find a direct association between obesity and coronary artery burden defined by CAD-RADS score in univariate or multivariate analysis. Obesity was constantlypresent at all levels of CAD-RADS, but not associated with the severity of it. Medakovic et , who reported a prevalence of 81% of above normal weight (48.8% overweight and 32.2% obese) in their study group, also did not find a direct association between the obesity and the degree of coronary stenosis (29). In a study conducted by Dores H et al, obesity assessed by BMI was an indicator of the presence of CAD, but it wasn't correlated with its severity (30). They also described an "obesity paradox", which was previously documented by other studies, with better outcomes after percutaneous coronary interventions at patients with a higher BMI (30). There is a controversy regarding obesity and several explanations are given for this paradox, the answer still being in debate (30).

One of the most powerful associations with an advanced CAD-RADS score was represented by male gender, over 56% at CAD-RDS 2, reaching 100% at CAD-RADS 5. This is one of the most established risk factors associated with coronary artery disease (27, 31-33).

Smoking, known as one of the factors that promotes inflammation, being thus involved in atherogenesis (31), was associated with the presence and severity of CAD, but not with obstructive CAD (CAD-RADS ≥ 3). This is rather a surprising fact, but there are also other studies published in literature where there was not found an association between smoking and high coronary artery burden (29) or between smoking and coronary artery calcium score for predicting patient mortality risk (33). Medakovic et al explained its possible lack of association because of the low prevalence of smokers in its study (12.3%) (29), but in our study, the prevalence of smokers was 46.3%, that being almost half of the patients. The same connection was found regarding diabetes mellitus and CAD-RADS, one explanation being that only 19.3% of our study group had diabetes as their comorbidity.

There is a direct association between calcium scoring and CAD-RADS score. Also, extensive calcified plaques (Ca scoring ≥ 400) (33) were corelated with coronary stenosis higher than 70% (CAD-RADS 4 and 5) in our results.

Limitations of the study

Our study has several limitations, the most important one being the fact that it is a retrospectively conducted one. Secondary**,** our results were confined to the experience of a single medical center and the findings of this study were based on a relatively small patient population. Regarding the risk factors, dyslipidemia was not analyzed by fractions of the cholesterol: LDL-C and HDL-C. Also, we did not analyze other additional risk factors like alcohol use, physical activity, anthropometric measurements or C-reactive protein levels. Taking the retrospective approach into consideration, our research assess only the association between tradionally known cardiovascular risk factors and coronary stenosis evaluated by CAD-RADS score and does not assess the incidence of major cardiac events after performing the CT angiography.

Conclusion

In conclusion, our study demonstrates that there is a significant association between multiple cardiovascular risk factors and a higher coronary atherosclerotic burden assessed using CAD-RADS score. We consider that the evaluation of CAD-RADS score as a predictive factor for acute cardiac events should be the main subject of future prospective investigation.

Author contributions:

- Conception (constructing the idea for research): Loredana E. Popa, Mircea M. Buruian
- Design (planning methodology to reach the conclusion): Loredana E. Popa, Diana Feier, Andrei Lebovici, Raluca Rancea
- Supervision (organising and supervising the course of the project): Loredana E. Popa, Mircea M. Buruian, Adrian Molnar
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- Analysis and interpretation: Bianca Petresc, Diana Feier
- Literature Review: Bianca Petresc, Calin Schiau, Cristina Catana, Claudia G. Moldovanu
- Writing of the manuscript: Loredana E. Popa, Bianca Petresc, Cristina Catana, Claudia G. Moldovanu
- Critical Review: Adrian Molnar, Andrei Lebovici, Diana Feier, Mircea M. Buruian

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Patient consent for publication: Not required.

Data sharing statement: Deidentified participant data are available upon request through the corresponding author BP. ORCID identifier 0000-0003-2167-9350.

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Table 1. Clinical and CCTA characteristics of the study population

Variable	Value
Age ˜	57.8 ± 13.2
Male sex*	217 (45.6%)
Hypertension*	354 (74.5%)
Dyslipidemia*	305 (64.2%)
Diabetes mellitus*	92 (19.3%)
Obesity*	201 (42.3%)
Smoking*	220 (46.3%)
Clinical presentation*	
Typical angina	222 (46.7%)
Atypical angina	123 (25.9%)
No chest pain	130 (27.4%)
Coronary artery calcium scoring (CACS) *	
0	177(37.2%)
1-10	52 (10.9%)
11-100	88 (18.6%)
101-400	83 (17.5%)
>400	75 (15.8%)
CAD-RADS*	
0	177(37.2%)
1	99 (20.8%)
2	80 (16.8%)
3	67 (14.1%)
4	44 (9.3%)
5	8 (1.8%)

˜ Results are presented as mean±SD
* Results are presented as number (%)

Table 2. Distribution of cardiovascular risk factors according to CAD-RADS categories

Variable	Value	CAD-RADS 0	CAD-RADS 1	CAD-RADS 2	CAD-RADS 3	CAD-RADS 4	CAD-RADS 5	p value
Age		48.8 ± 12.1	60.4 ± 11.9	63.6 ± 8.7	64.6 ± 10.5	66.1 ± 10.6	64.7 ± 11.1	**p<0.001***
Sex								**p<0.001***
	Male	55 (31.1%)	42 (42.4%)	45 (56.2%)	39 (58.2%)	28 (63.6%)	8 (100%)	
	Female	122 (68.9%)	57 (57.6%)	35 (43.8%)	28 (41.8 %)	16 (36.4%)	0 (0 %)	
Hypertension								**p<0.001***
	Yes	110 (62.2%)	70 (70.7%)	62 (77.5%)	63 (94.0%)	42 (95.4%)	7 (87.5%)	
	No	67(37.8%)	29 (29.3%)	18 (22.5%)	4 (6.0%)	2 (4.6%)	1 (12.5%)	
Dyslipidemia								**p<0.001***
	Yes	75 (42.3%)	68 (68.6%)	57 (71.2%)	57 (85.0%)	41 (93.1%)	7 (87.5%)	
	No	102 (57.7%)	31 (31.7%)	23 (28.8%)	10 (15.0%)	3(6.9%)	1(12.5%)	
Diabetes mellitus								**p<0.001***
	Yes	16 (9.0%)	21(21.2%)	21(26.2%)	12 (17.9%)	18 (40.9%)	4 (50.0%)	
	No	161 (91.0%)	78 (78.8%)	59 (73.8%)	55 (82.1%)	26 (59.1%)	4 (50.0%)	
Obesity								**p=0.63**
	Yes	68 (38.4%)	45 (45.4%)	38 (47.5%)	29 (43.2%)	19 (43.1%)	2 (25.0%)	
	No	109 (61.6%)	54 (54.6%)	42 (52.5%)	38 (56.8%)	25 (56.9%)	6 (75.0%)	
Smoking								**p<0.001***
	Yes	53 (30.0%)	44 (44.4%)	48 (60.0%)	44 (65.6%)	25 (56.9%)	6 (75.0%)	
	No	124 (70.0%)	55 (55.6%)	32 (40.0%)	23 (34.4%)	19 (43.1%)	2 (25.0%)	
Clinical presentation								**p<0.001***
	Typical angina	60 (33.9%)	35 (35.3%)	36 (45.0%)	45 (67.1%)	39 (88.6%)	7 (87.5%)	
	Atypical angina	70 (39.5%)	25 (25.2%)	20 (25.0%)	7 (10.4%)	1 (2.2%)	0 (0 %)	
	Nonanginal chest pain	47 (26.6%)	39 (39.5%)	24 (30.0%)	15 (22.5%)	4 (9.2%)	1 (12.5%)	
CACS		0 (0-0)	15 (6.2-36.6)	123 (55.1-284.5)	303 (134.8-500.7)	711.3 (444.7-958.3)	1611.4 (949.1-1921.4)	**p<0.001***

*Obtained p value was considered statistically significant after Bonferroni correction (p<0.005)
Results are presented as mean±SD, number (%), or median (25th-75th percentile)
Abbreviations: CACS: coronary artery calcium score

Table 3. Logistic regression analysis for the association between cardiovascular risk factors and obstructive CAD (CAD-RADS≥3)

Variable	Odds ratio (95% CI)	p value
Male sex	3.9992 (2.2603 – 5.0758)	<0.0001*
Age ≥ 60 years	1.8693 (1.0520 – 2.6213)	0.0329*
Hypertension	2.9038 (1.4536 - 3.9094)	0.0236*
Obesity	0.7052 (0.4200 - 1.1838)	0.1863
Diabetes mellitus	1.4711 (0.8123 - 2.6642)	0.2027
Dyslipidemia	3.2523 (1.9695 - 4.5395)	0.0015*
Smoking	1.6094 (0.9323 - 2.7784)	0.0876
Typical angina	5.1584 (3.9832 - 6.2198)	<0.0001*

*Statistically significant p<0.05

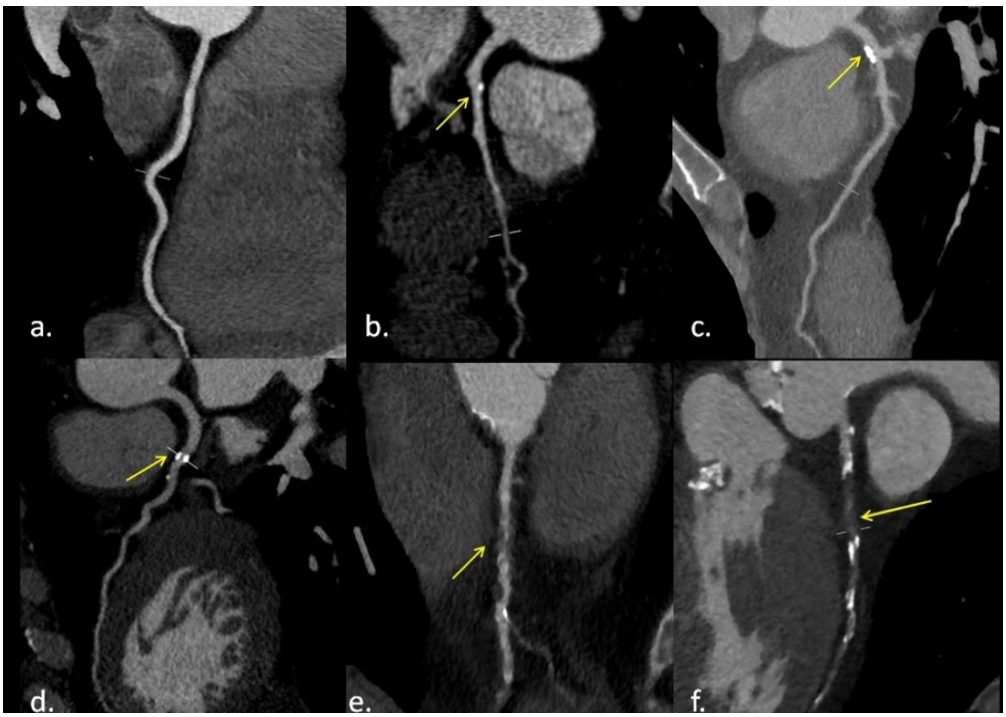
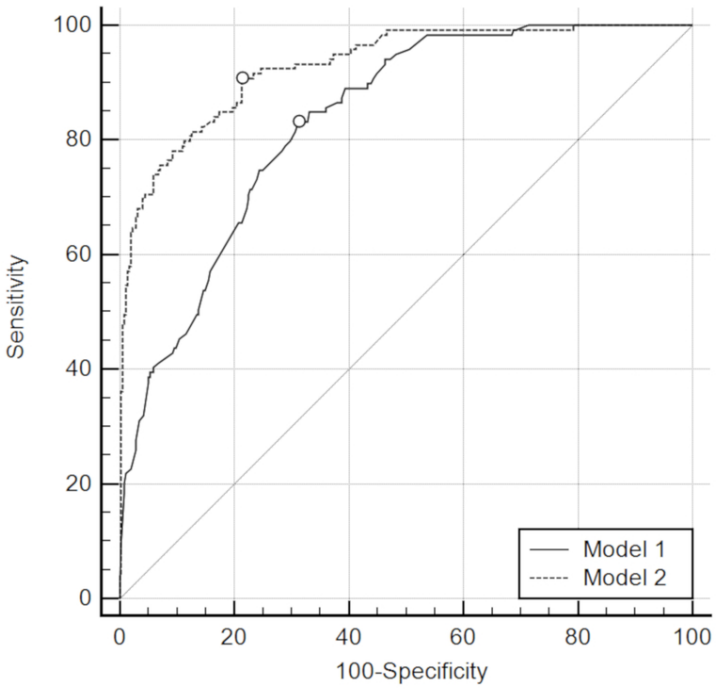


Fig. 1- MPR (multiplanar reconstruction) images showing different degrees of coronary artery stenosis (yellow arrows): a. normal RCA without any plaque or stenosis (CAD-RADS 0), b. small calcified plaque in the proximal LAD with minimal luminal narrowing < 25% (CAD-RADS 1), c. calcified plaque in the proximal LAD with 25-49% diameter stenosis (CAD-RADS 2), d. semi-circumferential calcified plaque in the proximal LAD with 50-69% diameter stenosis (CAD-RADS 3),e. non-calcified plaque in the proximal RCA with 70-99% diameter stenosis (CAD-RADS 4), f. total occlusion of proximal and mid LAD; calcified plaques above and beyond it supports the diagnosis of chronic total occlusion (CAD-RADS 5)

173x122mm (600 x 600 DPI)



Receiver-operating characteristics (ROC) curves for the prediction models of CAD-RADS score ≥ 3

90x67mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	*5*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5,6
		(*b*) Describe any methods used to examine subgroups and interactions	5,6
		(*c*) Explain how missing data were addressed	5,6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	5,6
		(*e*) Describe any sensitivity analyses	5,6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	6,7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7
		(*b*) Report category boundaries when continuous variables were categorized	6,7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6,7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8,9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Cardiovascular risk factors as predictors of coronary artery disease assessed using CAD-RADS classification: a cross-sectional study in Romanian population

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Cardiovascular risk factors as predictors of coronary artery disease assessed using CAD-RADS classification: a cross-sectional study in Romanian population

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Abstract

Objectives: The aim of this study was to evaluate the association between cardiovascular risk factors and CAD-RADS score in the Romanian population. CAD-RADS is a new, standardized method to assess coronary artery disease (CAD) using coronary computed tomography angiography (CCTA).

Design: A cross-sectional observational, patient-based study.

Setting: Referred imaging centre for coronary artery disease in Transylvania, Romania.

Participants: We retrospectively reviewed 674 patients who underwent CCTA between January 2017 and August 2018. The exclusion criteria included: previously known CAD, defined as prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery (n=91), cardiac CT for other than evaluation of possible CAD (n=85), significant arrhythmias compromising imaging quality (n=23). Finally, 475 patients fulfilled the inclusion criteria.

Methods: Demographical, clinical and CCTA characteristics of the patients were obtained. Coronary artery disease was evaluated using CAD-RADS score. Obstructive CAD was defined as ≥50% stenosis of ≥1 coronary segment on CCTA.

Results: We evaluated the association between risk factors and CAD-RADS score in univariate and multivariable analysis. We divided the patients into 2 groups according to the CAD-RADS system: group 1: CAD-RADS score between 0-2 (stenosis <50%) and group 2: CAD-RADS score≥3 (stenosis ≥50%). On univariate analysis, male gender, age, hypertension, dyslipidemia, smoking and diabetes mellitus were positively associated with a CAD-RADS score ≥ 3. On the multivariable analysis, male sex, age, dyslipidemia, hypertension and smoking remained major predictors of obstructive CAD.

Conclusion: This study demonstrated that there is a significant association between multiple cardiovascular risk factors and a higher coronary atherosclerotic burden assessed using CAD-RADS system in the Romanian population.

Keywords: coronary artery disease; coronary CT angiography; CAD-RADS; cardiovascular risk factors

Article Summary

Strengths and limitations of this study

- This is the first study to evaluate the association of cardiovascular risk factors and coronary artery disease assessed using coronary CT angiography in Romania.
- We quantified the coronary artery stenosis using the CAD-RADS classification, the newest, standardized method for reporting CAD.
- The patients were recruited from a single centre; therefore, the study population was relatively small.
- Another limitation is the design of the study: a cross-sectional, retrospective one.

Introduction

Coronary artery disease (CAD) is one of the major causes of morbidity and mortality worldwide. Despite the fact that CAD mortality rates have declined since 1980s, it still accounts for approximately one-third of all deaths of individuals aged over 35 years old(1,2).

It is well-known that atherosclerosis is the underlying cause of cardiovascular diseases and multiple risk factors augment the atherosclerotic process. These risk factors include non-modifiable ones such as age and sex and modifiable risk factors such as hypertension, dyslipidemia, obesity, diabetes mellitus and smoking (3-7). Studies suggest that the majority of patients with CAD have at least one modifiable risk factor and their presence has an impactful role in the progression of CAD (8, 9).

Prognostic assessment is very important in the management of the patients with CAD. Therefore, many risk-scoring systems have been developed such as Framingham and SCORE, which are based on the presence of various traditional cardiovascular risk factors (10, 11).

Moreover, with the recent advancements made in medical technology, coronary CT angiography (CCTA) has rapidly evolved into one of the most highly accurate methods for diagnosis and evaluation of CAD. It is an unique non-invasive test which can provide direct and accurate visualization of the coronary vessel lumen, being able to quantify the presence and extent of coronary stenosis and to assess the characteristics of coronary atherosclerotic plaques (12).

CCTA has been included in the latest ESC guideline on the management of stable artery disease, being categorized as class II LOE C recommendation. CCTA should be used for risk stratification in patients with stable CAD who are in the lower range of intermediate pre-test probability. Also, it can be considered for patients who are unable to exercise or to perform a stress test or for patients with inconclusive functional test results (13).

In recent years, many studies have been conducted to evaluate the short and long-term prognostic importance of CCTA. They demonstrate the fact that measurements of both stenosis severity and

plaque features provide powerful prognostic information superior to traditional cardiovascular risk factors (14-18).

In 2016, the Society of Cardiovascular Computed Tomography published the CAD-RADS grading system, which is a standardized reporting method of CCTA results. This is meant to facilitate communication of the results along with suggestions for consecutive management of the patients. The grading system ranges from 0 to 5, where CAD-RADS 0 score means complete absence of stenosis and CAD-RADS 5 represents total occlusion of at least 1 coronary segment (19).

The aim of this study is to evaluate the association between traditional cardiovascular risk factors and coronary artery disease evaluated using the CAD-RADS score.

Methods

Study population

We retrospectively reviewed 674 consecutive patients who underwent CCTA between January 2017 and August 2018 in our institution. The indications for CCTA were: atypical angina, typical angina with an inconclusive stress test, patients with intermediate/high-risk for major cardiac events. The exclusion criteria included: previously known CAD, defined as prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery (n=91), cardiac CT for other than evaluation of possible CAD (n=85), significant arrhythmias compromising imaging quality (n=23). Beside these exclusion criteria, patients with renal failure, documented contrast allergy or pregnant women did not perform the CT examination. Finally, 475 patients fulfilled the inclusion criteria.

Scan protocol

All CCTA scans were performed with a 64-sliced multi-detector CT (Sensation 64, Siemens, Forchheim, Germany). The scanning parameters were: slices/collimation 64/0.6 mm, tube voltage 120 kv, 850 mAs, gantry rotation time 330 ms, pitch 0.2, effective slice thickness 0.75 mm and reconstruction increment 0.4 mm. Patients with a heart-rate > 70 bpm received premedication with oral beta-blockers 1 hour prior the examination. Short-acting nitroglycerine sublingual spray was administered to all patients for coronary vasodilatation.

First, a non-contrast enhanced scan was performed in order to assess the coronary artery calcium score (CACS). This scan was followed by the coronary computed tomography angiography (CCTA) to evaluate the coronary artery lumen and to characterize the atherosclerotic plaques. A bolus of 80 ml of iodinated contrast medium was administered intravenously at 5 ml/sec, followed by 40 ml of saline injected at the same rate. After the acquisition, the images were transferred to a dedicated workstation for post-processing, which included multiplanar

reconstructions (MPR), maximum intensity projections (MIP) and volume rendering images (VRT).

Coronary artery analysis

All CCTA images were assessed by an experienced radiologist who was blinded to the study (LE.P.). CACS was calculated using a semi-automatically software, according to the Agatston method. Plaque composition was classified as: calcified, non-calcified or mixed, with coronary calcified plaque being defined as any structure with a density ≥130 HU.

Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. We evaluated only the coronary segments with a diameter greater than 1.5 mm.

Every patient receieved a final CAD-RADS score based on the extent of coronary stenosis (Figure 1). CAD-RADS score of 0 was assigned if there was total absence of coronary plaques or stenosis. Minimal coronary stenosis between 1-24% was considered CAD-RADS 1. CAD-RADS score 2 was given when there was a mild stenosis between 25-49%. CAD-RADS score of 3 corresponded to a moderate stenosis between 50-69%. CAD-RADS score of 4 was assigned if there was a single coronary stenosis between 70-99% or if the left main artery was depicted with a stenosis of more than 50%. Also, CAD-RADS score of 4 was given in the situation of 3-vessel obstructive disease, when there were stenosis of more than 70% involving all the three coronary arteries (left anterior descending artery, circumflex artery and right coronary artery). If total occlusion was identified in at least one coronary segment, a CAD-RADS score of 5 was assigned.

Obstructive CAD was defined as ≥ 50% stenosis of ≥1 coronary segments on CCTA.

Cardiovascular risk factors

Prior to CCTA, a detailed medical history with the risk factors was obtained from all patients. Hypertension was defined as blood pressure ≥ 140/90 mm Hg or treatment with antihypertensive medications (20). Dyslipidemia was defined as a total cholesterol level ≥ 5 mmol/L (21) or treatment with lipid-lowering medications. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dl or the use of insulin or oral antidiabetic agents. Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2. Self-reported smoking status was obtained by a query regarding both current and previous smoking history. Classification of symptoms (typical angina, atypical angina, non-anginal pain) was judged by cardiologists in patient interviews conducted prior to the CT examination.

Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables with normal distribution were expressed as means ± standard deviation, those with non-normal distribution as median with interquartile range. Normality was tested with the Kolmogorov-Smirnov test.

Differences between CAD-RADS groups were evaluated using one-way analysis of variance (ANOVA) for continuous variables and $\chi 2$ test for categorical variables. Whenever the distribution of continuous data was not normal, non-parametric Kruskal-Wallis test was used for comparison.

Cardiovascular risk factors that showed a significant association with the CAD-RADS score were included in multivariable logistic regression analysis in order to evaluate their simultaneous influence. Through logistic regression analysis, independent predictors for obstructive CAD (CAD-RADS score ≥ 3) were identified.

For all comparisons, a p value of <0.05 was considered statistically significant. The statistical analysis was performed using commercially available software (MedCalc for Windows, version 14.8, MedCalc Software, Ostend, Belgium).

Patient and Public Involvement

There was no involvement of patients and/or public in this study.

Results

Baseline characteristics of the study population

The clinical and angiographic characteristics of our study population according to the CAD-RADS classification are shown in Table 1. Among the 475 patients included in this study, the mean age was 57.8±13.2 years and the majority of them were females: 54.4%. There was a high prevalence of both hypertensive (74.5%) and dyslipidemic (69.7%) patients. The percentage of diabetic patients was relatively small, with only 19.3% individuals having this condition. Smoking was reported among 46.3% of the study group. The majority of the patients were symptomatic, 72.6 % presenting with either typical or atypical angina.

When we classified the patients according to the CAD-RADS score, 177 of them had CAD-RADS score=0, 99 patients had CAD-RADS score=1 while 80 patients CAD-RADS score=2. A percentage of 14.1% of people included in this study were diagnosed with CAD-RADS 3 score. Finally, 9.3% patients had severe stenosis, with a CAD-RADS score of 4 and 8 patients had total occlusion of a coronary segment (CAD-RADS score=5).

Patient gender, age, the presence of hypertension, dyslipidemia, diabetes mellitus as well as clinical presentation and coronary artery calcium score were significantly different across CAD-RADS scores ($p < 0.0001$ for all comparisons) (Table 1). However, our result did not reveal any association between obesity and different CAD-RADS scores ($p=0.63$) (Table 1).

CAD-RADS score and multiple cardiovascular risk factors

Using the cardiovascular risk factors mentioned above, we tested if there is any association regarding their presence and obstructive coronary artery disease, defined as coronary stenosis ≥50% and equivalent with a CAD-RADS score ≥ 3 (Table 2).

Our results show that a CAD-RADS score between 0-2 was more frequent in younger patients, with a mean age of 55.41 years in this subgroup, while patients older than 63-years old were more likely to develop obstructive coronary stenosis. Regarding the gender, patients with CAD-RADS scores higher than 3 were more frequently males The majority of the female patients (82.9%) received a CAD-RADS score of 0, 1 or 2 (Table 2).

Our findings indicated a positive association between systolic hypertension and CAD-RADS score, with over 90% of the patients with moderate/severe stenosis (CAD-RADS ≥ 3) being hypertensive (Table 2). Moreover, based on our results, patients with CAD-RADS scores ≥ 3 had a greater frequency of dyslipidemia, with more than 85% patients in these categories being also dyslipidemic (Table 2).

Furthermore, the proportion of smokers was larger among patients identified with higher CAD-RADS scores: almost two-third of the patients who received a CAD-RADS score ≥ 3 admitted the use of cigarettes (Table 2). On the other hand, in the CAD-RADS groups of 0, 1 and 2 the percentage of the smokers was less than 50% (Table 2).

Regarding the association between diabetes mellitus and CAD-RADS score, our results show increasing percents of diabetic individuals proportional with higher CAD-RADS scores: from 16.3% diabetic patients with CAD-RADS scores of 0-2 to 28.6% diabetic patients with CAD-RADS scores ≥ 3 (Table 2). However, the percentage of obese patients did not differ significantly among different CAD-RADS groups (Table 2).

Multivariable analysis

According to the multivariable analysis, male sex, age, hypertension, dyslipidemia and smoking remained major predictors of obstructive CAD defined as CAD-RADS score ≥ 3 (Table 3). Males had more than 3 times higher odds of developing significant coronary stenosis. The odds ratio for coronary stenosis ≥ 50% was approximately 3.5-fold greater in hypertensive individuals. Our results showed that having dyslipidemia significantly increased the odds of moderate/severe coronary stenosis by more than 2.5 times. Last but not least, smoking was associated with increased odds of having CAD-RADS score ≥ 3 by approximately 2 times.

Discussion

Romania is one of the high cardiovascular risk European countries according to data from the last European Society of Cardiology guideline for prevention of CVD (3). There are only a limited number of national epidemiological studies which estimate the prevalence and future trends of

cardiovascular risk factors in the Romanian population. (22-26). The latest study from 2017, Sephar III, shows an increasing trend regarding the majority of cardiovascular risk factors in our population (24). The prevalence of hypertension increased from 40.4% in 2011 to 45.1% in 2016 (23, 24). Moreover, the percentage of Romanians diagnosed with dyslipidemia is alarmingly high, reaching 77.3% in 2016, with 53.4% newly diagnosed cases (24). Furthermore, the prevalence of diabetes mellitus, another important risk factor for coronary artery disease, is 12.4% (25), a relatively high percentage that puts Romania on the 8th place in Europe regarding this medical condition (27). Overweight and obesity represent another medical issue encountered in our country. Both PREDATORR and Sephar III studies (24, 26) reported a prevalence of over 30% of obese patients based on BMI index, similar to the data from WHO database which shows an increasing trend of obesity in our country over the last 40 years (28). Last but not least, smoking can be considered another cause for the high incidence of cardiovascular disease in our country. Even if there is a decreasing trend regarding this habit in our country, Romania still occupies one of the leading places in European Union, with 28% of individuals reporting the use of cigarettes, a number higher than the average European percentage: 26% (29). According to the data by the National Institute for Public Health in Romania, tobacco is attributed to 16.3% CVD-Related deaths in Romania. (30).

In Europe, Romania records one of the greatest incidences of cardiovascular diseases, according to the latest statistics offered by EuroStat in 2018 (31). Our country occupies the second place in Europe regarding the percent of total deaths caused by diseases of the circulatory system (31). Concerning the standardized death rates caused by ischemic heart disease, Romania is also one of the leading countries, being on the 6th and 5th place in deaths of men and women respectively (31).

CAD-RADS is standardized radiological reporting system dating since 2016 and there are only a few studies published in the area of cardiac imaging using the CAD-RADS score (32-36). It is used to quantify coronary artery stenosis in patients with suspected or known coronary artery disease in order to provide a basis for further investigation, diagnosis, management and treatment, substantially reducing human error and improving data integrity (19).

To the best of our knowledge, our study is the first one to evaluate the association between multiple associations of cardiovascular risk factors and the severity of coronary artery disease assessed on CCTA and evaluated using CAD-RADS classification in the Romanian population.

The association between cardiovascular risk factors and cardiovascular events was first demonstrated by the Framingham study through an epidemiological approach (37). The INTERHEART study showed that the cumulative effect of risk factors increased the risk of CAD, especially of myocardial infarction worldwide, in both sexes and all ages worldwide (38).

Our research reports that male sex, age, dyslipidemia, hypertension and smoking are the significant predictors of obstructive CAD defined as CAD-RADS score ≥ 3, with the prevalence being increased by a cumulative effect on them.

Male sex and age are well-known risk factors for coronary atherosclerosis, being used in prediction models for the estimation of pretest probability of developing coronary artery disease (39, 40). Among medical risk factors, our study showed that hypertension and dyslipidemia were

positively associated with CAD-RADS score ≥ 3 in both univariate and multivariable analyses. Our results are in concordance with the latest data from European Heart Network which shows that systolic blood pressure and total cholesterol levels are the determinants with the greatest contribution to CVD mortality (41). Also, these two factors are included in the widely used SCORE charts (3) and there are many clinical models that add them for increasing the probability of obstructive CAD (42-45).

However, we did not find a direct association between obesity and coronary artery burden defined by CAD-RADS score. Our study is in concordance with Medakovic et al (46) and Dores H et al (47). According to Dores H et al, obesity assessed by BMI can be an indicator of the presence of CAD, but not necessarily associated with its severity (47). They also described an "obesity paradox" with better outcomes after percutaneous coronary interventions at patients with a higher BMI (47). Also, our multivariable analysis did not found an association between diabetes mellitus and obstructive CAD, one possible explanation being that only 19.3% of our study group had diabetes as their comorbidity.

Finally, our findings show that smoking is an independent risk factor for the presence of obstructive coronary disease, this being also one of the behavioral factors with the highest contribution for CVD mortality and morbidity rates across Europe (41).

Limitations of the study

Our study has several limitations, the most important one being the fact that it is a retrospectively conducted one. Secondary**,** our results were confined to the experience of a single medical center and the findings of this study were based on a relatively small patient population. Regarding the risk factors, dyslipidemia was not analyzed by fractions of the cholesterol: LDL-C and HDL-C. Also, we did not analyze other additional risk factors like alcohol use, physical activity, anthropometric measurements or C-reactive protein levels. Taking the retrospective approach into consideration, our research assess only the association between tradionally known cardiovascular risk factors and coronary stenosis evaluated by CAD-RADS score and does not assess the incidence of major cardiac events after performing the CT angiography.

Conclusion

In conclusion, our study demonstrates that there is a significant association between multiple cardiovascular risk factors and a higher coronary atherosclerotic burden assessed using CAD-RADS score in the Romanian population. Considering CAD as a priority for Romanian healthcare system, our study provides an overview of imaging and clinical characteristics of CAD and their association, offering valuable information for both cardiologists and radiologists in order to improve the management of the patients.

Author contributions:

- Conception (constructing the idea for research): Loredana E. Popa, Mircea M. Buruian
- Design (planning methodology to reach the conclusion): Loredana E. Popa, Diana Feier, Andrei Lebovici, Raluca Rancea
- Supervision (organising and supervising the course of the project): Loredana E. Popa, Mircea M. Buruian, Adrian Molnar
- Data Collection and Processing: Raluca Rancea, Calin Schiau, Cristina Catana, Claudia G. Moldovanu, Bianca Petresc
- Analysis and interpretation: Bianca Petresc, Diana Feier
- Literature Review: Bianca Petresc, Calin Schiau, Cristina Catana, Claudia G. Moldovanu
- Writing of the manuscript: Loredana E. Popa, Bianca Petresc, Cristina Catana, Claudia G. Moldovanu
- Critical Review: Adrian Molnar, Andrei Lebovici, Diana Feier, Mircea M. Buruian

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Ethics approval: The study was approved by the Ethics Committees of University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca (455/19.12.2018) and University of Medicine and Pharmacy Targu Mures (272/21.11.2018). Institutional review board approval was obtained for this study (1339/25.09.2018).

Patient consent for publication: Not required.

Data sharing statement: Deidentified participant data are available upon request through the corresponding author BP. ORCID identifier 0000-0003-2167-9350.

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FIGURE LEGENDS

Fig. 1- MPR (multiplanar reconstruction) images showing different degrees of coronary artery stenosis (yellow arrows): a. normal RCA without any plaque or stenosis (CAD-RADS 0), b. small calcified plaque in the proximal LAD with minimal luminal narrowing < 25% (CAD-RADS 1), c. calcified plaque in the proximal LAD with 25-49% diameter stenosis (CAD-RADS 2), d. semi-circumferential calcified plaque in the proximal LAD with 50-69% diameter stenosis (CAD-RADS 3),e. non-calcified plaque in the proximal RCA with 70-99% diameter stenosis (CAD-RADS 4), f. total occlusion of proximal and mid LAD; calcified plaques above and beyond it supports the diagnosis of chronic total occlusion (CAD-RADS 5)

Table 1. Baseline characteristics of the study population according to CAD-RADS categories

Variable	Value	CAD-RADS 0 (n=177)	CAD-RADS 1 (n=99)	CAD-RADS 2 (n=80)	CAD-RADS 3 (n=67)	CAD-RADS 4 (n=67)	CAD-RADS 5 (n=8)	p value
Age		48.8 ± 12.1	60.4 ± 11.9	63.6 ± 8.7	64.6 ± 10.5	66.1 ± 10.6	64.7 ± 11.1	**p<0.001***
Sex								**p<0.001***
	Male (n=217)	55 (31.1%)	42 (42.4%)	45 (56.2%)	39 (58.2%)	28 (63.6%)	8 (100%)	
	Female(n=258)	122 (68.9%)	57 (57.6%)	35 (43.8%)	28 (41.8 %)	16 (36.4%)	0 (0 %)	
Hypertension								**p<0.001***
	Yes(n=354)	110 (62.2%)	70 (70.7%)	62 (77.5%)	63 (94.0%)	42 (95.4%)	7 (87.5%)	
	No (n=121)	67(37.8%)	29 (29.3%)	18 (22.5%)	4 (6.0%)	2 (4.6%)	1 (12.5%)	
Dyslipidemia								**p<0.001***
	Yes (n=331)	91 (51.4%)	72 (72.7%)	61 (76.3%)	59 (88.1%)	41 (93.2%)	7 (87.5%)	
	No (n=144)	86 (48.6%)	27 (27.3%)	19 (23.8%)	8 (11.9%)	3(6.8%)	1 (12.5%)	
Diabetes mellitus								**p<0.001***
	Yes (n=92)	16 (9.0%)	21(21.2%)	21(26.2%)	12 (17.9%)	18 (40.9%)	4 (50.0%)	
	No (n=383)	161 (91.0%)	78 (78.8%)	59 (73.8%)	55 (82.1%)	26 (59.1%)	4 (50.0%)	
Obesity								**p=0.63**
	Yes (n=274)	68 (38.4%)	45 (45.4%)	38 (47.5%)	29 (43.2%)	19 (43.1%)	2 (25.0%)	
	No (n=201)	109 (61.6%)	54 (54.6%)	42 (52.5%)	38 (56.8%)	25 (56.9%)	6 (75.0%)	
Smoking								**p<0.001***
	Yes (n=220)	53 (30.0%)	44 (44.4%)	48 (60.0%)	44 (65.6%)	25 (56.9%)	6 (75.0%)	
	No (n=255)	124 (70.0%)	55 (55.6%)	32 (40.0%)	23 (34.4%)	19 (43.1%)	2 (25.0%)	
Clinical presentation								**p<0.001***
	Typical angina (n=222)	60 (33.9%)	35 (35.3%)	36 (45.0%)	45 (67.1%)	39 (88.6%)	7 (87.5%)	
	Atypica angina (n=123)	70 (39.5%)	25 (25.2%)	20 (25.0%)	7 (10.4%)	1 (2.2%)	0 (0 %)	
	Nonanginal chest pain (n=130)	47 (26.6%)	39 (39.5%)	24 (30.0%)	15 (22.5%)	4 (9.2%)	1 (12.5%)	
CACS		0 [0-0]	15 [6.2-36.6]	123 [55.1-284.5]	303 [134.8-500.7]	711.3 [444.7-958.3]	1611.4 [949.1-1921.4]	**p<0.001***

*Statistically significant p<0.05
Results are presented as mean±SD, number (%), or median (25th-75th percentile)
Abbreviations: CACS: coronary artery calcium score

Table 2. Univariate analysis for the association between cardiovascular risk factors and obstructive CAD classified using CAD-RADS categories

Variable	Value	CAD-RADS score 0-2 (stenosis<50%)	CAD-RADS score 3-5 (stenosis≥50%)	p value
Age		55.41 ± 13.11	63.10 ± 10.55	**p<0.001***
Sex				**p<0.001***
	Male	142 (39.2%)	75 (63.0%)	
	Female	214 (60.1%)	44 (37.0%)	
Hypertension				**p<0.001***
	Yes	242 (68.0%)	112 (94.1%)	
	No	114 (32.0%)	7 (5.9%)	
Dyslipidemia				**p<0.001***
	Yes	224 (62.9%)	107 (89.9%)	
	No	132 (37.01%)	12 (10.1%)	
Diabetes mellitus				**p=0.003***
	Yes	58 (16.3%)	34(28.6%)	
	No	298 (83.7%)	85 (71.4%)	
Obesity				**p=0.93**
	Yes	151 (42.4%)	50 (42.0%)	
	No	205 (57.6%)	69 (58.0%)	
Smoking				**p<0.001***
	Yes	145 (40.7%)	75 (63.0%)	
	No	211 (59.3%)	44 (37.0%)	
CACS		0.4 [0 - 39.5]	433.0 [182.4 - 924.8]	**p<0.001***

*Statistically significant p<0.05
Results are presented as mean±SD, number (%) or median [25th-75th percentile]
Abbreviations: CACS: coronary artery calcium score

Table 3. Logistic regression analysis for the association between cardiovascular risk factors and obstructive CAD (CAD-RADS score ≥3)

Variable	Odds ratio (95% CI)	p value
Male sex	3.136 (1.841 – 5.341)	<0.001*
Age	1.063 (1.036 – 1.090)	<0.001*
Hypertension	3.493 (1.444 – 6.251)	0.006*
Dyslipidemia	2.648 (1.283 – 5.466)	0.008*
Diabetes mellitus	1.207 (0.698 – 2.088)	0.501
Smoking	2.112 (1.236 – 5.466)	0.006*

*Statistically significant p<0.05

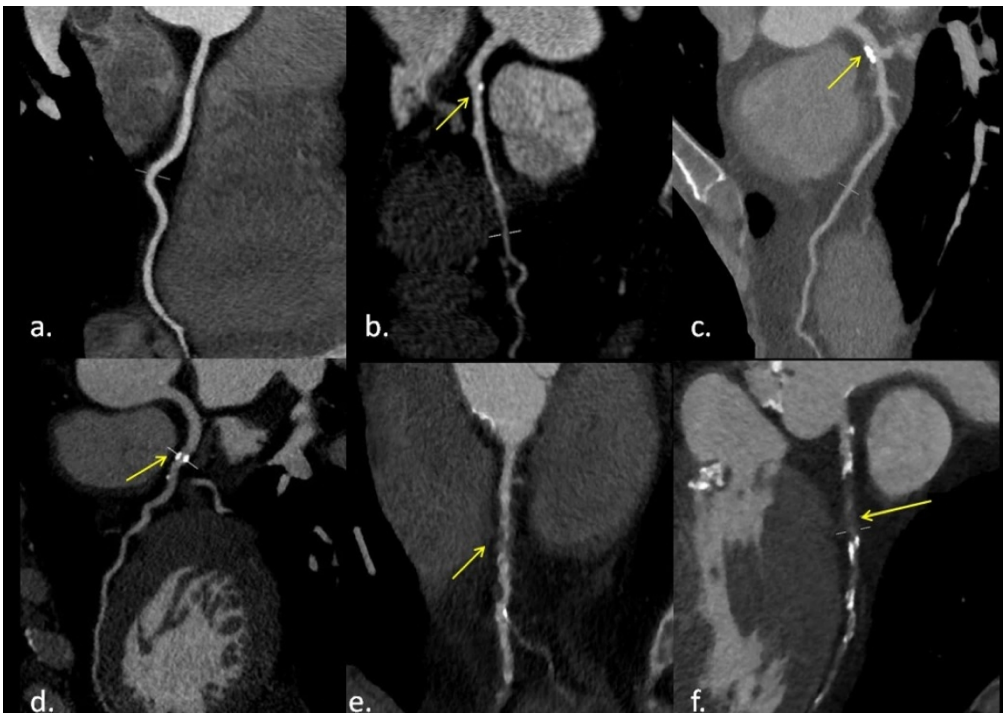

Fig. 1- MPR (multiplanar reconstruction) images showing different degrees of coronary artery stenosis (yellow arrows): a. normal RCA without any plaque or stenosis (CAD-RADS 0), b. small calcified plaque in the proximal LAD with minimal luminal narrowing < 25% (CAD-RADS 1), c. calcified plaque in the proximal LAD with 25-49% diameter stenosis (CAD-RADS 2), d. semi-circumferential calcified plaque in the proximal LAD with 50-69% diameter stenosis (CAD-RADS 3),e. non-calcified plaque in the proximal RCA with 70-99% diameter stenosis (CAD-RADS 4), f. total occlusion of proximal and mid LAD; calcified plaques above and beyond it supports the diagnosis of chronic total occlusion (CAD-RADS 5)

173x122mm (600 x 600 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	*5*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5,6
		(*b*) Describe any methods used to examine subgroups and interactions	5,6
		(*c*) Explain how missing data were addressed	5,6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	5,6
		(*e*) Describe any sensitivity analyses	5,6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	6,7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7
		(*b*) Report category boundaries when continuous variables were categorized	6,7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6,7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8,9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Cardiovascular risk factors as predictors of coronary artery disease assessed using CAD-RADS classification: a cross-sectional study in Romanian population

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Cardiovascular risk factors as predictors of coronary artery disease assessed using CAD-RADS classification: a cross-sectional study in Romanian population

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Abstract

Objectives: This study aimed to evaluate the association between cardiovascular risk factors and CAD-RADS score in the Romanian population. CAD-RADS is a new, standardized method to assess coronary artery disease (CAD) using coronary computed tomography angiography (CCTA).

Design: A cross-sectional observational, patient-based study.

Setting: Referred imaging center for coronary artery disease in Transylvania, Romania.

Participants: We retrospectively reviewed 674 patients who underwent CCTA between January 2017 and August 2018. The exclusion criteria included: previously known CAD, defined as prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery (n=91), cardiac CT for other than evaluation of possible CAD (n=85), significant arrhythmias compromising imaging quality (n=23). Finally, 475 patients fulfilled the inclusion criteria.

Methods: Demographical, clinical and CCTA characteristics of the patients were obtained. Coronary artery disease was evaluated using CAD-RADS score. Obstructive CAD was defined as ≥50% stenosis of ≥1 coronary segment on CCTA.

Results: We evaluated the association between risk factors and CAD-RADS score in univariate and multivariable analysis. We divided the patients into 2 groups according to the CAD-RADS system: group 1: CAD-RADS score between 0-2 (stenosis <50%) and group 2: CAD-RADS score≥3 (stenosis ≥50%). On univariate analysis, male gender, age, hypertension, dyslipidemia, smoking and diabetes mellitus were positively associated with a CAD-RADS score ≥ 3. On the multivariable analysis, male sex, age, dyslipidemia, hypertension and smoking remained significant predictors of obstructive CAD.

Conclusion: This study demonstrated a significant association between multiple cardiovascular risk factors and a higher coronary atherosclerotic burden assessed using CAD-RADS system in the Romanian population.

Keywords: coronary artery disease; coronary CT angiography; CAD-RADS; cardiovascular risk factors

Article Summary

Strengths and limitations of this study

- This is the first study to evaluate the association of cardiovascular risk factors and coronary artery disease assessed using coronary CT angiography in Romania.
- We quantified the coronary artery stenosis using the CAD-RADS classification, the newest, standardized method for reporting CAD.
- The patients were recruited from a single center; therefore, the study population was relatively small.
- Another limitation is the design of the study: a cross-sectional, retrospective one.

Introduction

Coronary artery disease (CAD) is one of the major causes of morbidity and mortality worldwide. Even though CAD mortality rates have declined since 1980s, it still accounts for approximately one-third of all deaths of individuals aged over 35 years old (1,2).

It is well-known that atherosclerosis is the underlying cause of cardiovascular diseases and multiple risk factors augment the atherosclerotic process. These risk factors include non-modifiable ones such as age and sex and modifiable risk factors such as hypertension, dyslipidemia, obesity, diabetes mellitus and smoking (3-7). Studies suggest that the majority of patients with CAD have at least one modifiable risk factor and their presence has an impactful role in the progression of CAD (8, 9). Many risk-scoring systems have been developed such as Framingham and SCORE which are based on the presence of various traditional cardiovascular risk factors (10, 11). Assessment of comorbidities and lifestyle together with basic laboratory investigations are recommended as step 2 and step 3 in the approach of patients with angina and suspected CAD (12). After identifying the potential cardiovascular risk factors and establishing the pretest probability and clinical likelihood of coronary artery disease, the next step is to select the appropriate tests for the diagnosis of CAD (12).

With the recent advancements made in medical technology, coronary CT angiography (CCTA) has rapidly evolved into one of the most highly accurate methods for diagnosis and evaluation of CAD. It is an unique non-invasive test which can provide direct and accurate visualization of the coronary vessel lumen, being able to quantify the presence and extent of coronary stenosis and to assess the characteristics of coronary atherosclerotic plaques (13).

In the latest ESC guideline for the diagnosis and management of chronic coronary syndromes, CCTA has been categorized as class I recommendation for diagnosing CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone. Also, it can be considered as an alternative investigation to invasive angiography if another non-invasive test is equivocal or non-diagnostic (12).

In 2016, the Society of Cardiovascular Computed Tomography published the CAD-RADS grading system, which is a standardized reporting method of CCTA results. This is meant to

facilitate communication of the results along with suggestions for consecutive management of the patients. The grading system ranges from 0 to 5, where CAD-RADS 0 score means a complete absence of stenosis and CAD-RADS 5 represents total occlusion of at least 1 coronary segment (14).

Among European countries, Romania is one of the leading countries regarding the CVD mortality burden, having the second highest standardized death rate caused by ischemic heart disease (15). Also, the prevalence of cardiovascular risk factors is relatively high in our country. Romania is on the fourth place in Europe concerning raised blood pressure, on the 8th place regarding the presence of diabetes mellitus (16, 17) and an increasing trend in the incidence of obesity (18).

The aim of this study is to evaluate the association between traditional cardiovascular risk factors and coronary artery disease evaluated using the CAD-RADS score in the Romanian population.

Methods

Study population

We retrospectively reviewed 674 consecutive patients who underwent CCTA between January 2017 and August 2018 in our institution. The indications for CCTA were: atypical angina, typical angina with an inconclusive stress test, patients with intermediate/high-risk for major cardiac events. The exclusion criteria included: previously known CAD, defined as prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery (n=91), cardiac CT for other than evaluation of possible CAD (n=85), significant arrhythmias compromising imaging quality (n=23). Besides these exclusion criteria, patients with renal failure, documented contrast allergy or pregnant women did not perform the CT examination. Finally, 475 patients fulfilled the inclusion criteria.

Scan protocol

All CCTA scans were performed with a 64-sliced multi-detector CT (Sensation 64, Siemens, Forchheim, Germany). The scanning parameters were: slices/collimation 64/0.6 mm, tube voltage 120 kv, 850 mAs, gantry rotation time 330 ms, pitch 0.2, effective slice thickness 0.75 mm and reconstruction increment 0.4 mm. Patients with a heart-rate > 70 bpm received premedication with oral beta-blockers 1 hour prior to the examination. Short-acting nitroglycerine sublingual spray was administered to all patients for coronary vasodilatation.

First, a non-contrast enhanced scan was performed in order to assess the coronary artery calcium score (CACS), followed by the coronary computed tomography angiography (CCTA) to evaluate the coronary artery lumen and to characterize the atherosclerotic plaques. A bolus of 80 ml of iodinated contrast medium was administered intravenously at 5 ml/sec, followed by 40 ml of saline injected at the same rate. After the acquisition, the images were transferred to a dedicated

workstation for post-processing, which included multiplanar reconstructions (MPR), maximum intensity projections (MIP) and volume rendering images (VRT).

Coronary artery analysis

All CCTA images were assessed by an experienced radiologist who was blinded to the study (LE.P.). CACS was calculated using a semi-automatically software, according to the Agatston method. Plaque composition was classified as: calcified, non-calcified or mixed, with calcified coronary plaque being defined as any structure with a density ≥130 HU.

Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. We evaluated only the coronary segments with a diameter greater than 1.5 mm.

Every patient received a final CAD-RADS score based on the extent of coronary stenosis (Figure 1). CAD-RADS score of 0 was assigned if there was a total absence of coronary plaques or stenosis. Minimal coronary stenosis between 1-24% was considered CAD-RADS 1. CAD-RADS score 2 was given when there was a mild stenosis between 25-49%. CAD-RADS score of 3 corresponded to a moderate stenosis between 50-69%. CAD-RADS score of 4 was assigned if there was a single coronary stenosis between 70-99% or if the left main artery was depicted with a stenosis of more than 50%. Also, CAD-RADS score of 4 was given in the situation of 3-vessel obstructive disease, when there were stenosis of more than 70% involving all the three coronary arteries (left anterior descending artery, circumflex artery and right coronary artery). If total occlusion was identified in at least one coronary segment, a CAD-RADS score of 5 was assigned.

Obstructive CAD was defined as ≥ 50% stenosis of ≥1 coronary segments on CCTA.

Cardiovascular risk factors

Prior to CCTA, a detailed medical history with the risk factors was obtained from all patients. Hypertension was defined as blood pressure ≥ 140/90 mm Hg or treatment with antihypertensive medications (19). Dyslipidemia was defined as a total cholesterol level ≥ 5 mmol/L (20) or treatment with lipid-lowering medications. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dl or the use of insulin or oral antidiabetic agents. Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2. Self-reported smoking status was obtained by a query regarding both current and previous smoking history. Classification of symptoms (typical angina, atypical angina, non-anginal pain) was judged by cardiologists using patient interviews conducted prior to the CT examination.

Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables with normal distribution were expressed as means ± standard deviation, those with non-normal distribution as median with interquartile range. Normality was tested with the Kolmogorov-Smirnov test.

Differences between CAD-RADS groups were evaluated using one-way analysis of variance (ANOVA) for continuous variables and $\chi 2$ test for categorical variables. Whenever the distribution of continuous data was not normal, non-parametric Kruskal-Wallis test was used for comparison.

Cardiovascular risk factors that showed a significant association with the CAD-RADS score were included in multivariable logistic regression analysis in order to evaluate their simultaneous influence. Through logistic regression analysis, independent predictors for obstructive CAD (CAD-RADS score ≥ 3) were identified.

For all comparisons, a p value of <0.05 was considered statistically significant. The statistical analysis was performed using commercially available software (MedCalc for Windows, version 14.8, MedCalc Software, Ostend, Belgium).

Patient and Public Involvement

There was no involvement of patients and/or public in this study.

Results

Baseline characteristics of the study population

The clinical and angiographic characteristics of our study population according to the CAD-RADS classification are shown in Supplementary Table 1. Among the 475 patients included in this study, the mean age was 57.8±13.2 years and the majority of them were females: 54.4%. There was a high prevalence of both hypertensive (74.5%) and dyslipidemic (69.7%) patients. The percentage of diabetic patients was relatively small, with only 19.3% individuals having this condition. Smoking was reported among 46.3% of the study group. The majority of the patients were symptomatic, 72.6 % presenting with either typical or atypical angina.

When we classified the patients according to the CAD-RADS score, 177 of them had CAD-RADS score=0, 99 patients had CAD-RADS score=1 while 80 patients CAD-RADS score=2. A percentage of 14.1% of people included in this study were diagnosed with CAD-RADS 3 score. Finally, 9.3% patients had severe stenosis, with a CAD-RADS score of 4 and 8 patients had total occlusion of a coronary segment (CAD-RADS score=5).

Patient gender, age, the presence of hypertension, dyslipidemia, diabetes mellitus as well as clinical presentation and coronary artery calcium score were significantly different across CAD-RADS scores ($p < 0.0001$ for all comparisons) (Supplementary Table 1). However, our results did not reveal any association between obesity and different CAD-RADS scores (p=0.63) (Supplementary Table 1).

CAD-RADS score and multiple cardiovascular risk factors

Using the cardiovascular risk factors mentioned above, we tested if there is any association regarding their presence and obstructive coronary artery disease, defined as coronary stenosis ≥50% and equivalent with a CAD-RADS score ≥ 3 (Table 1).

Our results show that a CAD-RADS score between 0-2 was more frequent in younger patients, with a mean age of 55.41 ± 13.11 years in this subgroup, while patients with CAD-RADS score ≥ 3 had a higher mean age of 63.1 ± 10.55 years (Table 1). Regarding gender, patients with CAD-RADS scores higher than 3 were more frequently males. The majority of the female patients (82.9%) received a CAD-RADS score of 0, 1 or 2 (Table 1).

Our findings indicated a positive association between systolic hypertension and CAD-RADS score, with over 90% of the patients with moderate/severe stenosis (CAD-RADS ≥ 3) being hypertensive (Table 1). Moreover, based on our results, patients with CAD-RADS scores ≥ 3 had a greater frequency of dyslipidemia, with more than 85% patients in these categories being also dyslipidemic (Table 1).

Furthermore, the proportion of smokers was larger among patients identified with higher CAD-RADS scores: almost two-third of the patients who received a CAD-RADS score ≥ 3 admitted the use of cigarettes (Table 1). On the other hand, in the CAD-RADS groups of 0, 1 and 2 the percentage of the smokers was less than 50% (Table 1).

Regarding the association between diabetes mellitus and CAD-RADS score, our results show increasing percents of diabetic individuals proportional with higher CAD-RADS scores: from 16.3% diabetic patients with CAD-RADS scores of 0-2 to 28.6% diabetic patients with CAD-RADS scores ≥ 3 (Table 1). However, the percentage of obese patients did not differ significantly among different CAD-RADS groups (Table 1).

Multivariable analysis

According to the multivariable analysis, male sex, age, hypertension, dyslipidemia and smoking remained major predictors of obstructive CAD defined as CAD-RADS score ≥ 3 (Table 2). Males had more than 3 times higher odds of developing significant coronary stenosis. The odds ratio for coronary stenosis ≥ 50% was approximately 3.5-fold greater in hypertensive individuals. Our results showed that having dyslipidemia significantly increased the odds of moderate/severe coronary stenosis by more than 2.5 times. Last but not least, smoking was associated with increased odds of having CAD-RADS score ≥ 3 by approximately 2 times.

Discussion

Romania is one of the high cardiovascular risk European countries according to data from the last European Society of Cardiology guideline for prevention of CVD (3). There are only a limited number of national epidemiological studies which estimate the prevalence and future trends of cardiovascular risk factors in the Romanian population. (21-25). The latest study from 2017, Sephar III, shows an increasing trend regarding the majority of cardiovascular risk factors in our

population (23). The prevalence of hypertension increased from 40.4% in 2011 to 45.1% in 2016 (22, 23). Moreover, the percentage of Romanians diagnosed with dyslipidemia is alarmingly high, reaching 77.3% in 2016, with 53.4% newly diagnosed cases (23). Furthermore, the prevalence of diabetes mellitus, another important risk factor for coronary artery disease, is 12.4% (24), a relatively high percentage that puts Romania on the 8th place in Europe regarding this medical condition (16). Overweight and obesity represent another medical issue encountered in our country. Both PREDATORR and Sephar III studies (23, 25) reported a prevalence of over 30% of obese patients based on BMI index, similar to the data from WHO database which shows an increasing trend of obesity in our country over the last 40 years (18). Last but not least, smoking can be considered another cause for the high incidence of cardiovascular disease in our country. Even if there is a decreasing trend regarding this habit in our country, Romania still occupies one of the leading places in European Union, with 28% of individuals reporting the use of cigarettes, a number higher than the average European percentage: 26% (26). According to the data by the National Institute for Public Health in Romania, tobacco is attributed to 16.3% CVD-Related deaths in Romania. (27).

In Europe, Romania records one of the greatest incidences of cardiovascular diseases, according to the latest statistics offered by EuroStat in 2018 (15). Our country occupies the second place in Europe regarding the percent of total deaths caused by diseases of the circulatory system (15). Concerning the standardized death rates caused by ischemic heart disease, Romania is also one of the leading countries, being on the 6th and 5th place in deaths of men and women respectively (15).

CAD-RADS is a standardized radiological reporting system dating since 2016 and there are only a few studies published in the area of cardiac imaging using the CAD-RADS score (28-32). It is used to quantify coronary artery stenosis in patients with suspected or known coronary artery disease in order to provide a basis for further investigation, diagnosis, management and treatment, substantially reducing human error and improving data integrity (14).

To the best of our knowledge, our study is the first one to evaluate the association between multiple associations of cardiovascular risk factors and the severity of coronary artery disease assessed on CCTA and evaluated using CAD-RADS classification in the Romanian population.

The association between cardiovascular risk factors and cardiovascular events was first demonstrated by the Framingham study through an epidemiological approach (33). The INTERHEART study showed that the cumulative effect of risk factors increased the risk of CAD, especially of myocardial infarction worldwide, in both sexes and all ages worldwide (34).

Our research reports that male sex, age, dyslipidemia, hypertension and smoking are the significant predictors of obstructive CAD defined as CAD-RADS score ≥ 3, with the prevalence being increased by a cumulative effect on them.

Male sex and age are well-known risk factors for coronary atherosclerosis, being used in prediction models for the estimation of pretest probability of developing coronary artery disease (12, 35). Among medical risk factors, our study showed that hypertension and dyslipidemia were positively associated with CAD-RADS score ≥ 3 in both univariate and multivariable analyses. Our results are in concordance with the latest data from European Heart Network which shows

that systolic blood pressure and total cholesterol levels are the determinants with the greatest contribution to CVD mortality (17). Also, these two factors are included in the widely used SCORE charts (3) and there are many clinical models that add them for increasing the probability of obstructive CAD (36-39).

Our multivariable analysis did not found an association between diabetes mellitus and obstructive CAD, one possible explanation being that only 19.3% of our study group had diabetes as their comorbidity.

Also, we did not find a direct association between obesity and coronary artery burden defined by CAD-RADS score. Our study is in concordance with Medakovic et al (40) and Dores H et al (41). According to Dores H et al, obesity assessed by BMI can be an indicator of the presence of CAD, but not necessarily associated with its severity (41). They also described an "obesity paradox" with better outcomes after percutaneous coronary interventions at patients with a higher BMI (41). One hypothesis for this paradox is that obese patients tend to be diagnosed at an earlier age and stage of CAD, therefore having lower morbidity and mortality rates (42, 43). Another potential reason for better outcomes of obese patients compared to those of underweight ones is that the latter group is more likely to have post procedural complications due to excessive anticoagulation which is usually not weight adjusted (44, 45). Moreover, underweight patients usually have more concomitant comorbidities which lead to worse prognosis (46). Another theory is that obesity is associated with higher amounts of lean mass and which can have a protective effect when not associated with increased systemic inflammation (47).

Finally, our findings show that smoking is an independent risk factor for the presence of obstructive coronary disease, this being also one of the behavioral factors with the highest contribution for CVD mortality and morbidity rates across Europe (17).

Limitations of the study

Our study has several limitations, the most important one being the fact that it is a retrospectively conducted one. Secondary**,** our results were confined to the experience of a single medical center and the findings of this study were based on a relatively small patient population. Regarding the risk factors, dyslipidemia was not analyzed by fractions of the cholesterol: LDL-C and HDL-C. Also, we did not analyze other additional risk factors like alcohol use, physical activity, anthropometric measurements or C-reactive protein levels. Taking the retrospective approach into consideration, our research assess only the association between tradionally known cardiovascular risk factors and coronary stenosis evaluated by CAD-RADS score and does not assess the incidence of major cardiac events after performing the CT angiography.

Conclusion

In conclusion, our study demonstrates that there is a significant association between multiple cardiovascular risk factors and a higher coronary atherosclerotic burden assessed using CAD-RADS score in the Romanian population. Considering CAD as a priority for Romanian healthcare system, our study provides an overview of imaging and clinical characteristics of CAD and their association, offering valuable information for both cardiologists and radiologists in order to improve the management of the patients.

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- Literature Review: Bianca Petresc, Calin Schiau, Cristina Catana, Claudia G. Moldovanu
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Patient consent for publication: Not required.

Data sharing statement: Deidentified participant data are available upon request through the corresponding author BP. ORCID identifier 0000-0003-2167-9350.

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FIGURE LEGENDS

Fig. 1- MPR (multiplanar reconstruction) images showing different degrees of coronary artery stenosis (yellow arrows): a. normal RCA without any plaque or stenosis (CAD-RADS 0), b. small calcified plaque in the proximal LAD with minimal luminal narrowing < 25% (CAD-RADS 1), c. calcified plaque in the proximal LAD with 25-49% diameter stenosis (CAD-RADS 2), d. semi-circumferential calcified plaque in the proximal LAD with 50-69% diameter stenosis (CAD-RADS 3),e. non-calcified plaque in the proximal RCA with 70-99% diameter stenosis (CAD-RADS 4), f. total occlusion of proximal and mid LAD; calcified plaques above and beyond it supports the diagnosis of chronic total occlusion (CAD-RADS 5)

Table 1. Univariate analysis for the association between cardiovascular risk factors and obstructive CAD classified using CAD-RADS categories

Variable	Value	CAD-RADS score 0-2 (stenosis<50%)	CAD-RADS score 3-5 (stenosis≥50%)	p value
Age		55.41 ± 13.11	63.10 ± 10.55	**p<0.001**
Sex				**p<0.001**
	Male	142 (39.2%)	75 (63.0%)	
	Female	214 (60.1%)	44 (37.0%)	
Hypertension				**p<0.001**
	Yes	242 (68.0%)	112 (94.1%)	
	No	114 (32.0%)	7 (5.9%)	
Dyslipidemia				**p<0.001**
	Yes	224 (62.9%)	107 (89.9%)	
	No	132 (37.01%)	12 (10.1%)	
Diabetes mellitus				**p=0.003**
	Yes	58 (16.3%)	34(28.6%)	
	No	298 (83.7%)	85 (71.4%)	
Obesity				**p=0.93**
	Yes	151 (42.4%)	50 (42.0%)	
	No	205 (57.6%)	69 (58.0%)	
Smoking				**p<0.001**
	Yes	145 (40.7%)	75 (63.0%)	
	No	211 (59.3%)	44 (37.0%)	
CACS		0.4 [0 - 39.5]	433.0 [182.4 - 924.8]	**p<0.001**

Results are presented as mean±SD, number (%) or median [25th-75th percentile]
Abbreviations: CACS: coronary artery calcium score

Table 2. Logistic regression analysis for the association between cardiovascular risk factors and obstructive CAD (CAD-RADS score ≥3)

Variable	Odds ratio (95% CI)	p value
Male sex	3.136 (1.841 – 5.341)	<0.001
Age	1.063 (1.036 – 1.090)	<0.001
Hypertension	3.493 (1.444 – 6.251)	0.006
Dyslipidemia	2.648 (1.283 – 5.466)	0.008
Diabetes mellitus	1.207 (0.698 – 2.088)	0.501
Smoking	2.112 (1.236 – 5.466)	0.006

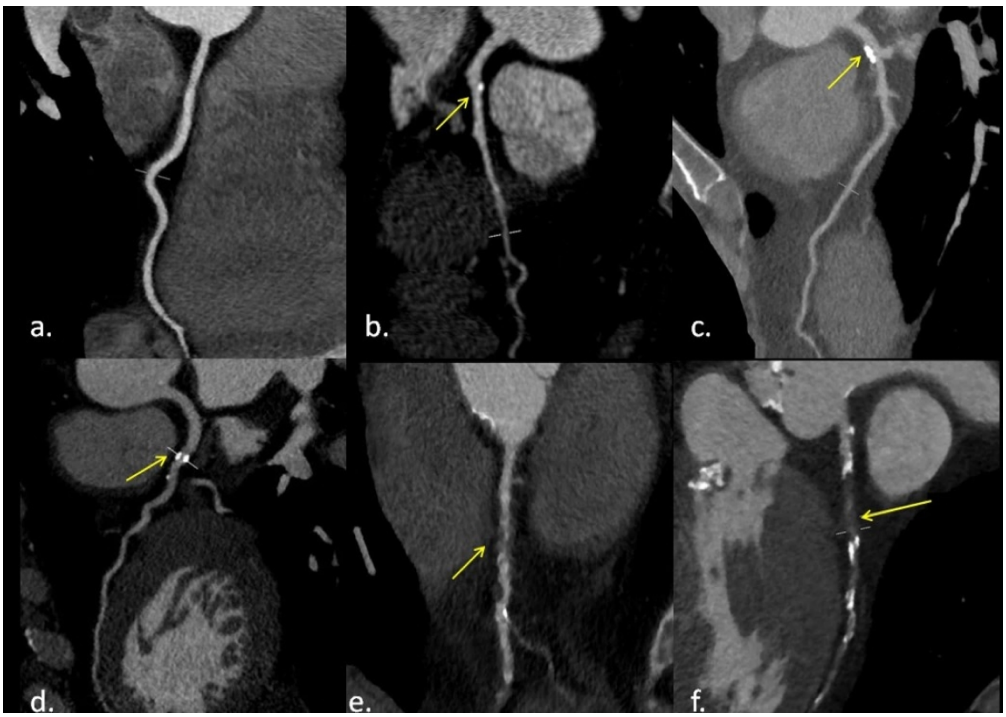

Fig. 1- MPR (multiplanar reconstruction) images showing different degrees of coronary artery stenosis (yellow arrows): a. normal RCA without any plaque or stenosis (CAD-RADS 0), b. small calcified plaque in the proximal LAD with minimal luminal narrowing < 25% (CAD-RADS 1), c. calcified plaque in the proximal LAD with 25-49% diameter stenosis (CAD-RADS 2), d. semi-circumferential calcified plaque in the proximal LAD with 50-69% diameter stenosis (CAD-RADS 3),e. non-calcified plaque in the proximal RCA with 70-99% diameter stenosis (CAD-RADS 4), f. total occlusion of proximal and mid LAD; calcified plaques above and beyond it supports the diagnosis of chronic total occlusion (CAD-RADS 5)

173x122mm (600 x 600 DPI)

Supplementary Table 1. Baseline characteristics of the study population according to CAD-RADS categories

Variable	Value	CAD-RADS 0 (n=177)	CAD-RADS 1 (n=99)	CAD-RADS 2 (n=80)	CAD-RADS 3 (n=67)	CAD-RADS 4 (n=67)	CAD-RADS 5 (n=8)	p value
Age		48.8 ± 12.1	60.4 ± 11.9	63.6 ± 8.7	64.6 ± 10.5	66.1 ± 10.6	64.7 ± 11.1	**p<0.001**
Sex								**p<0.001**
	Male (n=217)	55 (31.1%)	42 (42.4%)	45 (56.2%)	39 (58.2%)	28 (63.6%)	8 (100%)	
	Female(n=258)	122 (68.9%)	57 (57.6%)	35 (43.8%)	28 (41.8 %)	16 (36.4%)	0 (0 %)	
Hypertension								**p<0.001**
	Yes(n=354)	110 (62.2%)	70 (70.7%)	62 (77.5%)	63 (94.0%)	42 (95.4%)	7 (87.5%)	
	No (n=121)	67(37.8%)	29 (29.3%)	18 (22.5%)	4 (6.0%)	2 (4.6%)	1 (12.5%)	
Dyslipidemia								**p<0.001**
	Yes (n=331)	91 (51.4%)	72 (72.7%)	61 (76.3%)	59 (88.1%)	41 (93.2%)	7 (87.5%)	
	No (n=144)	86 (48.6%)	27 (27.3%)	19 (23.8%)	8 (11.9%)	3(6.8%)	1 (12.5%)	
Diabetes mellitus								**p<0.001**
	Yes (n=92)	16 (9.0%)	21(21.2%)	21(26.2%)	12 (17.9%)	18 (40.9%)	4 (50.0%)	
	No (n=383)	161 (91.0%)	78 (78.8%)	59 (73.8%)	55 (82.1%)	26 (59.1%)	4 (50.0%)	
Obesity								**p=0.63**
	Yes (n=274)	68 (38.4%)	45 (45.4%)	38 (47.5%)	29 (43.2%)	19 (43.1%)	2 (25.0%)	
	No (n=201)	109 (61.6%)	54 (54.6%)	42 (52.5%)	38 (56.8%)	25 (56.9%)	6 (75.0%)	
Smoking								**p<0.001**
	Yes (n=220)	53 (30.0%)	44 (44.4%)	48 (60.0%)	44 (65.6%)	25 (56.9%)	6 (75.0%)	
	No (n=255)	124 (70.0%)	55 (55.6%)	32 (40.0%)	23 (34.4%)	19 (43.1%)	2 (25.0%)	
Clinical presentation								**p<0.001**
	Typical angina (n=222)	60 (33.9%)	35 (35.3%)	36 (45.0%)	45 (67.1%)	39 (88.6%)	7 (87.5%)	
	Atypica angina (n=123)	70 (39.5%)	25 (25.2%)	20 (25.0%)	7 (10.4%)	1 (2.2%)	0 (0 %)	
	Nonanginal chest pain (n=130)	47 (26.6%)	39 (39.5%)	24 (30.0%)	15 (22.5%)	4 (9.2%)	1 (12.5%)	
CACS		0 [0-0]	15 [6.2-36.6]	123 [55.1-284.5]	303 [134.8-500.7]	711.3 [444.7-958.3]	1611.4 [949.1-1921.4]	**p<0.001**

Results are presented as mean±SD, number (%), or median (25th-75th percentile)
Abbreviations: CACS: coronary artery calcium score

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	*5*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5,6
		(*b*) Describe any methods used to examine subgroups and interactions	5,6
		(*c*) Explain how missing data were addressed	5,6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	5,6
		(*e*) Describe any sensitivity analyses	5,6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	6,7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7
		(*b*) Report category boundaries when continuous variables were categorized	6,7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6,7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8,9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between cardiovascular risk factors and coronary artery disease assessed using CAD-RADS classification: a cross-sectional study in Romanian population

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Association between cardiovascular risk factors and coronary artery disease assessed using CAD-RADS classification: a cross-sectional study in Romanian population

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Abstract

Objectives: This study aimed to evaluate the association between cardiovascular risk factors and CAD-RADS score in the Romanian population. CAD-RADS is a new, standardized method to assess coronary artery disease (CAD) using coronary computed tomography angiography (CCTA).

Design: A cross-sectional observational, patient-based study.

Setting: Referred imaging center for coronary artery disease in Transylvania, Romania.

Participants: We retrospectively reviewed 674 patients who underwent CCTA between January 2017 and August 2018. The exclusion criteria included: previously known CAD, defined as prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery (n=91), cardiac CT for other than evaluation of possible CAD (n=85), significant arrhythmias compromising imaging quality (n=23). Finally, 475 patients fulfilled the inclusion criteria.

Methods: Demographical, clinical and CCTA characteristics of the patients were obtained. Coronary artery disease was evaluated using CAD-RADS score. Obstructive CAD was defined as ≥50% stenosis of ≥1 coronary segment on CCTA.

Results: We evaluated the association between risk factors and CAD-RADS score in univariate and multivariable analysis. We divided the patients into 2 groups according to the CAD-RADS system: group 1: CAD-RADS score between 0-2 (stenosis <50%) and group 2: CAD-RADS score≥3 (stenosis ≥50%). On univariate analysis, male gender, age, hypertension, dyslipidemia, smoking and diabetes mellitus were positively associated with a CAD-RADS score ≥ 3. The multivariate analysis showed that male sex, age, dyslipidemia, hypertension and smoking were independently associated with obstructive CAD.

Conclusion: This study demonstrated a significant association between multiple cardiovascular risk factors and a higher coronary atherosclerotic burden assessed using CAD-RADS system in the Romanian population.

Keywords: coronary artery disease; coronary CT angiography; CAD-RADS; cardiovascular risk factors

Article Summary

Strengths and limitations of this study

- This is the first study to evaluate the association of cardiovascular risk factors and coronary artery disease assessed using coronary CT angiography in Romania.
- We quantified the coronary artery stenosis using the CAD-RADS classification, the newest, standardized method for reporting CAD.
- The patients were recruited from a single center; therefore, the study population was relatively small.
- Another limitation is the design of the study: a cross-sectional, retrospective one.

Introduction

Coronary artery disease (CAD) is one of the major causes of morbidity and mortality worldwide. Even though CAD mortality rates have declined since 1980s, it still accounts for approximately one-third of all deaths of individuals aged over 35 years old (1,2).

It is well-known that atherosclerosis is the underlying cause of cardiovascular diseases and multiple risk factors augment the atherosclerotic process. These risk factors include non-modifiable ones such as age and sex and modifiable risk factors such as hypertension, dyslipidemia, obesity, diabetes mellitus and smoking (3-7). Studies suggest that the majority of patients with CAD have at least one modifiable risk factor and their presence has an impactful role in the progression of CAD (8, 9). Many risk-scoring systems have been developed such as Framingham and SCORE which are based on the presence of various traditional cardiovascular risk factors (10, 11). Assessment of comorbidities and lifestyle together with basic laboratory investigations are recommended as step 2 and step 3 in the approach of patients with angina and suspected CAD (12). After identifying the potential cardiovascular risk factors and establishing the pretest probability and clinical likelihood of coronary artery disease, the next step is to select the appropriate tests for the diagnosis of CAD (12).

With the recent advancements made in medical technology, coronary CT angiography (CCTA) has rapidly evolved into one of the most highly accurate methods for diagnosis and evaluation of CAD. It is an unique non-invasive test which can provide direct and accurate visualization of the coronary vessel lumen, being able to quantify the presence and extent of coronary stenosis and to assess the characteristics of coronary atherosclerotic plaques (13).

In the latest ESC guideline for the diagnosis and management of chronic coronary syndromes, CCTA has been categorized as class I recommendation for diagnosing CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone. Also, it can be considered as an alternative investigation to invasive angiography if another non-invasive test is equivocal or non-diagnostic (12).

In 2016, the Society of Cardiovascular Computed Tomography published the CAD-RADS grading system, which is a standardized reporting method of CCTA results. This is meant to

facilitate communication of the results along with suggestions for consecutive management of the patients. The grading system ranges from 0 to 5, where CAD-RADS 0 score means a complete absence of stenosis and CAD-RADS 5 represents total occlusion of at least 1 coronary segment (14).

Among European countries, Romania is one of the leading countries regarding the CVD mortality burden, having the second highest standardized death rate caused by ischemic heart disease (15). Also, the prevalence of cardiovascular risk factors is relatively high in our country. Romania is on the fourth place in Europe concerning raised blood pressure, on the 8th place regarding the presence of diabetes mellitus (16, 17) and an increasing trend in the incidence of obesity (18).

The aim of this study is to evaluate the association between traditional cardiovascular risk factors and coronary artery disease evaluated using the CAD-RADS score in the Romanian population.

Methods

Study population

We retrospectively reviewed 674 consecutive patients who underwent CCTA between January 2017 and August 2018 in our institution. The indications for CCTA were: atypical angina, typical angina with an inconclusive stress test, patients with intermediate/high-risk for major cardiac events. The exclusion criteria included: previously known CAD, defined as prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery (n=91), cardiac CT for other than evaluation of possible CAD (n=85), significant arrhythmias compromising imaging quality (n=23). Besides these exclusion criteria, patients with renal failure, documented contrast allergy or pregnant women did not perform the CT examination. Finally, 475 patients fulfilled the inclusion criteria.

Scan protocol

All CCTA scans were performed with a 64-sliced multi-detector CT (Sensation 64, Siemens, Forchheim, Germany). The scanning parameters were: slices/collimation 64/0.6 mm, tube voltage 120 kv, 850 mAs, gantry rotation time 330 ms, pitch 0.2, effective slice thickness 0.75 mm and reconstruction increment 0.4 mm. Patients with a heart-rate > 70 bpm received premedication with oral beta-blockers 1 hour prior to the examination. Short-acting nitroglycerine sublingual spray was administered to all patients for coronary vasodilatation.

First, a non-contrast enhanced scan was performed in order to assess the coronary artery calcium score (CACS), followed by the coronary computed tomography angiography (CCTA) to evaluate the coronary artery lumen and to characterize the atherosclerotic plaques. A bolus of 80 ml of iodinated contrast medium was administered intravenously at 5 ml/sec, followed by 40 ml of saline injected at the same rate. After the acquisition, the images were transferred to a dedicated

workstation for post-processing, which included multiplanar reconstructions (MPR), maximum intensity projections (MIP) and volume rendering images (VRT).

Coronary artery analysis

All CCTA images were assessed by an experienced radiologist who was blinded to the study (LE.P.). CACS was calculated using a semi-automatically software, according to the Agatston method. Plaque composition was classified as: calcified, non-calcified or mixed, with calcified coronary plaque being defined as any structure with a density ≥130 HU.

Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. We evaluated only the coronary segments with a diameter greater than 1.5 mm.

Every patient received a final CAD-RADS score based on the extent of coronary stenosis (Figure 1). CAD-RADS score of 0 was assigned if there was a total absence of coronary plaques or stenosis. Minimal coronary stenosis between 1-24% was considered CAD-RADS 1. CAD-RADS score 2 was given when there was a mild stenosis between 25-49%. CAD-RADS score of 3 corresponded to a moderate stenosis between 50-69%. CAD-RADS score of 4 was assigned if there was a single coronary stenosis between 70-99% or if the left main artery was depicted with a stenosis of more than 50%. Also, CAD-RADS score of 4 was given in the situation of 3-vessel obstructive disease, when there were stenosis of more than 70% involving all the three coronary arteries (left anterior descending artery, circumflex artery and right coronary artery). If total occlusion was identified in at least one coronary segment, a CAD-RADS score of 5 was assigned.

Obstructive CAD was defined as ≥ 50% stenosis of ≥1 coronary segments on CCTA.

Cardiovascular risk factors

Prior to CCTA, a detailed medical history with the risk factors was obtained from all patients. Hypertension was defined as blood pressure ≥ 140/90 mm Hg or treatment with antihypertensive medications (19). Dyslipidemia was defined as a total cholesterol level ≥ 5 mmol/L (20) or treatment with lipid-lowering medications. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dl or the use of insulin or oral antidiabetic agents. Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2. Self-reported smoking status was obtained by a query regarding both current and previous smoking history. Classification of symptoms (typical angina, atypical angina, non-anginal pain) was judged by cardiologists using patient interviews conducted prior to the CT examination.

Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables with normal distribution were expressed as means ± standard deviation, those with non-normal distribution as median with interquartile range. Normality was tested with the Kolmogorov-Smirnov test.

Differences between CAD-RADS groups were evaluated using one-way analysis of variance (ANOVA) for continuous variables and $\chi 2$ test for categorical variables. Whenever the distribution of continuous data was not normal, non-parametric Kruskal-Wallis test was used for comparison.

Cardiovascular risk factors that showed a significant association with the CAD-RADS score were included in multivariable logistic regression analysis in order to evaluate their simultaneous influence. Through logistic regression analysis, independent relationship between cardiovascular risk factors and obstructive CAD (CAD-RADS score ≥ 3) was identified.

For all comparisons, a p value of <0.05 was considered statistically significant. The statistical analysis was performed using commercially available software (MedCalc for Windows, version 14.8, MedCalc Software, Ostend, Belgium).

Patient and Public Involvement

There was no involvement of patients and/or public in this study.

Results

Baseline characteristics of the study population

The clinical and angiographic characteristics of our study population according to the CAD-RADS classification are shown in Supplementary Table 1. Among the 475 patients included in this study, the mean age was 57.8±13.2 years and the majority of them were females: 54.4%. There was a high prevalence of both hypertensive (74.5%) and dyslipidemic (69.7%) patients. The percentage of diabetic patients was relatively small, with only 19.3% individuals having this condition. Smoking was reported among 46.3% of the study group. The majority of the patients were symptomatic, 72.6 % presenting with either typical or atypical angina.

When we classified the patients according to the CAD-RADS score, 177 of them had CAD-RADS score=0, 99 patients had CAD-RADS score=1 while 80 patients CAD-RADS score=2. A percentage of 14.1% of people included in this study were diagnosed with CAD-RADS 3 score. Finally, 9.3% patients had severe stenosis, with a CAD-RADS score of 4 and 8 patients had total occlusion of a coronary segment (CAD-RADS score=5).

Patient gender, age, the presence of hypertension, dyslipidemia, diabetes mellitus as well as clinical presentation and coronary artery calcium score were significantly different across CAD-RADS scores ($p < 0.0001$ for all comparisons) (Supplementary Table 1). However, our results did not reveal any association between obesity and different CAD-RADS scores (p=0.63) (Supplementary Table 1).

CAD-RADS score and multiple cardiovascular risk factors

Using the cardiovascular risk factors mentioned above, we tested if there is any association regarding their presence and obstructive coronary artery disease, defined as coronary stenosis ≥50% and equivalent with a CAD-RADS score ≥ 3 (Table 1).

Our results show that a CAD-RADS score between 0-2 was more frequent in younger patients, with a mean age of 55.41 ± 13.11 years in this subgroup, while patients with CAD-RADS score ≥ 3 had a higher mean age of 63.1 ± 10.55 years (Table 1). Regarding gender, patients with CAD-RADS scores higher than 3 were more frequently males. The majority of the female patients (82.9%) received a CAD-RADS score of 0, 1 or 2 (Table 1).

Our findings indicated a positive association between systolic hypertension and CAD-RADS score, with over 90% of the patients with moderate/severe stenosis (CAD-RADS ≥ 3) being hypertensive (Table 1). Moreover, based on our results, patients with CAD-RADS scores ≥ 3 had a greater frequency of dyslipidemia, with more than 85% patients in these categories being also dyslipidemic (Table 1).

Furthermore, the proportion of smokers was larger among patients identified with higher CAD-RADS scores: almost two-third of the patients who received a CAD-RADS score ≥ 3 admitted the use of cigarettes (Table 1). On the other hand, in the CAD-RADS groups of 0, 1 and 2 the percentage of the smokers was less than 50% (Table 1).

Regarding the association between diabetes mellitus and CAD-RADS score, our results show increasing percents of diabetic individuals proportional with higher CAD-RADS scores: from 16.3% diabetic patients with CAD-RADS scores of 0-2 to 28.6% diabetic patients with CAD-RADS scores ≥ 3 (Table 1). However, the percentage of obese patients did not differ significantly among different CAD-RADS groups (Table 1).

Multivariable analysis

According to the multivariable analysis, male sex, age, hypertension, dyslipidemia and smoking remained independently associated with obstructive CAD defined as CAD-RADS score ≥ 3 (Table 2). Males had more than 3 times higher odds of developing significant coronary stenosis. The odds ratio for coronary stenosis ≥ 50% was approximately 3.5-fold greater in hypertensive individuals. Our results showed that having dyslipidemia significantly increased the odds of moderate/severe coronary stenosis by more than 2.5 times. Last but not least, smoking was associated with increased odds of having CAD-RADS score ≥ 3 by approximately 2 times.

Discussion

Romania is one of the high cardiovascular risk European countries according to data from the last European Society of Cardiology guideline for prevention of CVD (3). There are only a limited number of national epidemiological studies which estimate the prevalence and future trends of

cardiovascular risk factors in the Romanian population. (21-25). The latest study from 2017, Sephar III, shows an increasing trend regarding the majority of cardiovascular risk factors in our population (23). The prevalence of hypertension increased from 40.4% in 2011 to 45.1% in 2016 (22, 23). Moreover, the percentage of Romanians diagnosed with dyslipidemia is alarmingly high, reaching 77.3% in 2016, with 53.4% newly diagnosed cases (23). Furthermore, the prevalence of diabetes mellitus, another important risk factor for coronary artery disease, is 12.4% (24), a relatively high percentage that puts Romania on the 8th place in Europe regarding this medical condition (16). Overweight and obesity represent another medical issue encountered in our country. Both PREDATORR and Sephar III studies (23, 25) reported a prevalence of over 30% of obese patients based on BMI index, similar to the data from WHO database which shows an increasing trend of obesity in our country over the last 40 years (18). Last but not least, smoking can be considered another cause for the high incidence of cardiovascular disease in our country. Even if there is a decreasing trend regarding this habit in our country, Romania still occupies one of the leading places in European Union, with 28% of individuals reporting the use of cigarettes, a number higher than the average European percentage: 26% (26). According to the data by the National Institute for Public Health in Romania, tobacco is attributed to 16.3% CVD-Related deaths in Romania. (27).

In Europe, Romania records one of the greatest incidences of cardiovascular diseases, according to the latest statistics offered by EuroStat in 2018 (15). Our country occupies the second place in Europe regarding the percent of total deaths caused by diseases of the circulatory system (15). Concerning the standardized death rates caused by ischemic heart disease, Romania is also one of the leading countries, being on the 6th and 5th place in deaths of men and women respectively (15).

CAD-RADS is a standardized radiological reporting system dating since 2016 and there are only a few studies published in the area of cardiac imaging using the CAD-RADS score (28-32). It is used to quantify coronary artery stenosis in patients with suspected or known coronary artery disease in order to provide a basis for further investigation, diagnosis, management and treatment, substantially reducing human error and improving data integrity (14).

To the best of our knowledge, our study is the first one to evaluate the association between multiple associations of cardiovascular risk factors and the severity of coronary artery disease assessed on CCTA and evaluated using CAD-RADS classification in the Romanian population.

The association between cardiovascular risk factors and cardiovascular events was first demonstrated by the Framingham study through an epidemiological approach (33). The INTERHEART study showed that the cumulative effect of risk factors increased the risk of CAD, especially of myocardial infarction worldwide, in both sexes and all ages worldwide (34).

Our research reports that male sex, age, dyslipidemia, hypertension and smoking are significantly associated with obstructive CAD defined as CAD-RADS score ≥ 3, with the prevalence being increased by a cumulative effect on them.

Male sex and age are well-known risk factors for coronary atherosclerosis, being used in prediction models for the estimation of pretest probability of developing coronary artery disease (12, 35). Among medical risk factors, our study showed that hypertension and dyslipidemia were

positively associated with CAD-RADS score ≥ 3 in both univariate and multivariable analyses. Our results are in concordance with the latest data from European Heart Network which shows that systolic blood pressure and total cholesterol levels are the determinants with the greatest contribution to CVD mortality (17). Also, these two factors are included in the widely used SCORE charts (3) and there are many clinical models that add them for increasing the probability of obstructive CAD (36-39).

Our multivariable analysis did not found an association between diabetes mellitus and obstructive CAD, one possible explanation being that only 19.3% of our study group had diabetes as their comorbidity.

Also, we did not find a direct association between obesity and coronary artery burden defined by CAD-RADS score. Our study is in concordance with Medakovic et al (40) and Dores H et al (41). According to Dores H et al, obesity assessed by BMI can be an indicator of the presence of CAD, but not necessarily associated with its severity (41). They also described an "obesity paradox" with better outcomes after percutaneous coronary interventions at patients with a higher BMI (41). One hypothesis for this paradox is that obese patients tend to be diagnosed at an earlier age and stage of CAD, therefore having lower morbidity and mortality rates (42, 43). Another potential reason for better outcomes of obese patients compared to those of underweight ones is that the latter group is more likely to have post procedural complications due to excessive anticoagulation which is usually not weight adjusted (44, 45). Moreover, underweight patients usually have more concomitant comorbidities which lead to worse prognosis (46). Another theory is that obesity is associated with higher amounts of lean mass and which can have a protective effect when not associated with increased systemic inflammation (47).

Finally, our findings show that smoking is an independent risk factor for the presence of obstructive coronary disease, this being also one of the behavioral factors with the highest contribution for CVD mortality and morbidity rates across Europe (17).

Limitations of the study

Our study has several limitations, the most important one being the fact that it is a retrospectively conducted one. Secondary**,** our results were confined to the experience of a single medical center and the findings of this study were based on a relatively small patient population. Regarding the risk factors, dyslipidemia was not analyzed by fractions of the cholesterol: LDL-C and HDL-C. Also, we did not analyze other additional risk factors like alcohol use, physical activity, anthropometric measurements or C-reactive protein levels. Taking the retrospective approach into consideration, our research assess only the association between tradionally known cardiovascular risk factors and coronary stenosis evaluated by CAD-RADS score and does not assess the incidence of major cardiac events after performing the CT angiography.

Conclusion

In conclusion, our study demonstrates that there is a significant association between multiple cardiovascular risk factors and a higher coronary atherosclerotic burden assessed using CAD-RADS score in the Romanian population. Considering CAD as a priority for Romanian healthcare system, our study provides an overview of imaging and clinical characteristics of CAD and their association, offering valuable information for both cardiologists and radiologists in order to improve the management of the patients.

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- Supervision (organising and supervising the course of the project): Loredana E. Popa, Mircea M. Buruian, Adrian Molnar
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- Literature Review: Bianca Petresc, Calin Schiau, Cristina Catana, Claudia G. Moldovanu
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- Critical Review: Adrian Molnar, Andrei Lebovici, Diana Feier, Mircea M. Buruian

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Patient consent for publication: Not required.

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FIGURE LEGENDS

Fig. 1- MPR (multiplanar reconstruction) images showing different degrees of coronary artery stenosis (yellow arrows): a. normal RCA without any plaque or stenosis (CAD-RADS 0), b. small calcified plaque in the proximal LAD with minimal luminal narrowing < 25% (CAD-RADS 1), c. calcified plaque in the proximal LAD with 25-49% diameter stenosis (CAD-RADS 2), d. semi-circumferential calcified plaque in the proximal LAD with 50-69% diameter stenosis (CAD-RADS 3),e. non-calcified plaque in the proximal RCA with 70-99% diameter stenosis (CAD-RADS 4), f. total occlusion of proximal and mid LAD; calcified plaques above and beyond it supports the diagnosis of chronic total occlusion (CAD-RADS 5)

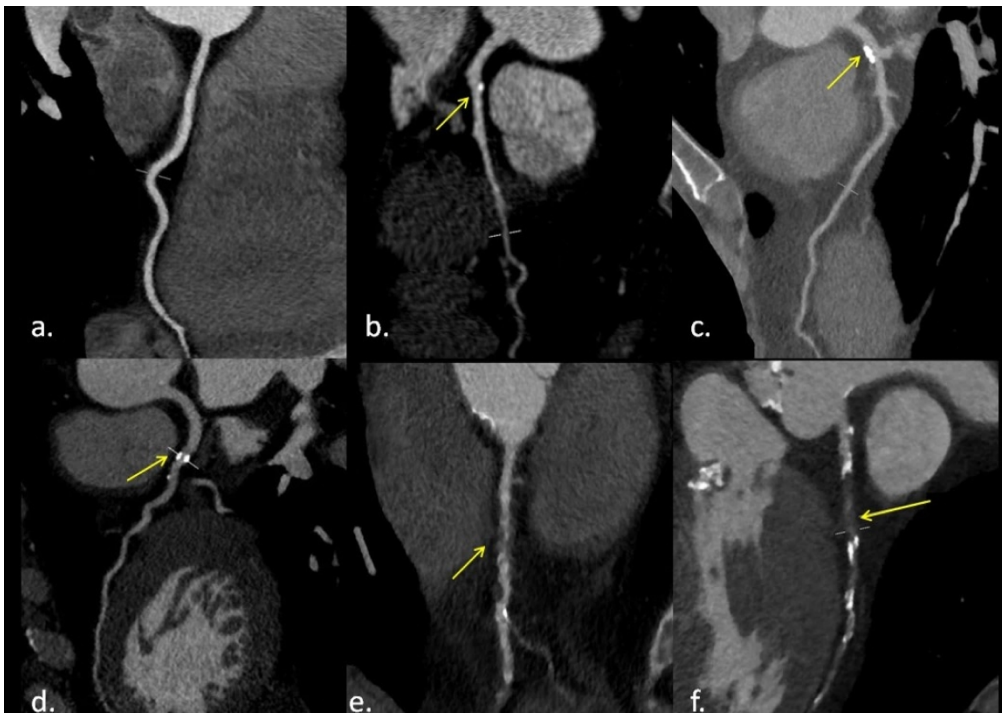
Table 1. Univariate analysis for the association between cardiovascular risk factors and obstructive CAD classified using CAD-RADS categories

Variable	Value	CAD-RADS score 0-2 (stenosis<50%)	CAD-RADS score 3-5 (stenosis≥50%)	p value
Age		55.41 ± 13.11	63.10 ± 10.55	**p<0.001**
Sex				**p<0.001**
	Male	142 (39.2%)	75 (63.0%)	
	Female	214 (60.1%)	44 (37.0%)	
Hypertension				**p<0.001**
	Yes	242 (68.0%)	112 (94.1%)	
	No	114 (32.0%)	7 (5.9%)	
Dyslipidemia				**p<0.001**
	Yes	224 (62.9%)	107 (89.9%)	
	No	132 (37.01%)	12 (10.1%)	
Diabetes mellitus				**p=0.003**
	Yes	58 (16.3%)	34(28.6%)	
	No	298 (83.7%)	85 (71.4%)	
Obesity				**p=0.93**
	Yes	151 (42.4%)	50 (42.0%)	
	No	205 (57.6%)	69 (58.0%)	
Smoking				**p<0.001**
	Yes	145 (40.7%)	75 (63.0%)	
	No	211 (59.3%)	44 (37.0%)	
CACS		0.4 [0 - 39.5]	433.0 [182.4 - 924.8]	**p<0.001**

Results are presented as mean±SD, number (%) or median [25th-75th percentile]
Abbreviations: CACS: coronary artery calcium score

Table 2. Logistic regression analysis for the association between cardiovascular risk factors and obstructive CAD (CAD-RADS score ≥3)

Variable	Odds ratio (95% CI)	p value
Male sex	3.136 (1.841 – 5.341)	<0.001
Age	1.063 (1.036 – 1.090)	<0.001
Hypertension	3.493 (1.444 – 6.251)	0.006
Dyslipidemia	2.648 (1.283 – 5.466)	0.008
Diabetes mellitus	1.207 (0.698 – 2.088)	0.501
Smoking	2.112 (1.236 – 5.466)	0.006



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Supplementary Table 1. Baseline characteristics of the study population according to CAD-RADS categories

Variable	Value	CAD-RADS 0 (n=177)	CAD-RADS 1 (n=99)	CAD-RADS 2 (n=80)	CAD-RADS 3 (n=67)	CAD-RADS 4 (n=67)	CAD-RADS 5 (n=8)	p value
Age		48.8 ± 12.1	60.4 ± 11.9	63.6 ± 8.7	64.6 ± 10.5	66.1 ± 10.6	64.7 ± 11.1	**p<0.001**
Sex								**p<0.001**
	Male (n=217)	55 (31.1%)	42 (42.4%)	45 (56.2%)	39 (58.2%)	28 (63.6%)	8 (100%)	
	Female(n=258)	122 (68.9%)	57 (57.6%)	35 (43.8%)	28 (41.8 %)	16 (36.4%)	0 (0 %)	
Hypertension								**p<0.001**
	Yes(n=354)	110 (62.2%)	70 (70.7%)	62 (77.5%)	63 (94.0%)	42 (95.4%)	7 (87.5%)	
	No (n=121)	67(37.8%)	29 (29.3%)	18 (22.5%)	4 (6.0%)	2 (4.6%)	1 (12.5%)	
Dyslipidemia								**p<0.001**
	Yes (n=331)	91 (51.4%)	72 (72.7%)	61 (76.3%)	59 (88.1%)	41 (93.2%)	7 (87.5%)	
	No (n=144)	86 (48.6%)	27 (27.3%)	19 (23.8%)	8 (11.9%)	3(6.8%)	1 (12.5%)	
Diabetes mellitus								**p<0.001**
	Yes (n=92)	16 (9.0%)	21(21.2%)	21(26.2%)	12 (17.9%)	18 (40.9%)	4 (50.0%)	
	No (n=383)	161 (91.0%)	78 (78.8%)	59 (73.8%)	55 (82.1%)	26 (59.1%)	4 (50.0%)	
Obesity								**p=0.63**
	Yes (n=274)	68 (38.4%)	45 (45.4%)	38 (47.5%)	29 (43.2%)	19 (43.1%)	2 (25.0%)	
	No (n=201)	109 (61.6%)	54 (54.6%)	42 (52.5%)	38 (56.8%)	25 (56.9%)	6 (75.0%)	
Smoking								**p<0.001**
	Yes (n=220)	53 (30.0%)	44 (44.4%)	48 (60.0%)	44 (65.6%)	25 (56.9%)	6 (75.0%)	
	No (n=255)	124 (70.0%)	55 (55.6%)	32 (40.0%)	23 (34.4%)	19 (43.1%)	2 (25.0%)	
Clinical presentation								**p<0.001**
	Typical angina (n=222)	60 (33.9%)	35 (35.3%)	36 (45.0%)	45 (67.1%)	39 (88.6%)	7 (87.5%)	
	Atypica angina (n=123)	70 (39.5%)	25 (25.2%)	20 (25.0%)	7 (10.4%)	1 (2.2%)	0 (0 %)	
	Nonanginal chest pain (n=130)	47 (26.6%)	39 (39.5%)	24 (30.0%)	15 (22.5%)	4 (9.2%)	1 (12.5%)	
CACS		0 [0-0]	15 [6.2-36.6]	123 [55.1-284.5]	303 [134.8-500.7]	711.3 [444.7-958.3]	1611.4 [949.1-1921.4]	**p<0.001**

Results are presented as mean±SD, number (%), or median (25th-75th percentile)
Abbreviations: CACS: coronary artery calcium score

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	*5*
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5,6
		(*b*) Describe any methods used to examine subgroups and interactions	5,6
		(*c*) Explain how missing data were addressed	5,6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	5,6
		(*e*) Describe any sensitivity analyses	5,6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	6,7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7
		(*b*) Report category boundaries when continuous variables were categorized	6,7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6,7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8,9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.