Original Article

Coronary artery features in the cases of atypical chest pain with a troponin-negative result

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Abstract

Objective: To analyze features of coronary artery disease (CAD), which consists of (1) degrees of stenosis and (2) presence of high-risk plaque, on CT angiography (CTA) in the cases of atypical chest pain with a troponin-negative result (TNEG), using the retrospective study of 4.5-year data documents, from January 2020 to April 2024.

Materials and Methods: There were 270 eligible cases of atypical chest pain with a troponin-negative result (TNEG), determined by data documents via Picture Archiving and Communication System (PACS) and Hospital Information System (HIS), from January 2020 to April 2024. The known cases of CAD, status post coronary stent (s), and surgical bypass graft (s) were excluded. Cardiovascular risk factors were analyzed in the eligible cases, determined by Framingham Risk Score (FRS), the degrees of coronary artery stenosis, the degrees of coronary artery calcification, and high-risk plaque features (HRPF) on CT angiography (CTA), using the standardized CAD reporting and data system (CAD-RADS) version 2.0 (2022) of American College of Cardiology (ACC)/American Heart Association (AHA). Logistic regression, t-test, Chi-square, Spearman's correlation, and Adjusted Odd ratio were adopted to analyze the significance of variables.

Results: The mean age [range] of 270 eligible cases was 57 [24-90] years. Evidence of coronary artery disease (CAD-RADS 1 to 5) was found in 118 cases (43.7%). The obstructive coronary artery (≥50% stenosis, CAD-RADS 3 to 5) was present in 66 cases (24.4%). The CAD-RADS O was found in 152 cases (63.3%). The HRPF was found in 48 cases (17.8%), with a mean age [range] of 61 [42-77] years. The age group of 50 to 99 years-old showed a significant association with CAD and obstructive CAD. There were 190 cases (70%) with intermediate to high cardiovascular risk (FRS). The intermediate FRS was associated with positive CAD at 6.34 times higher than the low FRS [Multivariate adjusted OR = 6.34 (95% CI (3.16-12.73)]. The high FRS was associated with positive CAD at 10.3 times higher than the low FRS [Multivariate adjusted OR = 10.3 (95% CI (4.40-24.20)]. Moreover, there were strong correlation between CAD-RADS 0 (0% stenosis) and the coronary artery calcium score (CACS) 0-100 [0 and P1], and moderate to strong correlation between the obstructive coronary artery (CAD-RADS 3-5) and CACS ≥ 301 [P3 and P4].

Conclusion: Atypical chest pain with a troponin-negative result (TNEG) in the age ≥ 50-year-old with intermediate to high cardiovascular risk (FRS) had significant obstructive coronary disease (≥ 50% stenosis, CAD-RADS 3 to 5) and presence of high-risk plaque features (HRPF), determined by CT angiography.

Keywords: Atypical chest pain, Framingham risk score, High-risk plaque features, Obstructive coronary artery disease, Troponin-negative.

Introduction

Atypical chest pain (or atypical angina), with the prevalence rate of 10-20% [1,2], is a common diagnosis in the emergency department (ED) and the outpatient department (OPD), usually found at the age ≥ 50-years-old. The exclusion of ischemic heart disease is only the first step in management.

According to the guidelines of the European Society of Cardiology [1,2,4], the non-invasive imaging (including CTA) can be used in all patients with a pre-test probability of >15% and can be considered in those with 5-15% of pre-test probability. The pre-test probability is based on the age and gender of the patient combined with the type of complaints: typical angina, atypical angina or non-angina chest pain.

Atypical chest pain meets two of the three criteria of the typical angina, consisting of (1) substernal chest discomfort of characteristic quality and duration, (2) provocation by exertion or emotional stress, and (3) relief by nitrates or rest within minutes. While, the non-angina chest pain does not meet the typical criteria or meets only one - several studies showed about 8.4 to 19.4% of the patients with atypical chest pain had a cardiac origin [3-6].- To exclude life-threatening causes (triple-rule-out: coronary artery occlusion, aortic dissection and pulmonary thromboembolism), the increasing amount of cardiac and thoracic computed tomography (CT) scan has been addressed in many hospitals and medical centers, in the past decades. Coronary CT angiography (CCTA) combined with the coronary calcium score (CACS) is highly sensitive and specific in the detection of coronary artery disease (CAD) and has been validated extensively [3].

The aim of the study was to analyze features of coronary artery disease on CT angiography (CTA), which consists of (1) degrees of stenosis and (2) presence of high-risk plaque, on CT angiography (CTA) in the cases of atypical chest pain with troponin-negative result (TNEG).

Research objective

To analyze features of coronary artery disease (CAD) on CT angiography (CTA) in the cases of atypical chest pain with troponin-negative result (TNEG), using the retrospective study of 4.5-year data documents, from January 2020 to April 2024, using CAD-RADS version 2.0.

Materials and methods

Study design, data collection, and participants

This study is retrospective analysis. The participants were eligible cases of atypical chest pain with troponin-negative result (TNEG), determined by data documents via Picture Archiving and Communication System (PACS) and Hospital Information System (HIS), during January 2020 to April 2024. All eligible cases received scans with the 256-slice CT scanner Philips with the standard protocol of CTA coronary artery.

Protocol of CTA-coronary used retrospectively ECG-gated helical scanning. The 8 cm Z-axis coverage field-of-view (FOV) was included. The heart rate of 65 – 90 bpm was accepted for a scan. All eligible cases had no need for premedication (betablocker).

A 0.5 mm collimation was performed, showing an axial 1-beat acquisition of the entire heart. The radiation exposure is approximately 6 mSv. The image reconstruction was performed on the workstation (Philips Intelligent Space Software).

Analysis of all coronary arteries and segments was used under cardiac-suit software with automated reconstruction and calculation of the stenotic degrees. The radiologists approved all reconstructed images, all automatic calculation values (degrees of stenosis), and the presence of the high-risk plaque feature (HRPF).

Inclusion criteria were applied in all cases of the age 20-99 years old that presented with atypical chest pain and troponin-negative result (TNEG), during January 2020 and April 2024, with available CT images to PACS. The underlying diseases of all eligible cases were recorded, according to HIS.

Exclusion criteria were known cases of coronary artery disease (CAD), status post coronary stent (s), and status post-surgical bypass graft (s).

Ethical consideration

The permission for data collection was accepted on April 10, 2024. The research was approved by the Human Research Ethics Review Board of Dhurakij Pundit University. There are three principles of consideration, as follows:

(1) For the respect for person, all variables and measurements are of non-identifiable personal data. All data collection cannot project to the patient's identification.
(2) For the beneficence, there is a lower than minimal risk, and no harms to the participants in this study. The personal information and information obtained from all participants will be kept confidential. However, the results of the study and various relative factors may be disclosed to the public for academic benefits. The name of research participants was not specified.
(3) For the justice, this study has a selection of subjects with clear inclusion and exclusion, for academic benefit.

CAD-RADS was used for determining the coronary features. CAD-RADS stands for Coronary Artery Disease Reporting and Data System [7,8] , was used for analyzing features on coronary artery, consisting of (1) degrees of coronary artery stenosis [0%stenosis: CAD-RADS 0, 1-24% stenosis: CAD-RADS 1, 25-49% stenosis: CAD-RADS 2, 50-69% stenosis: CAD-RADS 3, 70-99% stenosis: CAD-RADS 4, and 100% stenosis: CAD-RADS 5], (2) degrees of the coronary artery calcium score (CACS) [1-100: P1, 101-300:P2, 301-999: P3, and ≥1000: P4], and (3) High-risk plaque features (HRPF), consisting of the low attenuation plaque (≤ 30 H.U.), positive remodeling, spotty calcification, and napkin-ring sign.

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Post-processing images and reports were reviewed on PACS, consisting of 3D-cardiac image, Volume Rendering Technique (VRT) of the heart and coronary artery, Maximum Intensity Projection (MIP), Multi-planar reconstruction (MPR) of the coronary artery, the quantitative measurement for coronary artery stenosis, and evidence of high-risk plaque features (HRPF), seen in Figure 1, Figure 2, and Figure 3.

Framingham Risk Score (FRS) was classified into three categories: category 1: low cardiovascular risk (FRS ≤ 10%), category 2: intermediate cardiovascular risk (10% < FRS ≤ 19%), and category 3: high cardiovascular risk (FRS ≥ 20%). The potential parameters of FRS were age, gender, total cholesterol, HDL, systolic blood pressure, smoking, and diabetes.

Statistics used were the *t* test, Chi-square, Cramer' V, Spearman's correlation, and Logistic regression model. The adjustment of confounding factor (BMI) between FRS groups was used by adjusting the odd ratio. For all tests, p-value of <0.05 was considered to indicate statistical significance.

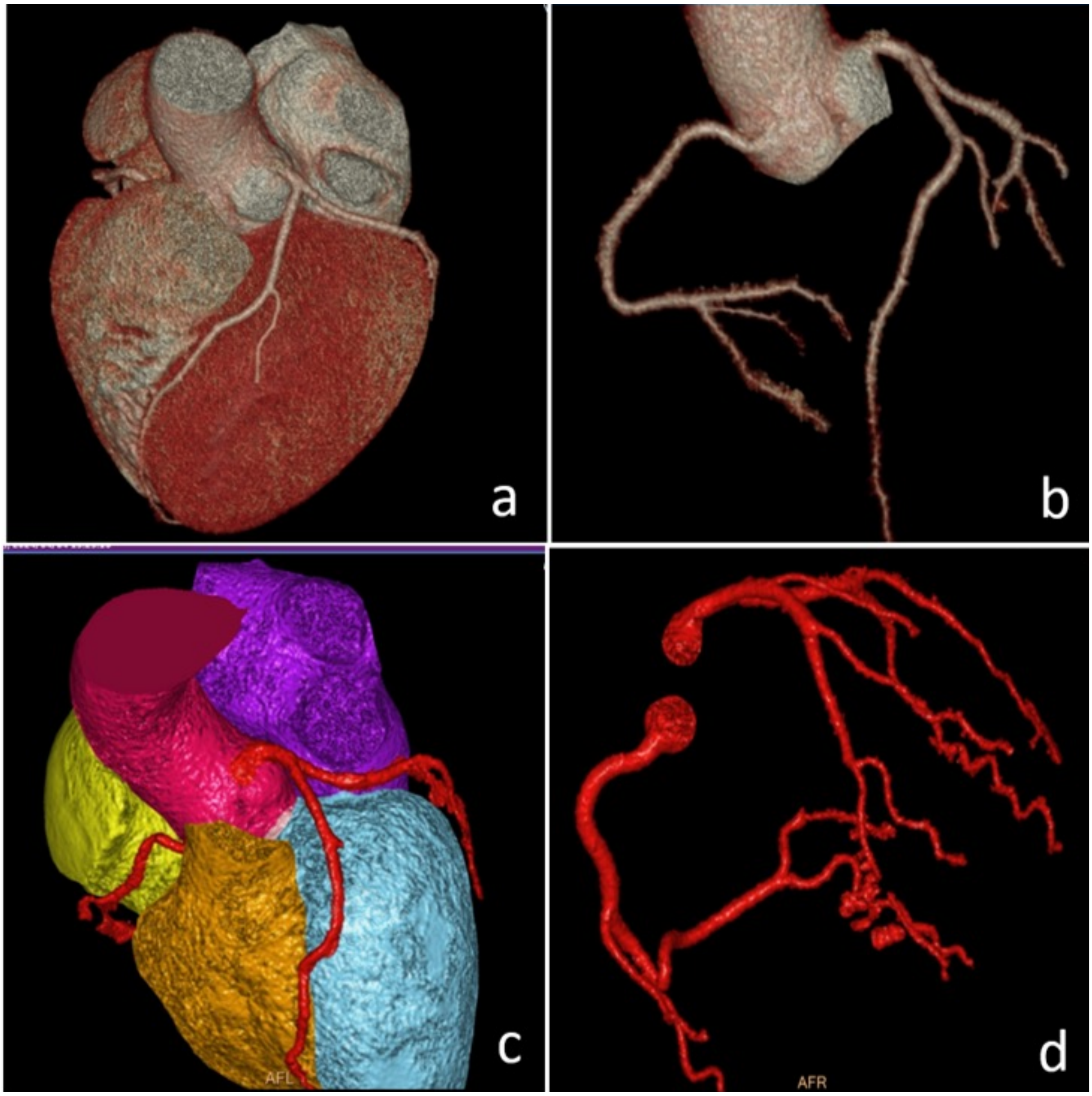

Figure 1. *Overview of the post-processing images on Coronary CTA, (a) 3D VRT whole heart, (b) 3D VRT coronary artery tree, (c) Color map 3D-VRT whole heart, (d) Color map VRT coronary artery tree.*

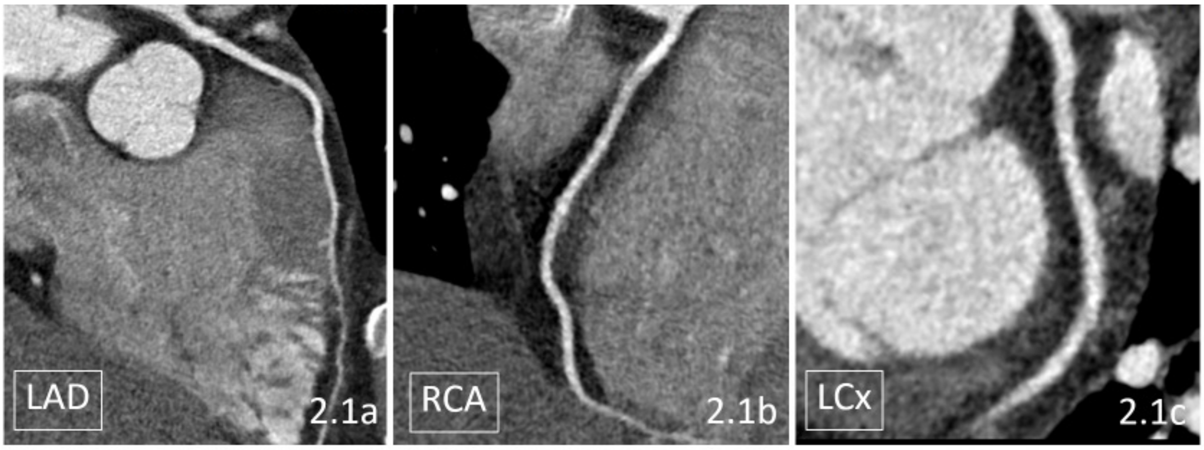

Figure 2. *Classification of coronary artery stenosis (CAD-RADS) and plaque burden (P),*

Figure ***2.1a-c:*** *Multi-planar reconstruction (MPR) of the coronary artery showed CAD-RADS 0, no coronary stenosis, absence of calcified and non-calcified plaque in the coronary tree, the classification P is not required for CAD-RADS 0,*

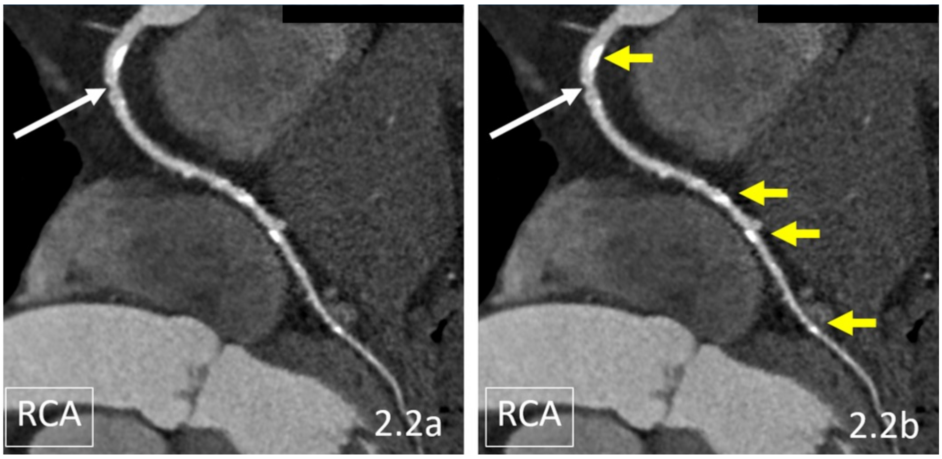

Figure 2.2a-b. *Multi-planar reconstruction (MPR) of the coronary artery showed CAD-RADS 1/P1 - Minimal coronary stenosis (1–24%). Figure 2.2a (a long white arrow) identified a non-calcified plaque with 20% stenosis at proximal RCA. Plaque Burden –P1: Mild amount of plaque burden. Figure 2.2b (yellow arrows) identified calcified plaques. CACS = 86.8,*

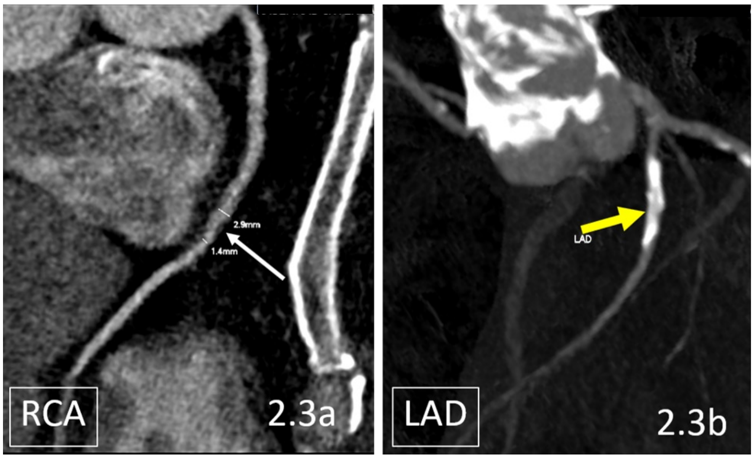

Figure 2.3a-b. *Multi-planar reconstruction (MPR) of the coronary artery showed CAD-RADS2/P2 - Mild coronary stenosis (25-49%). Figure 2.3a (a long white arrow) identified a non-calcified plaque with 45% stenosis at the middle segment RCA. Plaque Burden –P2: Moderate amount of plaque burden. Figure 2.3b (a yellow arrow) identified a "sheet- like" heavy calcification at proximal LAD. CACS = 267.71,*

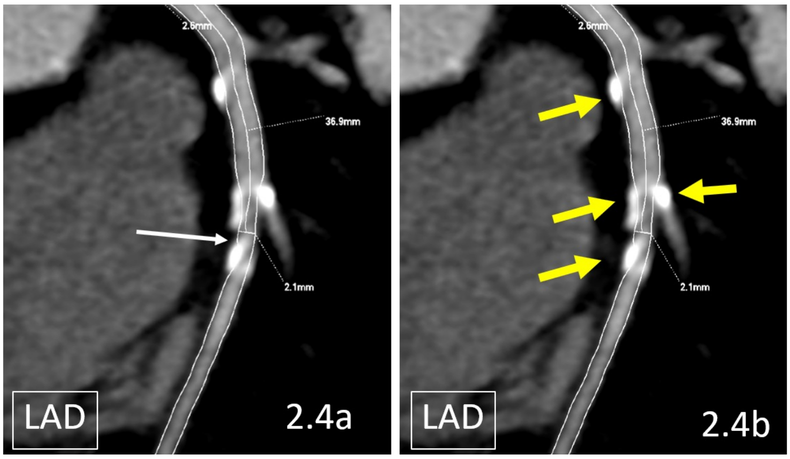

Figure 2.4a-b. *Multi-planar reconstruction (MPR) of the coronary artery showed CAD-RADS 3/P3 - Moderate coronary stenosis (50-69%). Figure 2.4a (a long white arrow) identified using a non-calcified plaque with 55% stenosis at the middle segment LAD. Plaque Burden –P3: Moderate amount of plaque burden; Figure 2.4b (yellow arrows) identified several calcified plaques along proximal and middle segments LAD. CACS = 426.5,*

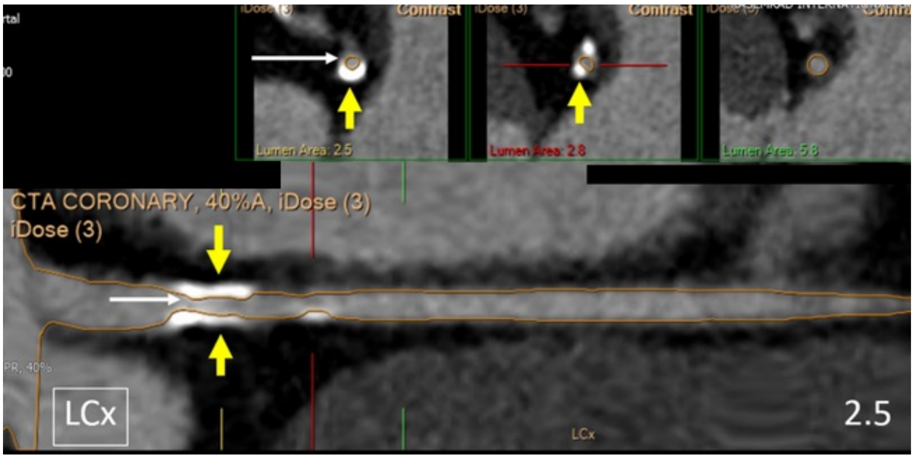

Figure 2.5. *Multi-planar reconstruction (MPR) of the coronary artery showed CAD-RADS 4/P4 - Severe coronary stenosis (70-99%). A long white arrow identified a non-calcified plaque with 75% stenosis at the origin and proximal LCx. Plaque Burden –P3: Severe amount of plaque burden (yellow arrows); CACS = 1007.93,*

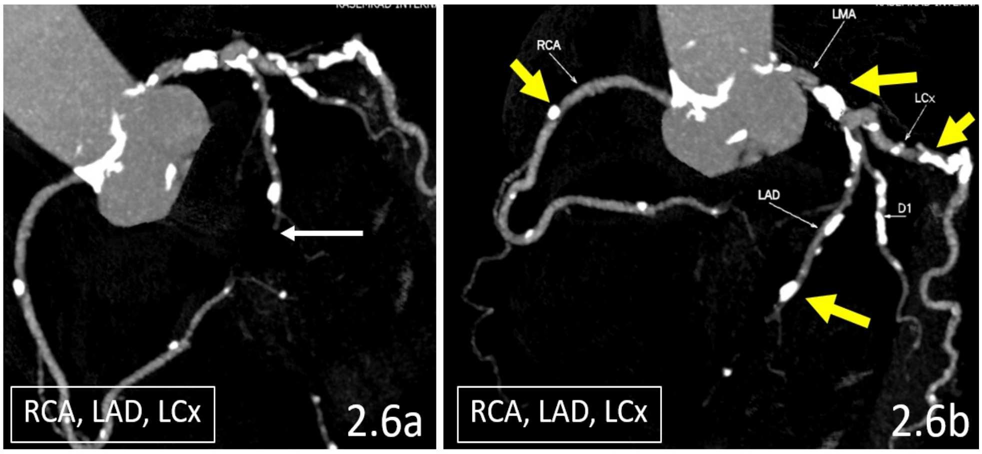

Figure 2.6a-b. *Maximum Intensity Projection (MIP) of coronary artery showed CAD-RADS 5/P4 – an occluded coronary stenosis (100%) at middle segment LAD (Figure 2.6a: a long white arrow). Plaque Burden –P4: Extensive amount of plaque burden along the course of all coronary arteries (Figure 2.6b: yellow arrows). CACS = 1,349.95.*

Results

The mean age [range] of 270 eligible cases was 57 [24-90] years. The median BMI [IQR] was 25.39 [22.8-29.0]. The baseline characteristics are presented in Table 1 and Table 2. There was no significant difference between genders and age groups (unpaired t-test, p-value =0.97). The percentage of the cases with low Framingham Risk Score (FRS), intermediate FRS, and high FRS was 29.6% (n=80), 52.6% (n=142), and 17.8% (n=48), respectively.

There was a significantly strong correlation between the 100% coronary artery stenosis [CAD-RADS 5] and the extensive coronary calcification [CACS ≥1000, P4] (Spearman's correlation = 0.80). A moderately correlation between the 50% to 99% coronary stenosis [CAD-RADS 3 and 4] and CACS 301-999 [P4] was seen (Spearman's correlation = 0.72 and 0.65, respectively). On the other hand, there was a significantly strong correlation between the CAD-RADS 0 (0% stenosis) and the CACS 0-100 [0 and P1] (Spearman's correlation = 0.84 and 0.82, respectively), seen in Table 3.

There was a significant association between age groups of 50-99 years and the positive coronary artery disease (CAD) and the obstructive CAD (stenosis ≥ 50%) [χ^2= 38.069 and 35.897, Cramer's V = 0.37 and 0.36, respectively], seen in Table 4.

On the other hand, there was a significant association between age groups of 20-49 years and the negative CAD and the non-obstructive CAD, seen in Table 4.

The cases of intermediate FRS were associated with positive CAD at 6.34 times more than the low FRS [Multivariate adjusted OR = 6.34 (95% CI (3.16-12.73)]. The cases of high FRS were associated with positive CAD at 10.3 times more than the low FRS [Multivariate adjusted OR = 10.3 (95% CI (4.40-24.20)], seen in Table 5.

Moreover, there was a significant association between the high-risk plaque features (HRPF) and the obstructive CAD [χ^2 = 37.174, Cramer's V = 0.56], seen in Table 6.

Table 1. *Baseline characteristics of the eligible cases (n = 270).*

Mean age years [range]	57 [24-90]
Male, n (%)	134 (49.6%)
Body mass index (kg/m2) median [IQR]	25.39 [22.8-29.0]
Diabetes, n (%)	51 (18.8%)
Hypertension, n (%)	155 (57.4%)
Dyslipidemia, n (%)	46 (17.0%)
Smoking, n (%)	13 (4.8%)
Low Framingham Risk Score (<10%), **n** (%)	80 (29.6%)
Intermediate Framingham Risk Score (<10-19%), **n** (%)	142(52.6%)
High Framingham Risk Score (≥ 20%), **n** (%)	48 (17.8%)

Table 2. *Baseline characteristics on age groups and genders of eligible cases with atypical chest pain and troponin-negative (n = 270).*

Age (yrs.)	Male (n =134, 49.6%)	Female (n = 136, 50.3%)	Total
20-29	3	4	7 (2.6%)
30-39	14	8	22 (8.1%)
40-49	29	22	51 (18.9%)
50-59	40	29	69 (25.5%)
60-69	31	42	73 (27.0%)
70-79	15	22	37 (13.7%)
80-89	1	9	10 (3.75%)
90-99	1	0	1 (0.37%)
Total	134	136	270

The unpaired t-test, p-value = 0.97

Table 3. *Correlation of coronary features between the coronary artery calcium score (CACS) and the degrees of coronary artery stenosis (CAD-RADS)*.*

CAD-RADS / CACS	CAD-RADS 0 0% stenosis	CAD-RADS 1 1-24 % stenosis	CAD-RADS 2 25-49 % stenosis	CAD-RADS 3 50-69 % stenosis	CAD-RADS 4 70-99 % stenosis	CAD-RADS 5 100 % stenosis	n = 270
CACS = 0 (n)	88 ***0.84**	7 *0.43	5 *-0.10	5 *-0.19	1 *-0.67	0 *-0.30	106
CACS 1-100 (n) **[P1]** Mild	54 ***0.82**	3 *0.45	6 *-0.13	1 *-0.20	3 *-0.61	0 *-0.25	67
CACS 101-300 (n) **[P2]** Moderate	10 *0.17	9 *-0.20	9 *-0.98	6 *-0.47	12 *0.22	0 *0.72	46
CACS 301-999 (n) **[P3]** Severe	0 *-0.88	3 *-0.01	10 *0.54	12 ***0.72**	6 ***0.65**	0 -0.02	31
CACS > 1000 (n) **[P4]** Extensive	0 *-0.68	0 *-0.79	0 *-0.47	7 *0.60	11 *0.44	2 ***0.80**	20
Total (n)	152	22	30	31	33	2	**270**

**Spearman's correlation*

Table 4. *Association between the age groups and coronary artery disease (CAD), and the obstructive coronary artery disease (stenosis > 50%).*

Age groups (years)	CAD (n=118)	Non-CAD (n=152)	P-value	Obstructive CAD (n = 66)	Non-obstructive CAD (n= 52)	P-value
50 -99	106	84	< 0.001*	61	**25**	< 0.001**
20- 49	12	68	< 0.001*	5	27	< 0.001**

* χ^2 = 38.069, *degree of freedom = 1, Cramer's V = 0.37* * *P-value < 0.05*
** χ^2 = 35.897, *degree of freedom = 1, Cramer's V = 0.36* ** *P-value < 0.05*

Table 5. *Logistic regression model of the positive coronary artery disease (CAD) in the eligible cases, determined by Framingham Risk Score (FRS)*.*

Eligible cases with Framingham Risk Score (FRS)	No. of cases with CAD (n=118)	Multivariate adjusted OR (95% CI)
Low Framingham Risk Score (<10%)	**12**	1.00 (reference)
Intermediate Framingham Risk Score (<10-19%)	**75**	6.34 (3.16-12.73)
High Framingham Risk Score (> 20%)	**31**	10.3 (4.40-24.20)
P for trend < 0.001**		

**Logistic regression model was used to estimate OR and 95% CI [Adjusted BMI and Diabetes]*
*** P-value < 0.05*

Table 6. *Association between the high-risk plaque features (HRPF) and the coronary artery disease (CAD-RADS 1 to 5).*

	Presence of HRPF	Absent of HRPF	P-value
Obstructive CAD (n = 66) [CAD-RADS 3, 4, and 5]	43	23	< 0.001*
Non-obstructive CAD (n= 52) [CAD-RADS 1 and 2]	5	47	< 0.001*

* χ^2 = 37.174, degree of freedom = 1, Cramer's V = 0.56 *P-value < 0.05*

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Discussion

1. Role of coronary CTA in the cases of atypical chest pain

According to the guidelines of the European Society of Cardiology [1,2,4], the non-invasive imaging (including CTA) can be used in all patients with a pre-test probability of >15% and can be considered in those with a pre-test probability between 5-15%. The pre-test probability is based on the age and gender of the patient combined with the type of complaints: typical angina, atypical angina or non-angina chest pain.

The current meta-analysis of 5332 patients from 65 prospective diagnostic accuracy studies [9] that compared the accuracy of Coronary CT angiography (CCTA) with cardiac catheterized coronary angiography in patients with any clinical probability of coronary artery disease (CAD) showed the overall sensitivity of CTA accounting for 95.2% (92.6% to 96.9%) and the specificity of 79.2% (74.9% to 82.9%) and was not significantly influenced by the angina pectoris type (typical angina, atypical, non-angina chest pain).

The available CCTA has a useful benefit as rapid non-invasive diagnostic tool in the case of atypical chest pain with intermediate to high cardiovascular risks, especially among 50-99-year-old age group, to exclude life-threatening cardiovascular causes (triple-rule-out: coronary artery occlusion, aortic dissection, and pulmonary thromboembolism).

2. Obstructive CAD and atypical chest pain

According to AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline 2021 [10], the intermediate-high risk patients have modest rates of obstructive CAD (~10%–20%) and a risk of clinical events (~1%–2% per year). CCTA is preferable in those < 65 years of age and not on optimal preventive therapies, while stress testing may be advantageous in those ≥ 65 years of age, because they have a higher likelihood of ischemia and obstructive CAD.

The top five of the causes of chest pain, at the age of 45-64 years, are (1) non-specific chest pain, about 56% of the population, followed by (2) coronary atherosclerosis, (3) painful respiration, (4) acute myocardial infarction, and (5) cardiac dysrhythmia [10].

In the cases of atypical chest pain with diabetes [6], there was a presence of extensive CAD, as well as more obstructive CAD, particularly in women.

As compared with our study, the obstructive CAD was found in 24.4% of eligible cases that presented with atypical chest pain and TNEG. Obstructive CAD should be concerned in the case with intermediate to high cardiovascular risks (FRS).

3. High-risk plaque features and CAD

High-risk plaque features (HRPF), consist of the low attenuation plaque (≤ 30 H.U.), positive remodeling, spotty calcification (<3mm), and napkin-ring sign. HRPF can be found in obstructive CAD and non-obstructive CAD, more likely in the obstructive CAD [11,12,13,14]. HRPF tends to rupture with subsequent intraluminal formation of thrombi which causes acute myocardial infarction (AMI) [13].

In 2018, the meta-analysis and systematic review [14] demonstrated that HRPF is most likely an independent predictor of major adverse cardiovascular events (MACE), which supports the inclusion of HRPF reporting in clinical practice. However, at this point, it remains unclear whether HRPF reporting has clinical implications.

The recent study on 2024 [15] showed the significant progression in the number of the high-risk plaques in the cases of non-obstructive coronary disease. The HRPF needs further studies, especially one related to radio-pathologic-clinical correlation.

Conclusion

Conclusion and suggestion

Coronary CT angiography (CCTA) appears to be a useful initial triage tool in the cases of atypical chest pain. When the CCTA result is negative, it allows safe early discharge because of its high negative predictive value. In the selected cases of the age > 50-year-old with intermediate to high cardiovascular risks (FRS), CCTA can detect the obstructive coronary disease and high-risk plaque features (HRPF) and allow further therapeutic intervention.

For ED physicians and cardiologists, the CCTA should be used more routinely in TNEG patients with intermediate to high cardiovascular risk, especially among 50-99-year-olds, to exclude life-threatening coronary artery obstruction.

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