Pericoronary adipose tissue differences among plaque types: a retrospective assessment Abstract

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Research Article

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Abstract

Purpose: To assess differences in pericoronary adipose tissue (PCAT) in patients with different plaque types by using several quantitative parameters of PCAT and investigate the relationship between PCAT and different plaque types.

Methods: We retrospectively recruited 488 patients diagnosed with stable coronary artery disease (CAD) via coronary computed tomographic angiography, including 279 with calcified plaques (CP), 153 with non-calcified plaques (NCP), and 56 with mixed plaques (MP). Volume, fat attenuation index (FAI), and 10^{th} percentile, 90^{th} percentile, median, and minimum Hounsfield unit (HU) values of PCAT surrounding plaques were quantified using semi-automated software. Clinical features and quantitative PCAT parameters were compared between different plaque types.

Results: No between-group differences were observed for age, sex, body mass index, risk factors, and plaque location. Length and PCAT volume in the NCP group were lower than those of the CP and MP groups ($P < 0.001$), whereas there were no significant differences between the CP and MP groups ($P > 0.05$). Patients with NCP and MP had a higher FAI and 10^{th} percentile, 90^{th} percentile, median, and minimum HU values of PCAT than CP ($P < 0.001$); however these values were not significantly different between the NCP and MP groups ($P > 0.05$).

Conclusion: The quantitative parameters of PCAT, as a biosensor for CAD, vary among the different plaque types.

1. Introduction

Coronary artery disease (CAD) is one of the major causes of death, estimated to cause approximately 7.4 million deaths annually [1]. Prior studies have shown that coronary artery inflammation is closely associated with the occurrence and development of CAD and high-risk plaque rupture [2]. The detection and quantification of coronary inflammation may help in earlier risk classification of patients with CAD, perhaps even for the advance of coronary plaque progression[3]. Therefore, the early identification of an inflammatory coronary artery status has the potential to prevent CAD and improve patient prognosis.

Studies have shown that the composition of pericoronary adipose tissue (PCAT) changes when coronary arteries are in an inflamed state [4]. PCAT is the adipose tissue surrounding the coronary artery connected to the outer coronary artery wall [5]. The adipose tissues are endocrine organs with unique functions [6] including the production of adipokines, including leptin, fat, and inflammatory cytokines [7]. Cytokines promote the macrophages and T cell infiltration, allowing the cells to produce additional chemokines and thereby initiate a feedforward cycle of inflammatory response that promotes atherosclerosis in the arterial wall [8, 9]. Furthermore, recent studies have shown that PCAT interacts with vascular inflammation [10, 11]; in this circumstance, an inflamed arterial wall releases pro-inflammatory cytokines that inhibit the adipocyte maturation of PCAT [4].

Therefore, use of a novel non-invasive imaging biomarker, the fat attenuation index (FAI), has been proposed [12, 13]. Use of the FAI allows for the visualization of coronary vasculature inflammation and its direct quantification by drawing PCAT fat attenuation spatial variation in coronary computed tomographic angiography (CCTA) images [4, 14]. To the best of our knowledge, differences in the PCAT of patients with CAD with different plaque types have rarely been studied. Consequently, in this study, we used the FAI and other quantitative parameters of PCAT on imaging to assess differences in PCAT among patients with different plaque types in order to discover the relationship between PCAT and different plaque types.

2. Methods

2.1. Patients

This study was approved by the Committee of Medical Ethics Experts of the Second Hospital of Lanzhou University (2021A-165). A total of 603 patients who had been diagnosed with stable CAD on CCTA at the Second Hospital of Lanzhou University between March 2020 and June 2021 were enrolled in this retrospective study. The exclusion criteria were as follows: (1) incomplete clinical data; (2) history of stent implantation, bypass history, coronary artery malformation, artificial valve, or cardiac pacemaker; (3) myocarditis, vasculitis, or myocardial infarction; (4) coronary plaques not located in the left circumflex branch, left anterior descending branch, or right coronary artery; (5) myocardial bridge located at the coronary plaque; (6) multiple coronary plaques; and (7) poor-quality CCTA images. After the exclusion criteria were applied, 488 patients were enrolled in the study. Among the enrolled participants, 284 were men and 204 were women. The average age of all participants was 58 (52 to 66) years. There were 488 total lesions identified in all patients, of which 279 were calcified plaques (CP), 153 were non-calcified plaques (NCP), and 56 were mixed plaques (MP). A flow chart describing study enrollment is shown in Fig. 1.

2.2. CCTA acquisition

CCTA was performed using Revolution computed tomography (CT) (GE Healthcare, Milwaukee, WI, USA) equipment. The breathing coordination of patients was checked before scanning. The scanning range used extended from 1 cm below the tracheal bifurcation to the bottom of the heart. The following CCTA parameters were applied: field of view, 240 mm × 240 mm; matrix, 512 × 512; tube voltage, 100 kV; tube current, 400–700 mA; adaptive statistical iterative reconstruction veo, 60%; rotation time, 0.28 s; and slice thickness, 0.625 mm. Enhanced scanning was performed using a high-pressure dual-cylinder syringe (Bayer Health Care, Berlin, Germany) to inject 0.9 ml/kg iopromide (370 mg/ml) through the median cubital vein at an injection rate of 5.0–5.5 mL/s. Subsequently, 40 ml normal saline was injected at the same rate for flushing.

2.3. Semi-automatic plaque analysis

After scanning, images were automatically uploaded to Shukun Coronary Artery Analysis Software (China Shukun Technology Co., Ltd., Shanghai, China) for post-processing. Then, auto-segmented coronary vessels were manually modified by an experienced cardiovascular radiologist. After coronary artery segmentation was complete, the location and nature of plaques were recorded using Shukun Coronary Artery Analysis Software.

Two radiologists, who each had more than 10 years of diagnostic cardiovascular imaging experience and were blinded to the results of the software analysis, independently completed the diagnosis of plaque using curved planar reformation and straightened curved planar reformation images. By the visual analysis of the two radiologists, plaques were classified as NCP, MP, and CP[15]. When the two cardiovascular radiologists and Shukun Coronary Artery Analysis Software provided different diagnoses, another cardiovascular radiologist with more experience made a final diagnosis.

2.4. Semi-automatic PCAT delineation

The CCTA images and Shukun Coronary Artery Analysis Software results were combined to identify the location of plaques. Then, PCAT was respectively delineated by the aforementioned radiologists using Pericoronary Adipose Tissue Analysis Software (China Shukun Technology Co., Ltd.). When delineating PCAT around a plaque, two rectangular regions of interest (ROIs) were drawn along the long axis of the coronary artery at the plaque site. The length of the ROIs corresponded to the maximum length of the plaque on straightened curved planar reformation images, and the width was the average diameter of the vessel. The ROIs had CT values that ranged from − 190 to − 30 Hounsfield units (HUs).

2.5. PCAT quantification

The volume, FAI, and 10th percentile, 90th percentile, median, and minimum HU values of PCAT were the quantitative parameters measured in this study. The two radiologists used the PCAT segmentation function (China Shukun Technology Co., Ltd.), and the quantitative parameters of the PCAT were automatically generated by the software. Finally, the measured results from the two radiologists were averaged to determine the final value. Figure 1 illustrates the quantification of PCAT surrounding the NCP and CP. PCAT surrounding both the NCP and CP were visualized using an adipose tissue HU color table.

2.6. Statistical analyses

All data were analyzed using SPSS 23.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8.0.2 (GraphPad Software Inc., San Diego, CA, USA) software. Continuous and classification variables of patients are indicated as medians (interquartile range) and frequencies (percentages), respectively. Continuous variables of all three groups were compared using the Kruskal-Wallis H test, and the Wilcoxon signed-rank test with a Bonferroni correction was used for post hoc, pairwise comparisons. Classification variables were analyzed using the chi-squared test. The intra- and interclass correlation coefficients (ICC) were used to quantify the consistency of measurements of the two radiologists. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Clinical data of different plaque types

As shown in Table 1, 279 CP, 153 NCP, and 56 MP were considered. Among the patients with different plaque types, no significant differences in age, sex, body mass index, smoking status, plaque location, or the presence of hypertension, hyperlipidemia, hyperglycemia were observed ($P > 0.05$). However, the length of plaques differed significantly between plaque types, with CP and MP being longer than NCP.

Table 1
Clinical data of different plaque types

	CP (n = 279)	NCP (n = 153)	MP (n = 56)	*P*-value
Age (years)	58.0(53.0 to 67.0)	57.0(50.0 to 65.0)	57.0(50.3 to 65.0)	0.056
Gender (%)				0.347
Male	163(58.42)	84(54.90)	37(66.07)	
Female	116(41.58)	69(45.10)	19(33.93)	
BMI (kg/m^2)	24.1(22.0 to 26.4)	23.7(22.0 to 25.2)	23.9(22.0 to 25.9)	0.190
Smoking (%)				0.794
Yes	143(51.25)	83(54.25)	28(50.00)	
No	136(48.75)	70(45.75)	28(50.00)	
Hypertension (%)				0.212
Yes	169(60.57)	80(52.29)	30(53.57)	
No	110(39.43)	73(47.71)	26(46.43)	
Hyperlipidemia (%)				0.088
Yes	162(58.06)	90(58.82)	24(42.86)	
No	117(41.94)	63(41.18)	32(57.14)	
Hyperglycaemia(%)				0.257
Yes	130(46.59)	77(50.33)	21(37.50)	
No	149(53.41)	76(49.67)	35(62.50)	
Location (%)				0.132
RCA	88(31.54)	61(39.87)	18(32.14)	
LCX	38(13.62)	10(6.54)	5(8.93)	
LAD	153(54.84)	82(53.59)	33(58.93)	
Plaque length (mm)	5.7 (5.0 to 7.3)	5.0(4.8 to 5.8)	6.7(5.1 to 8.6)*	0.000

CP, calcified plaque; NCP, noncalcified plaque; MP, mixed plaque; RCA, right coronary artery; LCX, left circumflex branch; LAD, left anterior descending branch; Compared with CP, *$P > 0.05$.

3.2. Interobserver agreement

Excellent agreement was obtained between the two radiologists regarding plaque length, PCAT volume, FAI value, and 10th percentile, 90th percentile, median, and minimum HU values of PCAT measurements (all ICC values > 0.80, Table 2).

Table 2
Comparison of measurement consistency between the two radiologists

	ICC	95%CI	*P*-value
Plaque length (mm)	0.936	0.925–0.947	0.000
PCAT			
volume (mm^3)	0.933	0.921–0.944	0.000
FAI value (HU)	0.893	0.873–0.909	0.000
10th percentile (HU)	0.909	0.892–0.923	0.000
90th Percentile (HU)	0.922	0.908–0.935	0.000
Median value (HU)	0.912	0.895–0.925	0.000
Minimum value (HU)	0.889	0.868–0.906	0.000

PCAT, pericoronary adipose tissue; FAI, fat attenuation index.

3.3. Comparison of quantitative parameters of PCAT based on plaque type

As shown in Table 3, the volume of PCAT was greater in CP (293.3 [222.3 to 382.4] mm^3) and MP (277.3 [185.8 to 416.0] mm^3) than in NCP (199.0 [137.3 to 281.8] mm^3, all $P < 0.001$). However, no significant differences were observed regarding PCAT volume ($P = 1.000$) when CP and MP were compared. FAI and 10th percentile, 90th percentile, median, and minimum HU values of PCAT among plaque types significantly differed ($P < 0.001$) and NCP as well as MP were found to be higher than CP. The same PCAT quantitative parameters did not significantly differ when values of NCP and MP were compared ($P =$ 0.141, 0.172, 0.291, 0.190, and 0.160, respectively). The box plot shows the difference in quantitative parameters of PCAT between different plaque types (Fig. 2).

Table 3
Comparison of quantitative parameters of pericoronary adipose tissue of different plaque types.

	CP (n = 279)	NCP (n = 153)	MP (n = 56)	*P*-value
PCAT volume (mm^3)	293.3(222.3 to 382.4)	199.0(137.3 to 281.8)	277.3(185.8 to 416.0)*	0.000
FAI value (HU)	-85.0(-92.0 to -80.0)	-73.0(-80.0 to -67.0)	-76.5(-83.75 to -70.0)#	0.000
10th percentile (HU)	-129.0(-140.0 to -118.0)	-112.0(-121.0 to -102.2)	-117.5(-126.0 to -107.0)#	0.000
90th Percentile (HU)	-43.0(-46.0 to -40.0)	-38.0(-41.7 to -36.0)	-39.5(-42.0 to -38.0)#	0.000
Median value (HU)	-83.0(-91.0 to -77.0)	-69.0(-77.5 to -63.5)	-72.5(-81.8 to -67.3)#	0.000
Minimum value (HU)	-188.0(-190.0 to -180.0)	-172.0(-189.0 to -157.0)	-181.5(-188.0 to -170.0)#	0.000

PCAT, pericoronary adipose tissue; FAI, fat attenuation index; CP, calcified plaque; NCP, noncalcified plaque; MP, mixed plaque; Compared with CP, *$P > 0.05$; Compared with NCP, #$P > 0.05$.

4. Discussion

This study utilized FAI and other quantitative parameters of PCAT from different plaque types measured on CCTA to find differences in PCAT between patients with different plaque types. The results indicated there were no differences in age, sex, body mass index, risk factors (smoking, hypertension, hyperlipemia, and hyperglycemia), or plaque location between patient groups with different plaque types, suggesting that clinical background likely had little influence on plaque types. Furthermore, the plaque length and PCAT volume were greater in CP and MP than in NCP. The FAI value and 10th percentile, 90th percentile, median, and minimum HU values of PCAT were higher in NCP and MP than in CP, whereas there were no significant differences between NCP and MP.

Although the "gold standard" for diagnosing the nature of plaques is invasive intravascular ultrasound, the usefulness of the modality is limited by its high cost and invasiveness [16]. An advantage of CCTA is that it can be used to non-invasively and accurately assess the nature of plaques and quantify PCAT [17]. In addition, PCAT is closely associated with the vascular inflammation that causes CAD [4]. However, the characteristics of PCAT surrounding different plaque types have not yet been determined in patients with CAD. To the best of our knowledge, this is the first report to use different quantitative PCAT parameters to explore the differences in PCAT between different plaque types. Our research showed that the plaque length and volume of PCAT in patients with NCP were smaller than those of patients with CP and MP. This could be because NCP is the early stage of atherosclerosis while MP and CP are the stages of atherosclerosis progression, therefore CP and MP have longer plaque lengths [18]. Further, in this study,

since the tissue with CT values of -190 to -30 HU was considered PCAT, the volume of PCAT not only depended on the length of the plaque but was also closely related to the inflammatory status of the coronary arteries surrounding the plaque. Research has shown the level of vascular inflammation in NCP to be higher than MP and CP [19], and high vascular inflammation will release more pro-inflammatory cytokines via a paracrine mechanism [5, 6], which will prevent more small, immature precursor adipocytes from differentiating into large, mature adipocytes thereby inhibiting more normal lipid accumulation in PCAT [4, 20]; thus PCAT volume in NCP was found to be smaller.

Higher FAI values indicate that the PCAT is subjected to an increased degree of pro-inflammatory effects due to vascular inflammation [21, 22]. In this study, we observed that the FAI values of NCP and MP were higher than those of CP. This may have been because inflammation plays a central role in the formation and development of atherosclerosis [19, 23]. Additionally, the early stages of atherosclerosis are characterized by more pronounced inflammation, whereas inflammation can be comparatively reduced as plaques become more stable and calcified [18]. When coronary inflammation occurs, it may prevent pre-adipocytes in PCAT from differentiating into mature adipocytes via paracrine signaling, thereby inhibiting the production of PCAT and inducing its decomposition [4, 10]. During the same period, edema forms around the coronary arteries, increasing the water/fat ratio near the inflamed blood vessel wall [4, 14]. When patients undergo CCTA, coronary vessels in an inflammatory state have elevated the FAI value of PCAT [24, 25]. Consequently, this study further demonstrated the key role of inflammation in the occurrence and development of early coronary atherosclerosis from an imaging point of view using a relatively large sample size.

Prior to this study, few scholars have investigated the differences in PCAT between plaque types and the different measurements of PCAT that may have an impact on the differences between plaque types. Marwan et al. [26] measured PCAT in the segment where the plaque was located and demonstrated that the mean CT value of PCAT in segments with plaques was − 34 ± 14 HUs, while the segment without plaque was − 56 ± 16 HUs. Further, no significant difference in PCAT density was observed when fibrous and lipid plaques were compared (− 35 ± 19 versus − 36 ± 16 HUs, $P = 0.8$). Runlei et al. [15] measured lesion-specific $PCAT_{MA}$ by extending 5 mm from the center to the narrowest plaque and showed that the lesion-specific $PCAT_{MA}$ of NCP (− 90.2[− 93.8 to − 86.7] HU) and MP (− 94.8[− 98.0 to − 91.6] HU) was higher than CP (− 96.6[− 98.6 to − 94.5] HU). In agreement with the results of Runlei et al., [15] we found that the FAI values of NCP (− 73.0 [− 80.0 to − 67.0] HU) and MP (− 76.5 [− 83.75 to − 70.0] HU) were higher than those of CP (− 85.0 [− 92.0 to − 80.0] HU). However, in our research, an average CT value for the entire volume of PCAT (FAI value), which was around the entire plaque, was calculated automatically using the semi-automatic delineation software. Therefore, in addition to factors such as tube voltage and age[27, 28], the FAI value may also be influenced by the measurement method.

In addition to the FAI value, other PCAT quantitative parameters of NCP and MP, including the 10th percentile, 90th percentile, median, and minimum HU values of PCAT, were higher than those of CP. No prior research has used these parameters to evaluate differences in plaques. Here, we demonstrated their potential to be used as novel tools for evaluating coronary inflammation in a manner similar to that of

FAI, which has already been proven to be useful. Additionally, some quantitative parameters of PCAT of the NCP and CP groups were not significantly different from those of the MP group. This may have been due to the formation of MP at an intermediate stage during the progression of atherosclerosis. Therefore, MP likely have characteristics of CP and NCP, making it difficult to distinguish using the quantitative parameters of PCAT. In addition, the sample size of the MP group in this study was significantly smaller than that of the other groups.

Our study had several limitations. First, as a retrospective single-center study, it may have had selection bias. Multi-center studies with larger sample sizes are needed in the future. Second, although sample size of this study was large, the number of MP assessed was small. Third, NCP was not characterized in detail. Therefore, further exploration of the plaques should be performed in the future. Finally, different doses of contrast agents may have had an impact on the FAI; the relationship between different doses of contrast agents and the FAI requires future exploration.

5. Conclusion

The volume of PCAT was greater in CP and MP than NCP. The FAI value and 10th percentile, 90th percentile, median, and minimum HU values of PCAT were higher in NCP and MP than CP. These results indicate that PCAT differed among different plaque types.

Declarations

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Competing Interests: All authors declare no conflicts of interest.

Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mengyuan Jing, Huaze Xi, Bin Zhang, Xiaoqiang Lin, Liangna Deng, Tao Han, and Junlin Zhou. The first draft of the manuscript was written by Jianqing Sun, Qing Zhou, Jiachen Sun, and Xiangwen Li, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Second Hospital of Lanzhou University (Mar.31,2021 /2021A-165), and did not require the informed consent due to the nature of retrospective research.

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Figures

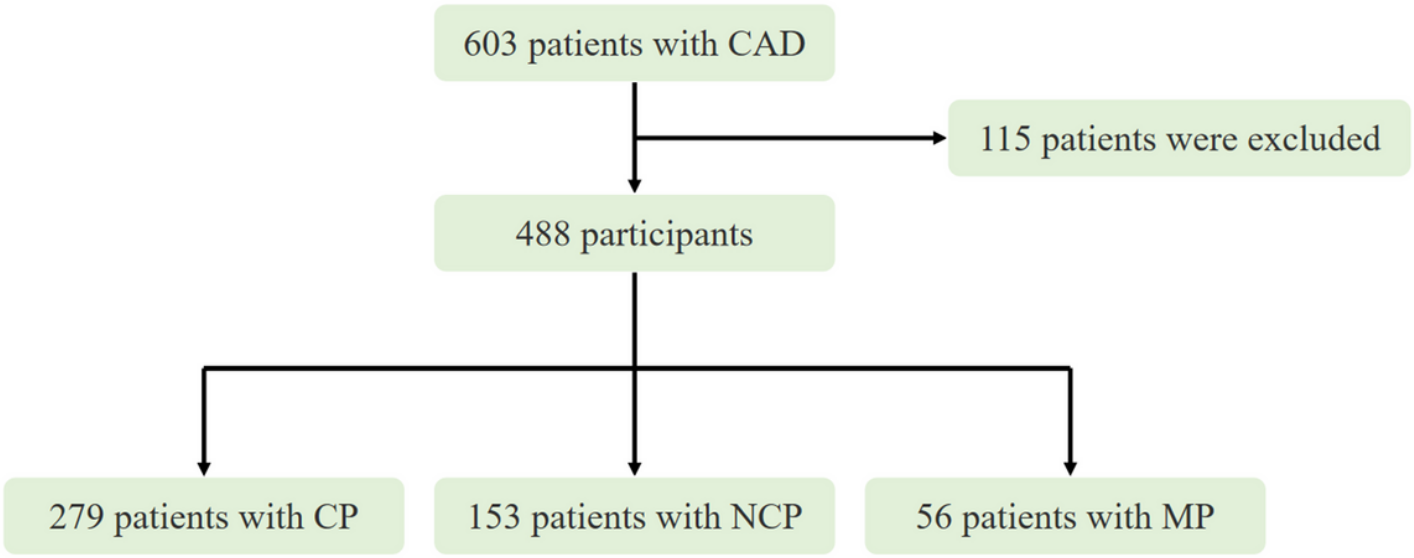

Figure 1

Flow diagram of patient selection.

CAD, coronary artery disease; CP, calcified plaque; NCP, noncalcified plaque; MP, mixed plaque.

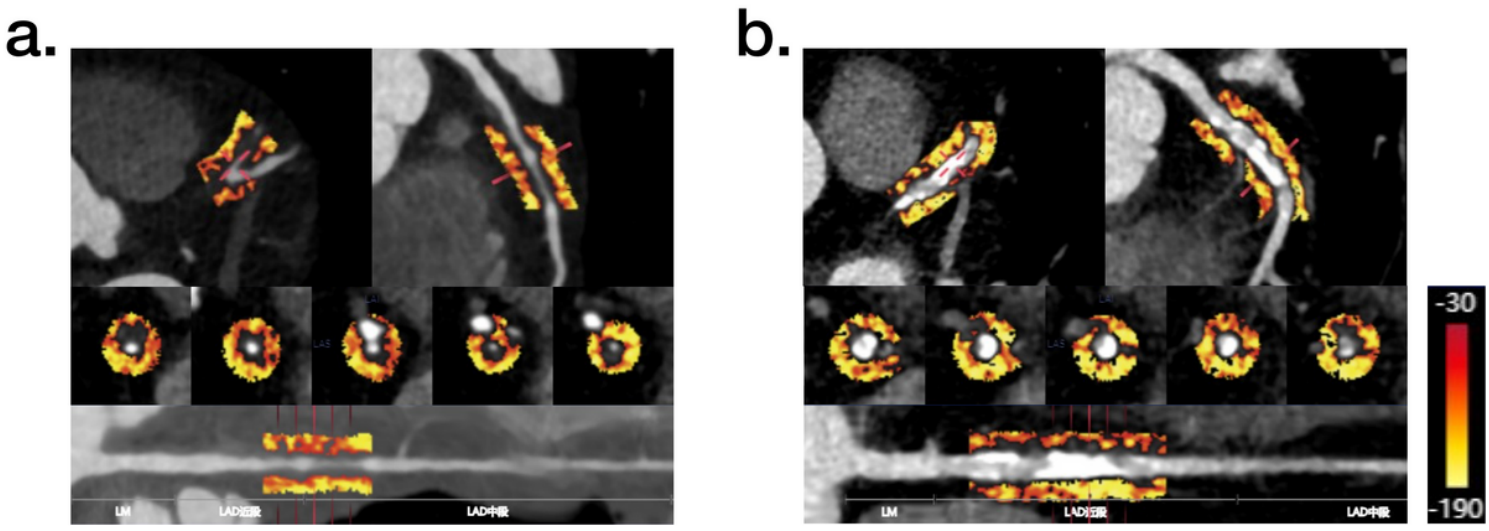

Figure 2

Adipose tissue Hounsfield unit color table for visualizing pericoronary adipose tissue quantification around non-calcified (2a) and calcified plaques (2b).

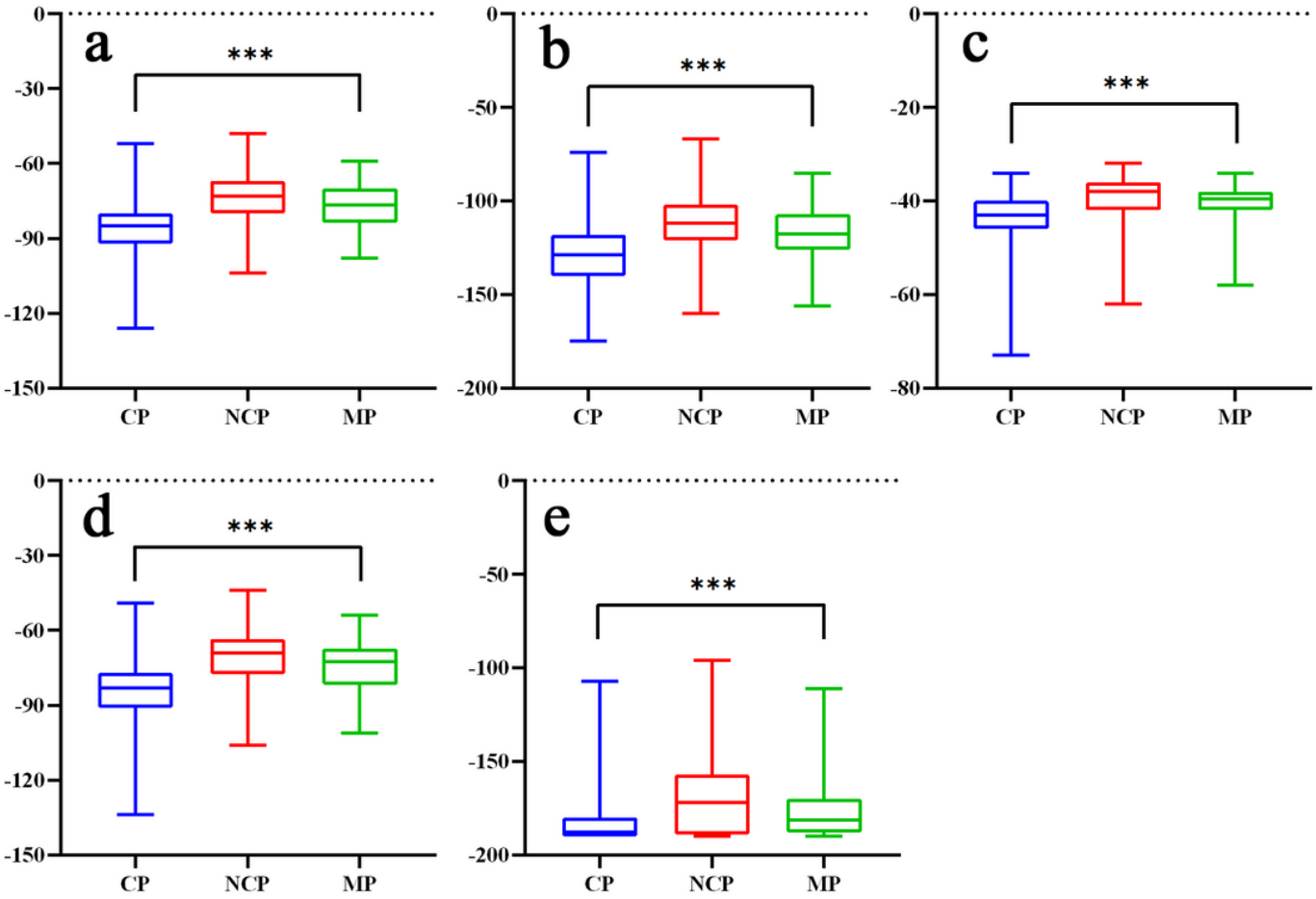

Figure 3

The box plots show the differences in the FAI value (3a) and 10th percentile (3b), 90th percentile (3c), median (3d), and minimum (3e) HU values of pericoronary adipose tissue between different plaque types.

FAI, fat attenuation index; CP, calcified plaque; NCP, noncalcified plaque; MP, mixed plaque.