ORIGINAL ARTICLE

Long-term prognostic implication of coronary plaque characterization as detected by 64-multidetector computed tomography in Egyptian population

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Abstract *Objectives:* We aimed to determine the role of multi-detector computed tomography (MDCT) in prognosis of patients with known or suspected coronary artery disease (CAD) by applying plaque characterization and whether obstructive versus non-obstructive plaque volume is a predictor of future cardiac events.

Background: Vulnerable plaques may occur across the full spectrum of severity of stenosis, underlining that also non-obstructive lesions may contribute to coronary events.

Methods: We included 1000 consecutive patients with intermediate pretest likelihood of CAD who were evaluated by 64-MDCT. Coronary artery calcium scoring, assessment of degree of coronary stenosis and quantitative assessment of plaque composition and volume were performed. The end point was cardiac death, acute coronary syndrome, or symptom-driven revascularization.

Results: After a median follow-up of 16 months, 190 patients had suffered cardiac events. In a multivariate regression analysis for events, the total amount of non-calcified plaque (NCP) in non-obstructive lesions was independently associated with an increased hazard ratio for non-fatal MI ($1.01–1.9$/100-mm^3 plaque volume increase, $p = 0.039$), total amount of obstructive plaque was independently associated with symptoms driven revascularization ($p = 0.04$) and coronary artery calcium scoring (CACS) was independently associated with cardiac deaths ($p = 0.001$).

Conclusion: MDCT is a non-invasive imaging modality with a prognostic utility in patients with known or suspected coronary artery disease by applying plaque characterization and it could identify vulnerable plaques by measuring the total amount of NCP in non-obstructive lesions which

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could be useful for detecting patients at risk of acute coronary syndrome (ACS) and guide further preventive therapeutic strategies. CACS was shown to be an independent predictor of mortality, while total amount of obstructive volume was shown to be an independent predictor of symptoms driven revascularization.

1. Background

Coronary artery disease (CAD) is the most common cause of hospitalization and premature mortality in both developed and developing countries; even with advances in the preventive cardiology its prevalence is still increasing.[1,2] Acute coronary syndrome (ACS) and sudden cardiac death (SCD) are frequently the first clinical manifestations of CAD. The term "atherosclerosis" is typically describing the association of fatty degeneration with vessel stiffening.[3] The atherosclerotic plaque which is the mainstay of established atherosclerosis, sometimes progresses to contain large amounts of lipid core and excess smooth muscle cell migration; when it becomes unstable, injury of the overlying endothelium, or plaque rupture, could result in thrombotic occlusion of the overlying vessel.[4] Vulnerable plaque rupture is the principal cause of luminal thrombosis in ACS occurring in 75% of patients dying of an acute myocardial infarction (AMI).[5] The introduction of the concept of plaque vulnerability in conjunction with an increased understanding of the limitations of plaque imaging was reflected on quantifying the risk based only on the severity of arterial stenosis. In several retrospective and prospective serial angiographic studies, the culprit lesion in nearly two-thirds of patients with ACS was documented to be less than 70% (often < 50%) diameter narrowing on a coronary angiography several weeks or even months before the occurrence of the serious events.[6,7] Early detection of vulnerable plaques and aggressive medical intervention of these high-risk plaques can lead to its stabilization and effectively reduce the incidence of future ACS and SCD. Hence, the refining of the available non-invasive imaging modalities to assess the natural progression of vulnerable plaque is of utmost importance.[8] Noninvasive imaging of the coronary arteries with multi-detector computed tomography (MDCT) has emerged as an important diagnostic tool in patients suspected of CAD. Detection of coronary plaque composition has become a rapid noninvasive modality for evaluation of the overall plaque burden in the coronary tree with characterization of calcified and non-calcified plaque (NCP) composition.[9] Plaque composition as evaluated by MDCT has a strong correlation to clinical outcomes in patients with CAD. Motoyama and colleagues[9,10] compared plaque morphology on MDCT in 38 patients with ACS versus 33 patients with stable angina pectoris and demonstrated that plaques associated with ACS showed lower density values, positive remodeling and spotty calcification. In this study we tested the hypothesis that MDCT carries prognostic role in-patient with CAD, via application of coronary plaque characterization and detection of vulnerable plaques.

2. Method

2.1. Patient selection and study design

It is an observational retrospective study conducted in single center in period from June 2010 to December 2012, One thousand patients with intermediate pretest likelihood of (CAD)[11] were evaluated by 64-slice MDCT included in this retrospective study. All patients were informed about the technique, an informed consent was obtained and the local ethics committee approved the protocol. Patients with renal impairment (GFR < 30 mL/min/1.73 m^2), pregnancy, atrial fibrillation, inability to stop breathing for 12 s, recent acute coronary syndrome and previous revascularization were excluded.

Patient's histories as regards their symptoms and CAD risk factors including DM, hypertension, smoking, dyslipidemia and family history of premature CAD were obtained. Patients were followed up for at least one year, and information was obtained by either clinical visits or telephone interviews. Hospital records of all patients were screened for the occurrence of clinical events to confirm the obtained information.

Clinical primary end points were Cardiac death (Defined as death caused by acute myocardial infarction, ventricular arrhythmias, or refractory heart failure), Non-fatal infarction (Defined based on criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the electrocardiogram) and symptoms driven revascularization.[12]

2.2. MDCT scan protocol

Patients were fasting for 4–6 h, flexible venous cannula catheters were placed in the antecubital vein and oral B-blocker was administered before the scan for those with a heart rate above 65 beats per minute.

Images were acquired using 64-MDCT (Aquilion 64 Toshiba Medical system). Scan parameters were as follows: slice collimation of 64×0.5 mm, a tube voltage of 120 kV, and a tube current of 70 mA s, gantry rotation time of 400 ms and slice thickness of 0.5 mm. First a non-contrast enhanced, prospectively electrocardiogram-triggered calcium score was performed at 75% of R-R interval and then a contrast enhanced scan obtained with helical retrospective gating using a bolus of 80 mL of intravenous non-ionic contrast (Iopamidol 370) (0.5–2.0 mL/kg, 80 mL maximum volume) was injected by mechanical power injector followed by a 10–30 mL saline flush at rates ranging from 1.5 to 2.5 mL/s during the scan, which was performed during an inspiratory breath hold of 12 s, and the MDCT data and ECG trace were acquired.

2.3. MDCT data analysis

MDCT data were reviewed independently by two operators, in the external workstation (Vitrea 3D, version 4.0, Vital Images, and Toshiba Medical Systems).

Reconstruction was obtained at 75% of the R-R interval for most of the cases, and reconstruction in more phases was left for the reader's preference. The image analysis was done by 3D multi-planar reconstruction, axial images, curved multi-planar reconstruction (MPR), volume rendering and maximum intensity projection (MIP).

2.4. Coronary plaque assessment

The coronary arteries were evaluated for the presence of any plaque with automatic detection of the outer contour of the vessel with a ray search technique on cross sections perpendicular to the vessel. Plaque was defined as the area between the outer contour of the vessel and the lumen border, plaque analyzed accordingly:

- Plaque length was manually traced from the site of transition from normal to involved wall till the vessel changes into normal again.
- The total plaque volume was calculated as the sum of all contiguous voxels between the outer vessel contour and the lumen border.
- Plaque content exceeding a threshold of 130 Hounsfield units (HU) was calculated as the calcium volume and plaque content below 130 HU as NCP volume.[13]

2.5. The degree of coronary stenosis

The degree of stenosis was determined on cross-sectional images; the contrast-enhanced portion of the coronary lumen was manually traced at the site of maximal luminal narrowing and a proximal and distal reference site. The reference sites were defined as the segments without detectable plaque proximal and distal to and as close as possible to the respective coronary lesion (in the absence of a segment without plaque, the least-diseased segment between the lesion and the coronary ostium or major bifurcations). The degree of stenosis was calculated as the ratio between the luminal area at the site of maximal stenosis and the mean luminal area of the proximal and distal reference site.

Finally, it was determined whether the lesion was obstructive or not, using a threshold of 50% luminal narrowing for the existence of significant stenosis. For each patient, the number of diseased coronary segments, number of segments with obstructive and non-obstructive lesions, and number of each type of plaque were calculated. The sum of all recorded non-obstructive volumes (mm^3)/patient was calculated.

2.6. Statistical analysis

Statistical analyses were performed with SPSS (version 20). Numerical values are presented as means and SD, and categorical values are presented as frequencies and percentages unless otherwise stated. For statistical correlations, a 2-tailed t test for independent samples was used for continuous values, and the chi-square test was used for categorical variables.

To determine independent predictors of the composite end point, multivariate analysis of MDCT variables with $p \leqslant 0.05$ is considered significant.[14,15]

3. Results

MDCT coronary angiographies were performed in 1000 patients. All CT data were successfully acquired without complications and no patient had to undergo repeated scan for non-diagnostic examination. Patients' characteristics are demonstrated in Table 1.

The mean heart rate on examination was 60.3 ± 10.3 beat/min (ranged from 51 to 70 beats/min). The estimated radiation dose ranged between 7.6 and 14 mSv with a mean of 10.7 ± 3.1 mSv.

Coronary Calcium score (CAC) of the examined patients was graded as follows:[16] Zero score: in 98 patients (9.8%), minimal score (1–10): in 96 patients (9.6%), mild score (11–100): in 354 patients (35.4%), moderate score (101–400): in 324 patients (32.4%) and high score ($\geqslant$400): in 128 patients (12.8%). Among 5040 examined coronary arteries in 1000 consecutive patients, 1987 coronary arteries had atherosclerotic plaques, distributed along a total of 2272 segments. They were affecting the left main artery (LMCA) in 78 (3.9%), left anterior descending (LAD) in 852 (42.8%), Ramus branch in 39 (2%), left circumflex artery (LCX) in 356 (18%), right coronary artery (RCA) in 398 (20%), diagonal branch in 172 (8.7%) and marginal branch in 92 (4.6%) patients.

3.1. Plaque analysis

By analyzing the plaque composition: 1115 (49%) were calcified plaques, 603 (26.6%) were non-calcified and 554 (24.4%) were mixed plaques. Further assessment of plaques as regards different plaque volumes means/patient: mean obstructive plaque volumes 500 ± 280 mm^3, mean non-obstructive plaque volumes 285 ± 220 mm^3, mean calcified plaque volumes in non-obstructive plaques 54 ± 40 mm^3, mean non-calcified plaque volume in non-obstructive plaque 240 ± 200 mm^3. The atherosclerotic plaques were obstructive in 1340 (58.9%) segments and non-obstructive in 932 (41.1%) segments. The sum of all segments with atherosclerotic plaques per patient ranged from 1 to 5 segments (mean 3.5 ± 1.3 segments).

After a follow-up period ranged between 12 and 24 months with a mean of (14 ± 1.3 months), 190 patients had cardiac events, 102 of them underwent symptoms driven revascularization (73 PCI and 29 CABG), 65 patients had non-fatal MI and 23 patients had cardiac deaths.

Table 1 Baseline risk factors in the study population.

Risk factors	Frequency
Age	Mean 59.5 ± 9.3 years
DM	456 (45.6%)
Hypertension	744 (74.4%)
Smoking	340 (34%)
Dyslipidemia	612 (61.2%)
Family history of CAD	352 (35.2%)

Our study demonstrated that in univariate analysis significant MDCT predictors of cardiac events were CAC associated with cardiac death ($\chi^2_P = 0.001$), mean obstructive plaque volume/patient association with symptoms driven revascularization ($r = 0.4$, $p = 0.04$), mean non-obstructive plaque volume/patient, mean non-obstructive non-calcified plaque volume/patient and non-fatal MI ($r = 0.4$, $p = 0.04$) ($r = 0.38$, $p = 0.01$) respectively. In multivariate analysis of MDCT predictors only the total amount of NCP in non-obstructive lesions was independently associated with an increased hazard ratio for non-fatal MI ($1.01–2/100$-mm^3 plaque volume increase, $p = 0.039$) and all the data are demonstrated in Tables 2–5 and Figs. 1–3. Two case examples have been illustrated in Figs. 4 and 5.

4. Discussion

In patients presenting with CAD, assessment of prognosis is essential in selecting appropriate patient management and has positive impact on risk factor modifications. The prognosis and management of patients with CAD in current practice depends on initial clinical evaluation, with the low-risk patients being reassured and the high-risk patients being referred for further invasive angiography.[17] However, most of these patients are in the intermediate risk group, in whom prognosis and management are less well defined. Accordingly, these patients need additional testing with one or more of the established noninvasive modalities, which include exercise electrocardiography, stress SPECT imaging, or stress echocardiography.[18] All these techniques aim at detecting ischemia, and proved to be predictive of future cardiac events when abnormalities were found and were associated with a low risk for events when the test results were normal.[19,20] MDCT coronary angiography is a highly accurate, non-invasive imaging technique for the diagnosis of CAD; in particular, the negative predictive value of MSCT approach 100%, allowing CAD to be ruled out.[21] In this retrospective study, the hypothesis that global coronary plaque burden in non-obstructive lesions measured with MDCT predicts clinical outcomes in patients with suspected or known CAD was tested. Actually, non-obstructive plaque volume, non-obstructive calcified and non-obstructive non-calcified NCP volumes were better predictors of future cardiac events than clinical variables. Furthermore, we demonstrated that NCP was a stronger predictor of non-fatal MI than both the CACs and total obstructive plaque volume, demonstrated before by Kristensen et al.,[22] in patient presented with NSTEMI to determine plaque burden.

Table 2 Patients with cardiac events distribution in relation to the total obstructive plaque volumes.

Cardiac events	Total obstructive plaque volume/patient, mm³								Test of significance
	1 = (52–552) mm³		2 = (553–1053) mm³		3 = (1054–1554) mm³		4 = (1555–1735) mm³		p
	No.	%	No.	%	No.	%	No.	%	
Symptoms driven revascularization	70	88.8	11	64.7	5	100	3	75	0.04*
Non-fatal MI	8	10	6	35.3	0	0.0	1	25	0.2
Cardiac deaths	1	1.2	0	0	0	0	0	0.0	0.2

* Significant P ⩽ 0.05.

Table 3 Patients with cardiac events distribution in relation to the total non-obstructive plaque volumes.

Cardiac events	Total non-obstructive plaque volume/patient, mm³						Test of significance
	1 = (77–577) mm³		2 = (578–1078) mm³		3 = (1079–1662) mm³		P
	No.	%	No.	%	No.	%	
Symptoms driven revascularization	20	38.4	0	0.0	1	8	0.6
Non-fatal MI	30	57.6	9	100	11	92	0.04*
Cardiac deaths	2	3.8	0	0.0	0	0.0	0.9

* Significant P ⩽ 0.05.

Table 4 Patients with cardiac events distribution in relation to the total non-obstructive non-calcified plaque volumes.

Cardiac events	Total non-obstructive non-calcified plaque volume/patient, mm³						Test of significance
	1 = (67–567) mm³		2 = (568–1068) mm³		3 = (1069–1545) mm³		P
	No.	%	No.	%	No.	%	
Symptoms driven revascularization	4	19	0	0.0	0	0.0	0.6
Non-fatal MI	16	76	8	100	22	100	0.01*
Cardiac deaths	1	5	0	0.0	0	0.0	0.3

* Significant P ⩽ 0.05.

Table 5 Multivariate regression analysis of MDCT predictors as regards non-fatal MI.

Multivariate regression analysis of MDCT predictors	P	OR	HR (95% of CI)	
			Lower	Higher
Non obstructive non-calcified plaque volume	0.039[*]	1.003	1.07	1.999
Non obstructive calcified plaque volume	0.675	1.002	0.992	1.012
Total non obstructive plaque volume	0.078	1.002	0.999	1.005

P is significant if < 0.05, OR: odds ratio, HR: hazard ration, CI: confidence interval.
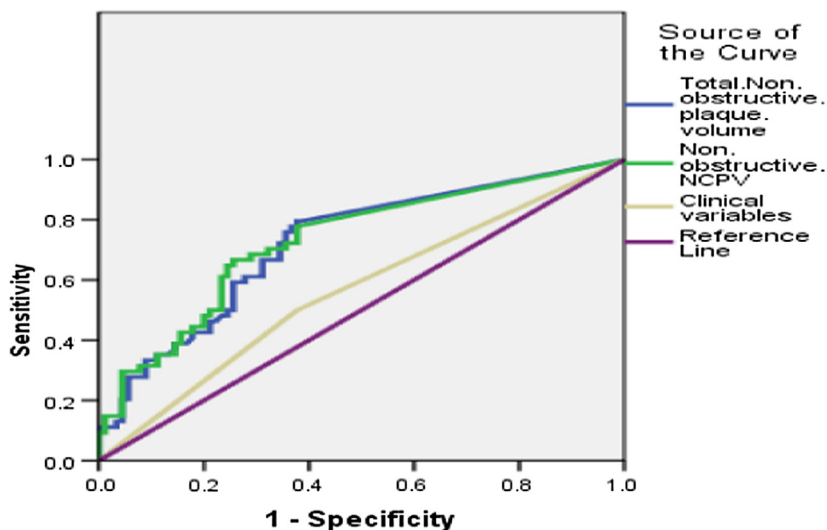[*] Significant P ⩽ 0.05.

Figure 1 ROC curve demonstrating the incremental ability of calculated mean non-obstructive NCP volume/patient and the total obstructive plaque volume/patient in predicting the development of non-fatal MI, and the area under the curve was 0.7 in comparison with the clinical variables in which the area under the curve was 0.5.
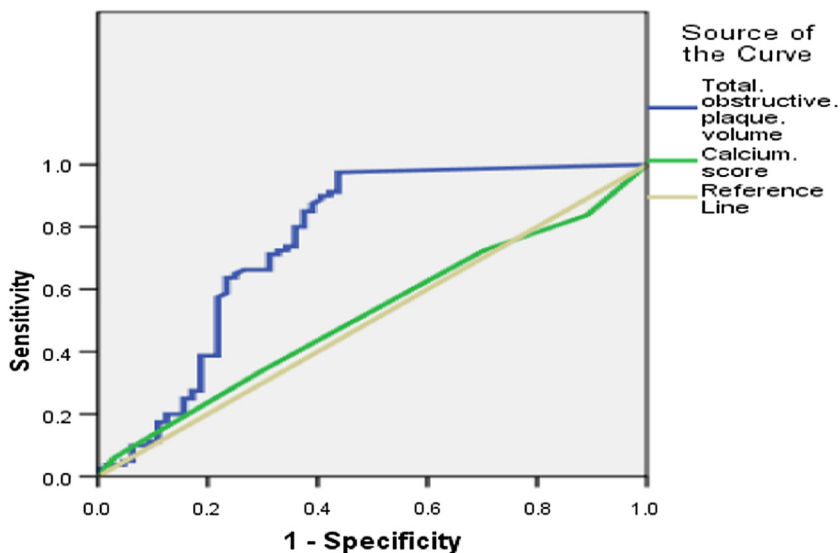

Figure 2 ROC curve demonstrating the incremental ability of calculated total obstructive plaque volume/patient in predicting cardiac events, and the area under the curve was 0.8 in comparison with the CACS in which the area under the curve is 0.5.
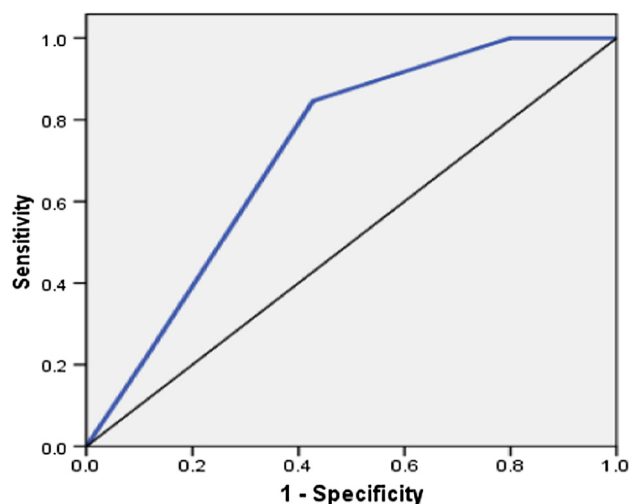
Figure 3 ROC curve demonstrating the incremental ability of CACS score in predicting cardiac deaths, and the area under the curve was 0.7.

The importance of identifying non-culprit vulnerable plaques has previously been demonstrated in patients with MI. Both Goldstein et al.[23] and Rioufol et al.[24] showed that patients with multiple complex lesions had worse clinical outcomes than patients with a single lesion. However, the clinical implications of detecting additional vulnerable plaques remain controversial, and imaging criteria to identify patients at risk are still being evaluated. Comparisons of MDCT with IVUS for the characterization of plaque morphology have shown an excellent agreement for the identification of non-calcified and calcified plaques.[13,25] Thus, our current understanding is driven by the recognition that these potentially life-threatening events are caused not only by vascular changes but also by alterations in the nature of the circulating blood and the myocardium. As such, these three components: vulnerable vessel, vulnerable blood, and vulnerable myocardium characterize what is today referred to as the vulnerable patient, who is defined as a patient with a high risk for the development of cardiovascular complications and higher risk for development of adverse cardiac events, and in our study we were focusing on vascular changes in form of detection of vulnerable plaque by MDCT for detecting vulnerable patients.

5. Study limitations

- Follow-up data were obtained from hospital discharge reports and phone calls which did not permit evaluation of new culprit lesions in the event group in comparison with our MDCT data. Larger studies with longer follow-up and
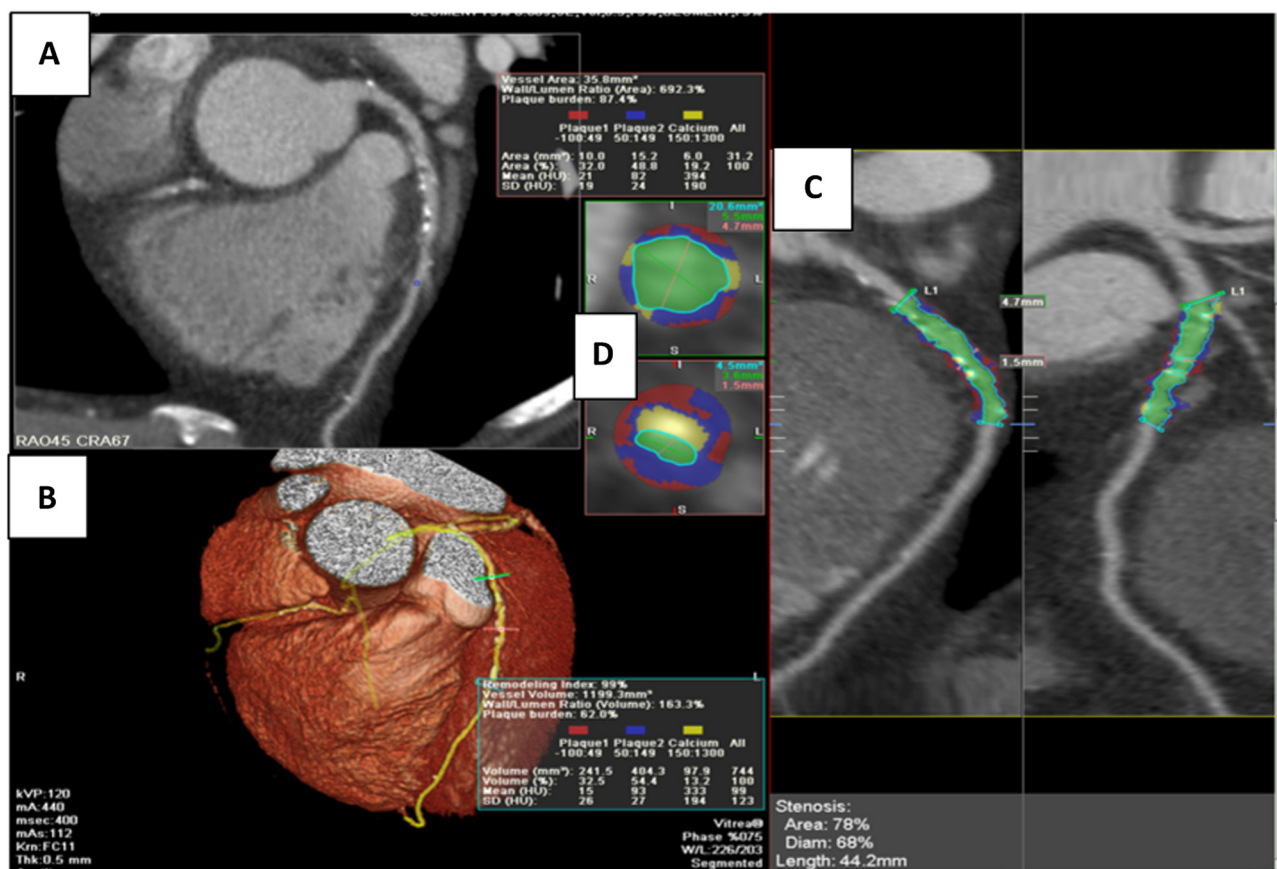

Figure 4 Case example (1): Volume rendering (A and B) Multiplanar reformatting (C) MSCT images showing obstructive plaque involving mid LAD, the plaque analysis tool applied to lesion in curved MPR and transverse images (C and D) the blue and red colors represent non-calcified components while the yellow represents calcified one in patient 243, who had elective PCI with one DES.
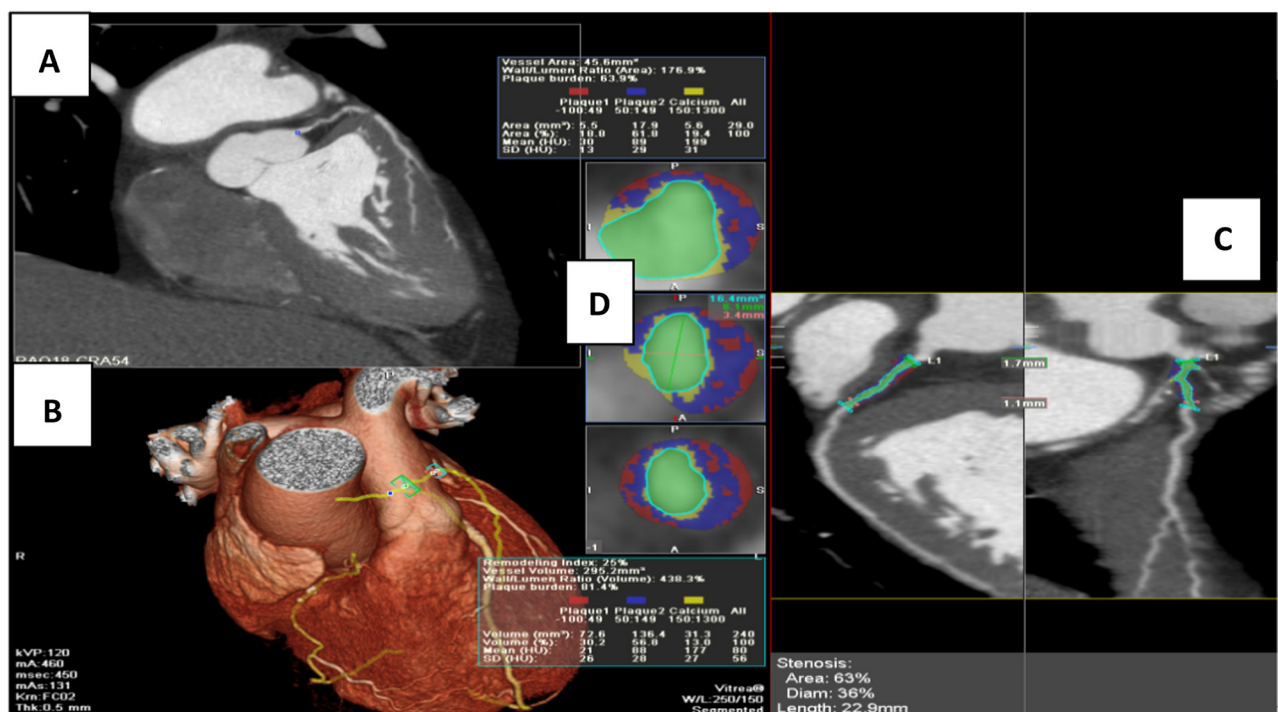
Figure 5 Case example (2): Volume rendering (A and B) and Multiplanar reformatting (C) MSCT images showing non-obstructive plaque involving proximal LCX, the plaque analysis tool applied to lesion in curved MPR and transverse images (C and D) the blue and red colors represent non-calcified components while the yellow represents calcified one in patient 640, who had ACS 3 month later on.

comparison with event-driven invasive coronary angiography are required to further establish MDCT criteria of plaque vulnerability.

- The prognostic value of MSCT in the present study was evaluated in patients presenting with a wide spectrum of different conditions, including patients with no previous history of CAD and patients with previous myocardial infarction. Accordingly, treatment strategies may have differed substantially within the studied population, and future studies will need to address the prognostic role of MSCT coronary angiography in more homogeneous patient populations.
- The lack of IVUS was a gold standard for plaque characterization, although previous studies demonstrated a strong correlation between MDCT and IVUS measurements for the assessment of the composition of coronary atherosclerotic plaque as well as for the measurement of plaque dimensions.

Conflict of interest

The authors declare that there is no conflict of interest.

6. Conclusion

MDCT is a non-invasive imaging modality with a prognostic utility in patients with known or suspected CAD by applying plaque characterization and it could identify vulnerable plaques by measuring the total amount of NCP in non-obstructive lesions which could be useful for detecting patients at risk of ACS and guiding new preventive therapeutic strategies. CAC was shown to be an independent predictor of mortality. On the other hand total amount of obstructive volume was shown to be an independent predictor of symptoms driven revascularization.

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