

RESEARCH

Open Access



# High risk plaque criteria by multislice coronary CT angiography in patients with stable vs. unstable coronary artery disease: analytic cross-sectional study

Asmaa Safa Oraby<sup>1\*</sup>, Reda Abdelsamie Alarabawy<sup>1</sup>, Taymour Mostafa Abd Alla<sup>2</sup> and Mohammed Mahmoud Dawoud<sup>1</sup>

## Abstract

**Background:** Coronary atherosclerotic plaques susceptible to rupture have distinct morphology in comparison to the stable one. Those with high lipid core overlaid by fibrous cap are considered to be the most vulnerable one triggering thrombosis and acute coronary syndrome. The purpose of this study was to evaluate the role of 320-row multidetector CT as a non-invasive imaging modality for detection of high-risk plaque criteria via semi-automated quantitative coronary plaque analysis.

**Results:** Fifty-eight atherosclerotic plaques were evaluated by multislice coronary CT angiography; 36 lesions were detected at unstable patient group and 22 lesions were detected at stable patient group. Non-calcified plaques were more prevalent at unstable patient group, whereas calcified lesions were more prevalent at stable patient group. There was strong correlation between plaque characteristics and clinical presentation represented by OR and 95% CI (NRS; OR 11.870 and 95% CI was 2.65–53.08, LAP; OR was 6.015 and 95% CI was 2.56–14.12). So, NRS and LAP are considered to be high-risk plaque criteria.

**Conclusion:** Multislice coronary CT angiography could non-invasively detect high-risk plaque criteria. NRS and LAP < 60 are considered to be high-risk plaque criteria suggesting their integration into coronary risk stratification, as well as an intensification of preventive measures.

**Keywords:** Low attenuation plaque, Remodeling index, Napkin ring, High-risk plaque, Hounsfield unit

## Background

Despite the development of anti-atherosclerotic medical therapies, many patients still continue to suffer from coronary events. This residual risk indicates the need for better risk stratification and additional therapies to achieve more reductions in cardiovascular risk. Currently, emerging research is focusing on improving coronary risk stratification tools by using CT angiography (CTA) parameters which recently showed high accuracy [1, 2].

The degree of coronary luminal narrowing is commonly used to guide diagnosis and therapeutic interventions in

clinical cardiology. However, CT imaging is not restricted to coronary luminography as it provides additional information on the coronary atherosclerotic plaque itself, including plaque morphology, plaque burden, and the degree of plaque remodeling [3, 4].

Increased lipid content, macrophage infiltration, intra-plaque hemorrhage, and thin-cap fibroatheroma (TCFA) and positive remodeling index are typical pathological features of vulnerable atherosclerotic plaques. In several instances, atheromatous plaques with these characteristics are non-flow limiting, but they are prone to rupture and produce acute coronary syndrome nevertheless [5, 6].

Such lesion events may contribute to a staccato pattern of plaque growth wherein intra-plaque hemorrhage induces sudden lesion expansion underlying rapid transition

\* Correspondence: [asmaasafa159@gmail.com](mailto:asmaasafa159@gmail.com)

<sup>1</sup>Radiodiagnosis & Medical Imaging Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Full list of author information is available at the end of the article

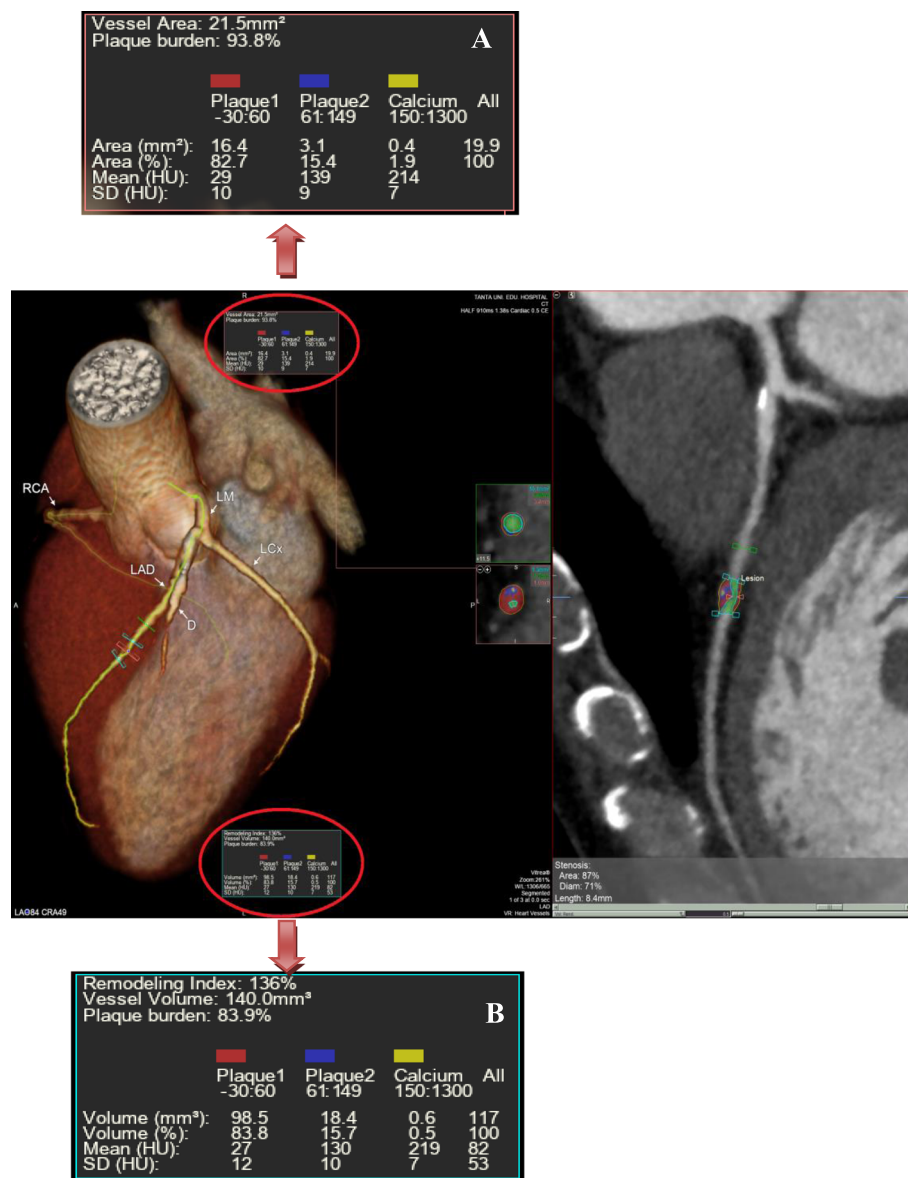
from a non-flow-limiting plaque to a flow-limiting stenosis; the resulting exertional angina is considered clinically stable once present for several months; it may in fact represent the effects of chronic unstable plaque events [4].

Clinical prospective studies confirmed that angiographically mild lesions may be responsible for adverse cardiovascular events at long-term follow-up, especially if a TCFA causing plaque burden (PB) 70% was identified with intravascular ultrasound evaluation [7].

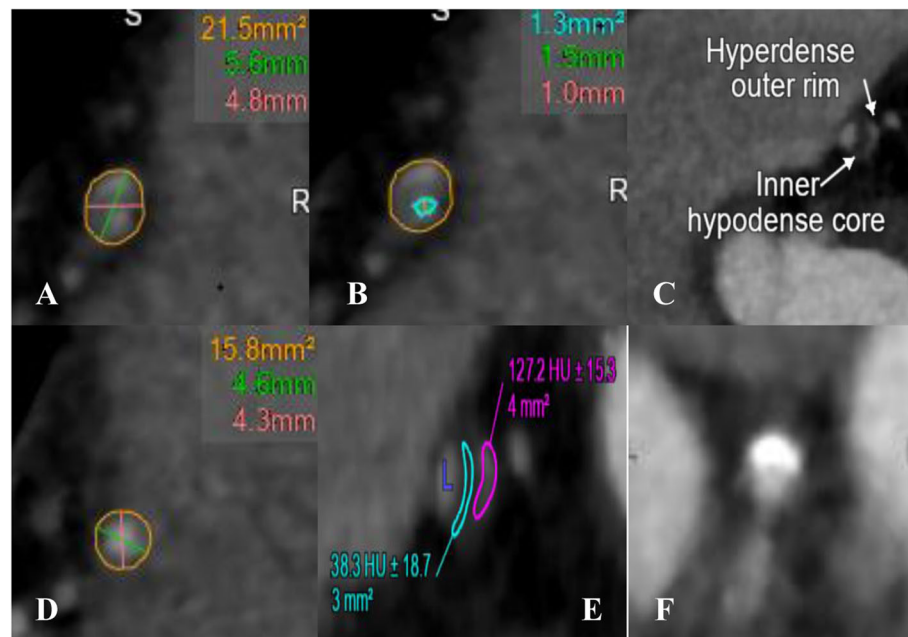
## Methods

### Study design and population

Analytic cross-sectional study was conducted on two groups of patients; the first group included patients with stable coronary artery disease including patients with atypical chest pain and those with stable angina (class I angina; anginal pain with prolonged exertion relieved by rest and class II angina; slight limitation of ordinary activity were included as candidates for stable coronary



**Fig. 1** Cross-sectional measurements at the site of the maximal plaque burden at the point of the lesion marked red. **a.** Plaque components; area represented the area of all pixels on the cross-section corresponding to the plaque component. Average HU; the mean value of the intensity of the pixels on the cross-section corresponding to the plaque component. Standard deviation; the standard deviation of the intensity of the pixels on cross-section corresponding to the plaque component. Volume measurements of the whole plaque at highlighted blue marks. **b** Calculated for each defined lesion; remodeling index and plaque components; remodeling index is the ratio of the vessel area at the point of the lesion marked red to the proximal reference area marked green



**Fig. 2** Plaque characterization by CCTA; positive remodeling index was obtained from the ratio of lesion plaque area (**a**) and reference lumen area at **d**; in the case represented  $RI = 21.5 \text{ mm}^2 / 15.8 \text{ mm}^2 = 1.36$ . Plaque burden was obtained by the ratio of lesion plaque area (**a**) minus lesion lumen area at **b**; in the case represented  $PB = (21.5 \text{ mm}^2 - 1.3 \text{ mm}^2) / 21.5 \text{ mm}^2 = 0.939$ . In **c**, napkin ring lesion is illustrated with inner hypodense core and hyper dense outer rim. In **e**, ROI was applied on NR lesion and revealed inner LAP ( $38.3 \text{ HU} \pm 18.7$ ) and outer hyperattenuating rim ( $127.2 \text{ HU} \pm 15.3$ ). In **f**, stable calcified lesion (non-high-risk atherosclerotic plaque) is illustrated

artery disease). The second group including patients with unstable patient group including those with class III angina; marked limitation of ordinary daily activity and class IV; chest discomfort on any daily activity were included as candidates for unstable coronary artery disease, and patients who had experienced major adverse cardiac events (non-ST segment elevated myocardial infarction (NSTEMI) or (STEMI) that relieved medically (diagnosed by referring doctor, follow up discharge card, or patients admitted to coronary care unit)). The study duration was 1 year from March 2018 to March 2019. Exclusion criteria were patient who is clinically unstable to withstand the duration or technique of CT examination, patients with unstable angina that needs urgent

intervention, high coronary calcium score (more than 400), pregnancy, and patient with previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG).

Invasive coronary angiography was performed after MDCT later on by the referring cardiologist as a gold standard for comparison of CT results.

#### MDCT angiography of coronary arteries

##### Scan protocol

All patients were scanned using 320-row MDCT scanner (Aquillion One, Toshiba Medical Systems, Otawara, Japan). Initial scanogram was obtained first to plan the scanning range of coronary CTA, then non-contrast calcium scoring.

**Table 1** Comparison between the two patients groups according to plaque burden and degree of stenosis

Variable	Total (n = 58)	Unstable group (n = 36)	Stable group (n = 22)	T	P
Plaque burden					
Min.–Max.	45.20–100.0 (%)	45.20–100.0 (%)	47.80–99.70 (%)	2.954*	0.004*
Mean ± SD.	79.04 ± 14.87	82.35 ± 12.35	70.62 ± 17.07		
Median	79.80	79.95	70.80		
Stenosis					
Min.–Max.	32.0–94.0	38.0–93.0	32.0–94.0	1.489	0.141
Mean ± SD.	56.49 ± 15.95	58.48 ± 12.72	53.50 ± 19.63		
Median	54.0	56.0	47.0		

**Table 2** Correlation between remodeling index with plaque burden and stenosis in total sample ( $n = 58$ )

	Remodeling index (R.I)	
	$r_s$	$P$
Plaque burden	0.218	0.019*
Stenosis	-0.229	0.016*

$r_s$  Spearman coefficient, R.I remodeling index

\*Statistically significant at  $P \leq 0.05$

Acquisition parameters: 0.35 s gantry rotation time, variable mA selected automatically by the scanner according to patient body habitus (range 300–580 mA), variable kV according to body habitus. A breathing exercise was performed to measure the heart rate during breath holding period of 10 s after which the scanner automatically adjusted the exposure window settings for optimal temporal resolution. Prospective ECG-triggered acquisition was performed routinely for patients with heart rate below 60 bpm exposing only 70–80% of R-R interval. For those with higher heart rate, acquisition was done by widening the exposure window to include 30–80% of R-R interval. During the rest of R-R interval, X-ray was turned off completely by the scanner to reduce radiation exposure.

#### Image reconstruction

Images were reconstructed with a slice thickness of 0.5 mm with 0.3 mm interval using soft and sharp reconstruction kernel at 75% of R-R interval and also at the best diastolic phase. The best systolic phase was reconstructed also if the exposure window included 30–80% of R-R interval.

#### Post processing

The reconstructed images were transferred to a workstation (Vitrea FX, Vital Images, USA) to review axial images and also to obtain multiplanar reformatted images at sagittal and coronal planes. Also, maximum intensity projection images, 3D volume rendered images, semi-transparent 3D volume rendered images, and curved planar reformations were obtained for detailed assessment of coronary plaques.

#### Image analysis

All coronary computed tomography angiography (CCTA) scans were evaluated for the presence of non-valuable segments. Coronary arteries were divided into

17 segments according to American Heart Association Classification. Coronary plaques were defined as structures at least 1 mm<sup>2</sup> within and/or adjacent to artery lumen, clearly distinguishable from the vessel lumen and surrounded by pericardial tissue.

Quantitative CTA lesion analysis was performed on all plaques > 25% by automated software that automatically segments vessel margins, separate different plaque components by using attenuation thresholds (30–60 for lipid plaque, 61–149 for fibrous plaque and 150–1300 for calcium) and provide color map of plaque compositions. CT density was screened with pixels and Hounsfield unit (HU) was recorded; the area of pixels with predetermined attenuation threshold was calculated via semi-automated quantitative analysis and plaque attenuation is represented with mean and standard deviation (Fig. 1).

Degree of stenosis was defined as referential diameter–luminal diameter/referential diameter. In turn, referential diameter was defined as the diameter located in the proximal normal vessel or distal normal vessel if the lesion is ostial. The stenosis severity is graded as minimal < 10%, mild  $\leq 49\%$ , moderate 50–69%, severe  $\geq 70\%$ , subtotal > 90%, and total occlusion per coronary segment (AHA-modified 17 segment classification).

All plaques > 25% stenoses were analyzed for morphologic features. Parameters analyzed including plaque burden of the whole plaque and at area of maximal narrowing = (lesion plaque area - lesion lumen area/lesion plaque area), low attenuation plaque (LAP); CT density was recorded with quantitative CTA analysis and area of region of interest (ROI) (LAP is defined as hypo-attenuation with CT density < 150 HU). Napkin ring sign (NRS) was defined as an outer high-density rim with inner hypodense area not adjacent to calcification and present on minimum of two adjacent axial 1 mm slices; remodeling index (R.I) was calculated as the ratio of maximal cross-sectional vessel area, including the plaque and the lumen and its closest proximal (or distal in ostial lesion) normal reference vessel area and spotty calcification was defined as calcification < 3 mm (Fig. 2).

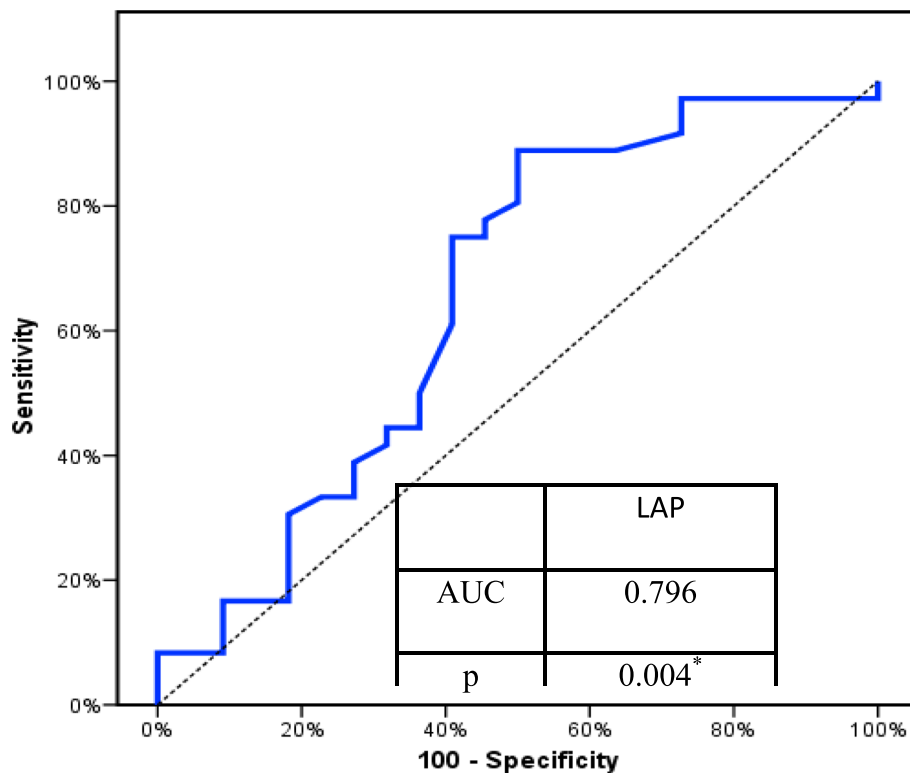
#### Statistical analysis

Statistical analysis was performed using SPSS software. Qualitative data were described using number and percent. Quantitative data were described using range

**Table 3** Comparison between the two studied groups according to plaque type

Plaque type	Total ( $n = 58$ )		Unstable group ( $n = 36$ )		Stable group ( $n = 22$ )		$\chi^2$	$P$
	No.	%	No.	%	No.	%		
Calcified	14	24.1	3	8.3	11	50.0	25.893*	<0.001*
Mixed	13	22.3	6	16.7	7	31.8	3.330	0.142
Non calcified	31	53.4	27	75.0	4	18.2	35.435	<0.001*

$\chi^2$  Chi-square test



**Fig. 3** ROC curve for LAP to detect unstable cases

(minimum and maximum), mean, standard deviation, and median. Significance of the obtained results was judged at the 5% level.

Chi-square test for categorical variables was used to compare between different groups. Student *t* test for normally distributed quantitative variables was used to compare between two studied groups. Mann-Whitney test for abnormally distributed quantitative variables was used to compare between two studied groups.

Receiver operating characteristic curve (ROC) generated by plotting sensitivity (TP) on Y axis versus 1-specificity (FP) on X axis at different cut off values. The area under the ROC curve denotes the diagnostic performance of the test. Area more than 50% gives acceptable performance and area about 100% is the best performance for the test.

The ROC curve allows also a comparison of performance between two cutoff values.

## Results

### Clinical characteristics

The study included 30 patients: 18 were with stable coronary artery disease and 12 were with unstable coronary artery disease, referred to rule out coronary artery disease; among those, 19 were males while 11 patients were females. The mean age population was  $53.7 \pm 8.4$  years.

### CTA stenosis severity and plaque burden

Plaque burden significantly increased at unstable patient group and showed good statistical performance ( $P = 0.004$ ).

**Table 4** Characterization of non-calcified plaque as regard plaque attenuation of both studied patient groups

	Total	Unstable group (n = 36)	Stable group (n = 22)	Test of sig.
CT density (HU)	$36.2 \pm 31.3$	$23.8 \pm 22.7$	$48.6 \pm 48$	$<0.001^{*a}$
Quantitative analysis (QA)	$71.96 \pm 30.35$	$35.12 \pm 22.7$	$108.8 \pm 42$	$<0.001^{*a}$
Area ROI				
LAP < 30 (QA) n, %	3 (5.6%)	2 (5.5%)	1 (4%)	$^{FE}P = 0.922^b$
LAP < 60 (QA) n, %	32 (55%)	29 (80.5%)	3 (13.6%)	$<0.001^{*b}$
LAP < 90 (QA) n, %	11 (18.3%)	4 (11.1%)	7 (31.8%)	$<0.001^{*b}$

HU Hounsfield unit, LAP low attenuation plaque

<sup>a</sup>t test

<sup>b</sup> $\chi^2$  test



Contrary, there was no significant difference between two patient groups as regard degree of stenosis) (Table 1). Significant positive relation between plaque burden and remodeling index ( $r_s$  0.218,  $P = 0.019$ ) was noticed. However, there was significant negative relation between degree of stenosis and remodeling index ( $r_s$  - 0.229,  $P = 0.016$ ) (Table 2).

### Plaque types

Coronary artery disease instability significantly correlated with increasing non-calcified component ( $P < 0.001$ ). However, calcified plaques were more prevailing at stable patient group (Table 3).

### Quantitative high-risk plaque analysis

The cumulative CT number is significantly lower at the unstable patient group. However, the cumulative CT number was higher at the stable group ( $P = 0.001$ ). By quantitative analysis, LAP < 60 was more prevalent at unstable group ( $P \leq 0.001$ ) and LAP < 90 was more prevalent at the unstable group ( $P \leq 0.001$ ). By receiver operator characteristic curve (ROC curve), LAP < 60 is identified as optimal cut off value (sensitivity 80.5%, specificity 86.1%) to detect unstable cases (AUC = 0.796,  $P = 0.004$ ) (Fig. 3, Table 4).

Coronary plaque characteristics significantly correlated with coronary artery disease instability considering LAP < 60 HU ( $P \leq 0.001$ ) and NRS ( $P \leq 0.001$ ). However, there was no significant difference between two patient groups as regard R.I at two different cutoff values > 1.1 and > 1.4 (Table 5).

The statistical relationship between plaque characteristics and clinical presentation was represented by odds ratio (OR) and 95% confidence interval (CI). As regard NRS, OR was 11.870 and 95% CI was 2.65–53.08 and as regard LAP < 60, OR was 6.015 and 95% CI was 2.56–14.12. So, NRS and LAP < 60 HU could be considered

**Table 6** Comparison between high risk plaque criteria as regard sensitivity, specificity, and OR

HRP criteria	Sensitivity	Specificity	OR	95% CI	P value
NRS	36.1	95.4	11.870*	2.65–53.08	<0.001
LAP < 60	80.5	86.3	6.015*	2.56–14.12	<0.001

high-risk plaque criteria. Napkin ring sign (NRS) has the best specificity (95.4%), but lower sensitivity (36.1%) which is due to its low prevalence. Low attenuation plaque (LAP < 60) has moderate sensitivity (80.5) and specificity (86.3) (Table 6).

Atherosclerotic lesions with positive napkin ring sign were more prevalent at proximal LAD, tend to be non-obstructive, and tend to be positively remodeled. Those lesions characterized by inner hypodense core with density  $43.93 \pm 8.39$  HU and hyper dense outer rim with density  $127.93 \pm 12.58$  HU (Table 7).

### Discussion

The concept of high-risk plaque (HRP) criteria has recently emerged as specific indicators for ‘vulnerable plaque’ which may allow an early identification of patients at risk for future major adverse cardiac event. Thus, they could further sharpen risk calculators. However, little prospective outcome data are available to date for enrolling small sample size or collecting short- or mid-term outcomes [8] (Figs. 4, 5, 6, and 7).

Besides, a variety of different HRP criteria have been proposed: the napkin-ring (NR) sign, a pathohistological correlate for advanced/vulnerable atherosclerotic lesions, positive remodeling and spotty calcification (SC), and low-attenuation plaque (LAP) with < 30 Hounsfield units (HU) measured by plaque ‘area ROI’ (region of interest) or by ‘pixel lens’ screening techniques. In contrast, ex vivo

**Table 5** Comparison between two patient groups as regard variable plaque characteristics

	Total (n = 58)		Unstable group (n = 36)		Stable group (n = 22)		$\chi^2$	P
	No.	%	No.	%	No.	%		
NRS	14	25.00	13	36.1	1	4.5	14.860*	<0.001* <sup>a</sup>
LAP < 60	32	55.17	29	80.5	3	13.6	49.44	<0.001* <sup>a</sup>
SC	6	10.34	6	22.2	0	0.0	11.342*	0.001* <sup>a</sup>
R.I > 1.1	17	29.3	11	30.5	6	35.5	0.2916	0.08 <sup>a</sup>
R.I > 1.4	8	22.4	4	11.1	4	18.2	0.7301	0.3928 <sup>a</sup>
Calcium score								
Min.–Max.	6.0–348.0		22.0–348.0		6.0–259.0		$U = 318.0$	0.272 <sup>b</sup>
Mean $\pm$ SD.	76.36 $\pm$ 77.13		90.58 $\pm$ 92.76		65.69 $\pm$ 62.42			
Median	52.0		66.0		50.0			

NRS napkin ring sign, LAP low attenuation plaque, SC spotty calcification, R.I remodeling index, p p value

\*Statistically significant at  $P \leq 0.05$

<sup>a</sup> $\chi^2$  test

<sup>b</sup>Mann-Whitney test

**Table 7** Characterization of lesions with positive napkin ring sign (NRS)

Napkin ring sign (NRS) ( <i>n</i> = 14)		
Patient groups		
Unstable group		Stable group
13 (92.8)		1 (7.2%)
Site		
Proximal LAD ( <i>n</i> , %)		Mid LAD ( <i>n</i> , %)
8 (57.2%)		6 (42.8%)
Degree of stenosis		
Non obstructive ( <i>n</i> , %)		Obstructive ( <i>n</i> , %)
13 (92.3%)		1 (7.75%)
Remodeling index (R.I)		
R.I > 1.1 ( <i>n</i> , %)		R.I < 1.1 ( <i>n</i> , %)
12 (89.3%)		2 (10.7%)
Hypo dense core		
Min. Max.	32.0–59.0	120.0–150.0
Mean ± SD.	43.93 ± 8.39	127.93 ± 12.58
Median	44.0	129.50

studies identified LAP < 60 and < 90 HU as optimal cut-offs for lipid-core plaque [9, 10].

First, our analytic cross-sectional study identified LAP < 60 HU and NR sign are the most powerful high risk criteria. Other applied threshold (LAP < 30 and LAP < 90 were less. Additionally, HRP criteria were at higher strength than SC and stenosis severity which is concordant with Yang et al. [11] stating that there was no significant difference between stable and unstable group concerning degree of stenosis. Contrary, plaque burden exhibited better statistical performance than stenosis severity ( $P = 0.004$ ) which was in line with study encountered by Nakazato et al. [12]; they

assumed that aggregate plaque volume which represent plaque burden improve identification of ischemic lesion.

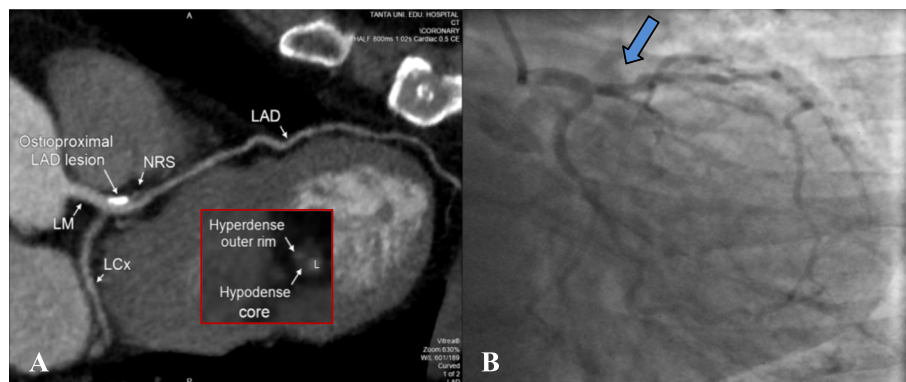
Currently, our study revealed significant positive relationship between remodeling index and plaque burden ( $r_s = 0.218$ ,  $P = 0.019$ ). On the other hand, there is a significant negative relationship between remodeling index and degree of stenosis ( $r_s = -0.229$ ,  $P = 0.016$ ). As the coronary vessel expands, plaque enlargement occurs with delayed onset of luminal narrowing. These findings agreed with well-designed systematic review established by Kolossváry et al. [13]; they reported that atherosclerotic plaques initially tend to grow outward leaving lumen integrity unchanged. This could explain why plaque burden performed better in our study.

Second, we found increasing non-calcifying plaque component at the unstable patient group compared to the stable group ( $P \leq 0.001$ ). However, calcified plaques were more prevailing at the stable. Our findings are in line with study conducted by Feuchtner et al. [14]. They observed increasing non-calcified component in patient who had experienced major adverse cardiac event (MACE).

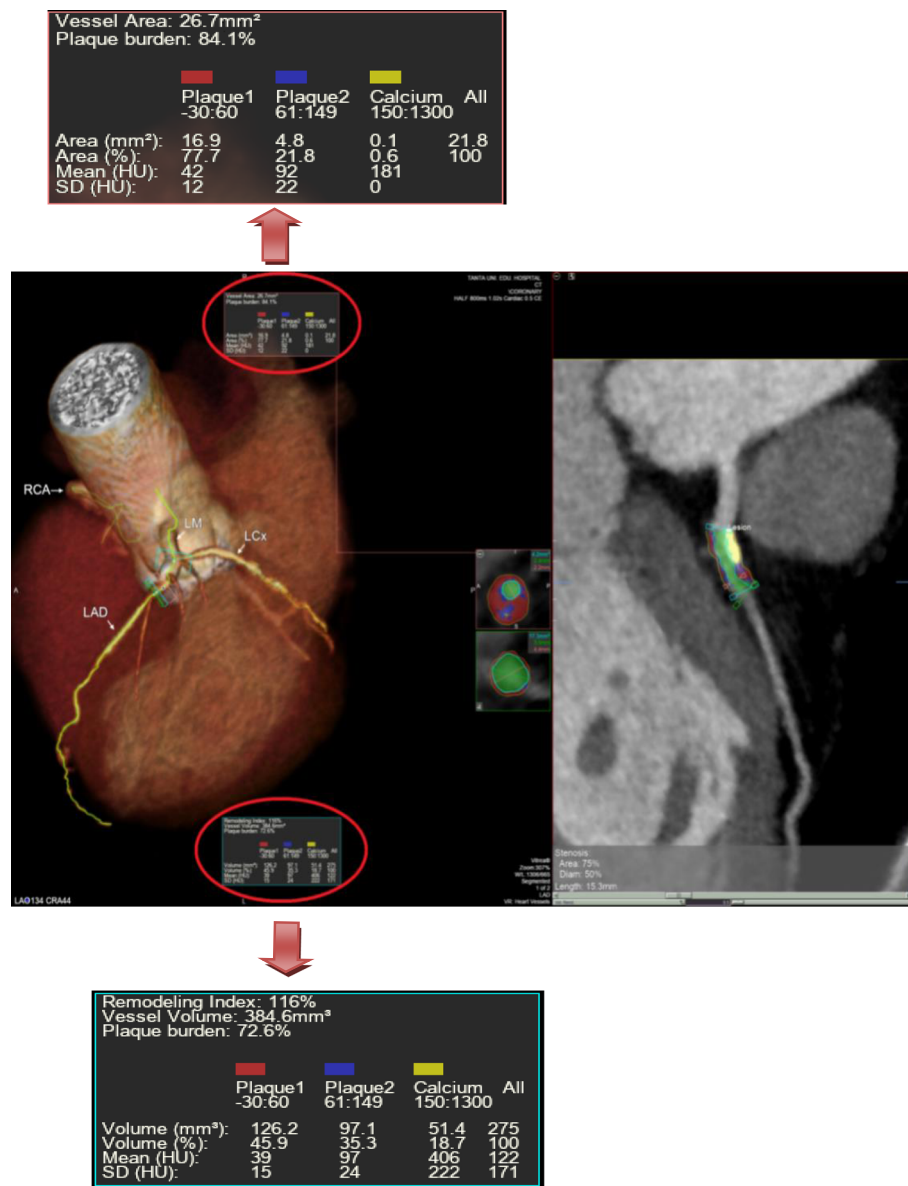
Third, we identified high-risk plaque criteria as NRS and LAP < 60 HU LAP < 60 (LAP OR 6.015 and 95% CI 2.56–14.12), NRS (OR 11.870 and 95% CI 2.65–53.08) which is in line with the study encountered by Feuchtner et al. [14]; they reported that NRS and LAP < 60 are the most powerful predictors of major adverse cardiac events.

We proposed cutoff value for LAP < 60 as optimal threshold to detect unstable cases; AUC was 0.796 ( $P = 0.004$ ) and 60 HU (sensitivity 80.5%, specificity 86.3%) which is closely in line with the aforementioned same study. They proposed cutoff 63HU as optimal threshold; AUC was 0.89 ( $P \leq 0.001$ ) and 63 HU (sensitivity 89.2%, specificity 82.3%).

In different circumstances, a prospective mid-term outcome study was done by Motoyama et al. [15]. The



**Fig. 4** A 55-year-old male patient, hypertensive with dyslipidemia presented with recurrent attacks of typical chest pain on usual daily activities (Class III). **a** Curved multiplanar reformatted image showed moderate ostio-proximal LAD lesion exerted by mixed plaque, cross-sectional analysis of non-calcified component showed NRS with hypodense core and hyper dense outer rim. **b** Invasive coronary angiography RAO CAU view showed ostio-proximal LAD lesion (blue arrow) with moderate degree of stenosis



**Fig. 5** Semi-automated quantitative coronary plaque analysis with 3D volume rendered image and cMPR images revealed mixed plaque (calcium = 18.7%) with predominant non calcified portion (81.3%). Plaque characterization at area of maximal plaque burden revealed high-risk plaque characteristics; positively remodeled mixed plaque with predominate non calcified portion (R.I = 1.16) with plaque burden > 0.7 (P.B 84.1%), NRS (inner hypodense lipid core representing 77.7% of plaque area, low CT number  $42 \pm 12$  and hyper dense fibrotic outer rim, high CT number  $92 \pm 22$  HU

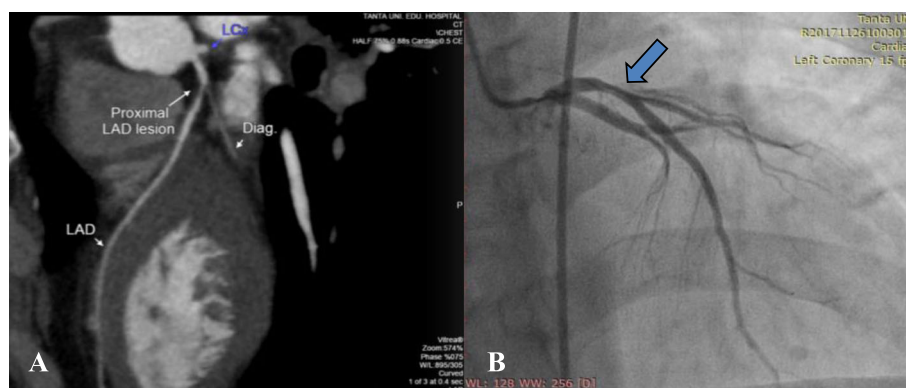
study was encountered on larger sample size and defined high-risk plaque based on LAP < 30 as an independent predictor of major adverse cardiac event which disagreed with our findings; the criterion LAP < 30 had very low prevalence in unstable patient group. Further, the criterion LAP < 30 is based on only culprit lesion analysis that caused acute coronary syndrome, thus thrombotic apposition on the studied lesion that is characterized by lower CT densities. This may explain why LAP < 60 performed better in our study where all lesions are studied.

Liu et al. [16] suggested that both cutoff values < 30 and < 60 were considered to be high-risk plaque features.

Additionally, our findings were in line with an ex vivo study done by Schlett et al. [17], showing LAP < 60 by ROI as valuable marker for lipid core plaque detection.

We observed increasing the number of plaques with increasing CT density indicating more stable fibrous plaque at the stable patient group. Similarly, long-term follow up study done by Feuchtnner et al. [14] reported





**Fig. 6** A 26-year-old male patient, smoker presented with acute attack of typical severe persistent chest pain admitted to Tanta University educational hospital coronary care unit, diagnosed as NSTEMI and controlled medically, then referred to rule out coronary artery disease. **a** Curved multiplanar reformatted image showed proximal LAD lesion graded as moderate stenosis. **b** Invasive coronary angiography RAO CRA view showed moderate proximal LAD lesion (blue arrow)

more stable fibrous plaques in patients who remained MACE free. In vivo studies utilizing optical coherence tomography as standard reference demonstrated that high-risk plaques have lower CT numbers as compared to stable lesions (35–45 vs. 62–79 HU;  $P \leq 0.001$ ) [12].

Remodeling index was higher in unstable patient group but not significant ( $P = 0.08$  and  $0.39$  at  $R.I > 1.1$  and  $1.4$  respectively) due to high prevalence of calcified and mixed plaques with predominate calcified portion that were usually associated with positive remodeling. Those findings agreed with what was suggested by Feuchtner et al. [14]; they stated that remodeling index (R.I) was higher in patients who had experienced major adverse cardiac events but no significant predictive due to inclusion of calcified nodules which appear larger on CTA (positively remodeled).

Our study revealed that NRS has excellent specificity to detect unstable cases (95.4%) which is matched with Liu et al. [16]. They stated that NRS had the best specificity to identify advanced lesions (98.9%, CI 97.6–100%). Notably, its low prevalence limits its sensitivity which is in line with study done by Feuchtner et al. [14]. They stated low prevalence of napkin ring sign in patient with major adverse cardiac event.

Napkin ring sign is caused by difference in CT attenuation between its lipid-rich core corresponding to central low attenuation area and fibrous plaque corresponding to rim of high CT attenuation. The current study showed that the CT number of the inner hypo dense core  $43.93 \pm 8.39$  HU, while the CT number of hyper dense outer rim  $141.93 \pm 12.58$  HU which is matched with the study done by Maurovich-Horvat et al. [9]. They stated that the average CT number of the hypodense core approximately 50–60 HU and higher CT number of the outer rim representing significant amount of fibrous tissue.

Our study was different from those who defined the napkin ring sign as higher CT attenuation of the outer ring than the inner and not more than 130 HU [18, 19].

We set higher threshold for the outer rim ( $< 150$ ) while lower CT number for inner core ( $< 60$ ); the outer rim may contain dense fibrous tissue and micro calcification which may lead higher HU than 130 [20].

Additionally, napkin ring sign lesions were usually associated with positive remodeling with high tendency to be non-obstructive as well as special distribution at left anterior descending (LAD). Consistently, these findings are in line with study done by Kashiwagi et al. [19]. They reported that napkin ring sign were more prevalent at left anterior descending (LAD) especially at its proximal segment.

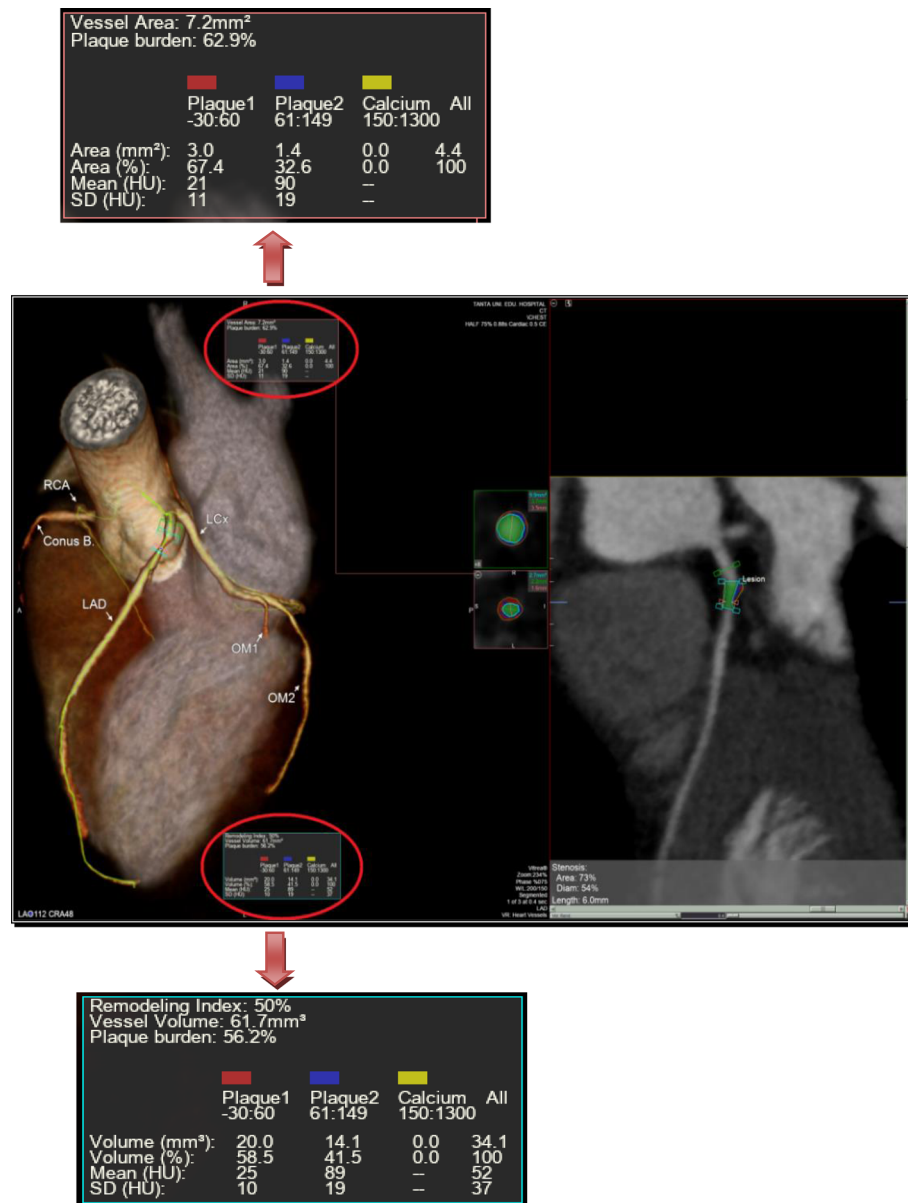
Seifarth et al. [20] investigated the histological correlate of the napkin ring sign and concluded the detection of this specific plaque attenuation linked to lipid core, the size of the plaque, and the vessel area as measured in histology.

As regard spotty calcification (SC) criterion, it was prevalent only at the unstable patient group which hinders assessment of its risk despite being statistically significant ( $P = 0.001$ ).

Up till now, high-risk plaques criteria are still research point with no standardization or verification. However, intensification of preventive measures is recommended in patients with high-risk criteria. Statins have proven beneficial effect in reducing mortality even in reducing mortality even in patients with non-obstructive CAD on CTA, related to stabilizing effect on lipid-rich fibroatheroma by increasing dense fibro calcified plaque component [21].

#### Study limitations

- The lack of intravascular ultrasound as reference to assess plaque morphology could be considered a



**Fig. 7** Semi-automated quantitative coronary plaque analysis with 3D volume rendered and cMPR images of the previously mentioned lesion revealed non-calcified plaque (calcium = 0%). Its length 5 mm, graded as moderate stenosis (45%) in relation to proximal referential diameter. Plaque characterization at area of maximal plaque burden revealed LAP < 30 (HU 21 ± 11) represented 67.4% of plaque area (high-risk plaque criterion)

limitation, although previous studies have shown strong correlation between multislice CT and intravascular ultrasound (IVUS) measurements of the composition of coronary atherosclerotic plaques.

- We did not measure intraluminal CT density which influences plaque attenuation and may show minor deviation along individual contrast bolus transient time.
- Spotty calcification was a common finding within outer high attenuation rim of napkin ring sign, so its prevalence may be overestimated.

- Another drawback of this study is the fact that the patient population of both patient groups was still rather small.

### Conclusion

Multislice coronary CT angiography could non-invasively detect high-risk plaque criteria. NRS and LAP < 60 are considered to be high-risk plaque criteria suggesting their integration into coronary risk stratification, as well as an intensification of preventive measures.

## Abbreviations

CABG: Coronary artery bypass graft; CCTA: Coronary computed tomography angiography; CTA: CT angiography; HRP: High-risk plaque; HU: Hounsfield unit; LAP: Low attenuation plaque; NR: Napkin ring; PCI: Percutaneous coronary intervention; RI: Remodeling index; ROI: Region of interest; SC: Spotty calcification

## Acknowledgment

Not applicable.

## Authors' contributions

ASO have the idea of research, follow up cases, writing, publishing, and analysis the data. RAA have the final revision and supervision. TMA refer the cases and adjust any clinical problem and feedback of patients. MMD meticulous aid in writing. All authors read and approved the final manuscript.

## Funding

Not applicable.

## Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

This study was conducted according to the guidelines of the ethics committee of our university and was approved by our institutional review board. All patients gave written informed consent to be imaged in our study. Ethics committee's reference number (N/A).

## Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

## Competing interests

The authors declare that they have no competing interests.

## Author details

<sup>1</sup>Radiodiagnosis & Medical Imaging Department, Faculty of Medicine, Tanta University, Tanta, Egypt. <sup>2</sup>Cardiology Department, Faculty of Medicine, Tanta University, Tanta, Egypt.

Received: 15 August 2019 Accepted: 8 January 2020

Published online: 27 January 2020

## References

1. Honda S, Kataoka U, Kanaya T et al (2016) Characterization of coronary atherosclerosis by intravascular imaging modalities. *Cardiovasc Diagn Ther* 6: 386–381
2. Min JK, Dunning A, Gransar H et al (2015) Medical history for prognostic risk assessment and diagnosis of stable patients with suspected coronary artery disease. *Am J Med* 128:871–878
3. Mark DB, Berman DS, Budoff MJ et al (2010) Expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation* 121:2509–2543
4. Motoyama S, Kondo T, Sarai M et al (2007) Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol* 50:319–326
5. Virmani R, Burke AP, Farb A et al (2006) Pathology of the vulnerable plaque. *J Am Coll Cardiol* 47:C13–C18
6. Finn AV, Nakano N, Narula J et al (2010) Concept of vulnerable/unstable plaque. *Arterioscler Thromb Vasc Biol* 30:1282–1292
7. Calvert PA, Obaid DR, O'Sullivan M et al (2011) Association between IVUS findings and adverse outcomes in patients with coronary artery disease. *J Am Coll Cardiol Imaging* 4:894–901
8. Puchner SB, Liu T, Mayrhofer T et al (2014) High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. *J Am Coll Cardiol* 64:684–692
9. Maurovich-Horvat P, Schlett CL, Alkahlidi H et al (2012) The napkin-ring sign indicates advanced atherosclerotic lesions in coronary CT angiography. *JACC Cardiovasc Imaging* 5:1243–1252
10. Schlett CL, Ferencik M, Celeng C et al (2013) How to assess non-calcified plaque in CT angiography: delineation methods affect diagnostic accuracy of low-attenuation plaque by CT for lipid-core plaque in histology. *Eur Heart J Cardiovasc Imaging* 14:1099–1105
11. Yang X, Gai L, Dong W et al (2013) Characterization of culprit lesions in acute coronary syndromes compared with stable angina pectoris by dual source computed tomography. *Int J Card Imaging* 29:945–953
12. Nakazato R, Shalev A, Doh JH et al (2013) Aggregate plaque volume by coronary computed tomography is superior and incremental to of luminal narrowing for diagnosis of ischemic lesions of intermediate stenosis severity. *J Am Coll Cardiol* 62:460–467
13. Kolossváry M, Szilveszter B, Merkely B et al (2017) Plaque imaging with CT, a comprehensive review on coronary CT angiography based risk assessment. *CardiovascDiagnTher* 7:489–506
14. Feuchtnr G, Kerber J, Burghard P et al (2017) The high-risk criteria low-attenuation plaque <60 HU and the napkin ring sign are the most powerful predictors of MACE: a long-term follow-up study. *Eur Heart J Cardiovasc Imaging* 18:772–779
15. Motoyama S, Ito H, Sarai M et al (2015) Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol* 66:337–346
16. Liu T, Maurovich-Horvat P, Mayrhofer T et al (2018) Quantitative coronary plaque analysis predicts high risk plaques morphology on coronary computed tomography: results from the ROMICAT II trial. *Int J Card Imaging* 34:311–319
17. Schlett CL, Maurovich-Horvat P, Ferencik M et al (2013) Histogram analysis of lipid-core plaques in coronary computed tomographic angiography: ex vivo validation against histology. *Investig Radiol* 48:646–653
18. Otsuka K, Fukuda S, Tanaka A et al (2013) Napkin ring of CT coronary angiography for the prediction of acute coronary syndrome. *JACC Cardiovasc Imaging* 6:448–457
19. Kashiwagi M, Tanaka A, Shimada K et al (2013) Distribution, frequency and clinical implication of napkin ring sign assessed by multidetector computed tomography. *J Cardiol* 61:399–403
20. Seifarth H, Schlett CL, Nakano M et al (2012) histopathological correlation of the napkin ring sign plaque in coronary CT angiography. *Atherosclerosis* 224:90–96
21. Auscher S, Heinsen L, Nieman K et al (2015) Effects of intensive lipid-lowering therapy on coronary plaques composition in patients with acute myocardial infarction: assessment with serial coronary CT angiography. *Atherosclerosis* 241:579–587

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Submit your manuscript to a SpringerOpen<sup>®</sup> journal and benefit from:**

- Convenient online submission
- Rigorous peer review
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► [springeropen.com](https://www.springeropen.com)