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REVIEW ARTICLE

Evaluation of pericoronary adipose tissue attenuation on CT

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ABSTRACT

Pericoronary adipose tissue (PCAT) is the fat deposit surrounding coronary arteries. Although PCAT is part of the larger epicardial adipose tissue (EAT) depot, it has different pathophysiological features and roles in the atherosclerosis process. While EAT evaluation has been studied for years, PCAT evaluation is a relatively new concept. PCAT, especially the mean attenuation derived from CT images may be used to evaluate the inflammatory status of coronary arteries non-invasively. The most commonly used measure, PCAT_{MA}, is the mean attenuation of adipose tissue of 3 mm thickness around the proximal right coronary artery with a length of 40 mm. PCAT_{MA} can be analyzed on a per-lesion, per-vessel or per-patient basis. Apart from PCAT_{MA}, other measures for PCAT have been studied, such as thickness, and volume. Studies have shown associations between PCAT_{MA} and anatomical and functional severity of coronary artery disease. PCAT_{MA} is associated with plaque components and high-risk plaque features, and can discriminate patients with flow obstructing stenosis and myocardial infarction. Whether PCAT_{MA} has value on an individual patient basis remains to be determined. Furthermore, CT imaging settings, such as kV levels and clinical factors such as age and sex affect PCAT_{MA} measurements, which complicate implementation in clinical practice. For PCAT_{MA} to be widely implemented, a standardized methodology is needed. This review gives an overview of reported PCAT methodologies used in current literature and the potential use cases in clinical practice.

INTRODUCTION

Inflammation plays a key role in the genesis of coronary artery disease (CAD), as suggested by the presence of immune cells in early phase atherosclerotic lesions.¹ Studies have shown that approximately 60% of all myocardial infarctions occur in patients without significant coronary artery stenosis, caused by plaque or rupture of non-obstructive, presumably vulnerable, highly inflamed atherosclerotic plaques.^{2,3} Therefore, biomarkers that reflect this inflammation may be a potential early indicator of CAD risk. Pericoronary adipose tissue (PCAT), an indicator of coronary inflammation, has become a biomarker of interest, however, clinically available and validated measurements have been proven challenging. This review gives an overview of PCAT methodologies used in current literature and the potential use cases.

VISCERAL ADIPOSE TISSUE

Adipose tissue is distributed throughout the human body; its main role is to store energy in the form of lipids, while it also shields and insulates tissue and organs. In the last decades, its critical role in endocrine signalling has been recognized. Adipose tissue can be categorized into white, brown, and beige fat, and can be classified into two main categories according to metabolic characteristics and location: subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT).⁴ VAT is the hormonally active component of total body fat, and produces molecules and hormones such as leptin, adiponectin, estrogen, resistin, and cytokines, which influence normal and pathological processes in the human body, both systematically and locally. In certain conditions, such as obesity, VAT mass can increase ectopic and may influence the susceptibility to comorbidities such as diabetes and atherosclerosis.

THE ROLE OF EPICARDIAL ADIPOSE TISSUE

Epicardial adipose tissue (EAT) is the VAT fat depot located between myocardium and visceral layer of the pericardium and covers 80% of the cardiac surface.⁵ Due to contact with myocardium, factors released from EAT have a direct paracrine effect on cardiomyocytes, and a potential role in the development of CAD.⁶ These characteristics support the concept of EAT as a biomarker of CAD.^{7–9} EAT serves as a local regulator of free fatty acid (FFA) homeostasis, releasing FFAs into the coronary microcirculation and storing them depending on energy requirements. This adipose tissue is more sensitive to lipogenesis than other VAT compartments,¹⁰ and can release or uptake FFA at a higher rate than other fat depots while under metabolic stress.¹¹ Pathological conditions, such as obesity and diabetes, but also genetic and environmental factors, may drive the shift towards dysfunctional EAT characterized by a pro-inflammatory and pro-atherosclerotic phenotype.¹² In these conditions EAT becomes hypertrophic, leading to failure of triglyceride storage, increased lipolysis and inflammation.⁵ The role of vascular inflammation in the development of coronary atherosclerosis and rupture of vulnerable plaques, resulting in acute coronary syndrome (ACS), has long been postulated.¹³ One study supports the association of dysfunctional EAT with coronary inflammation and plaque severity¹⁴; while another study even suggests a strong relation between EAT and plaque vulnerability features.¹⁵ CT allows calculation of EAT volume, which is by now a known marker to estimate cardiac inflammation in relation to CAD severity and risk of adverse cardiac events.¹⁶

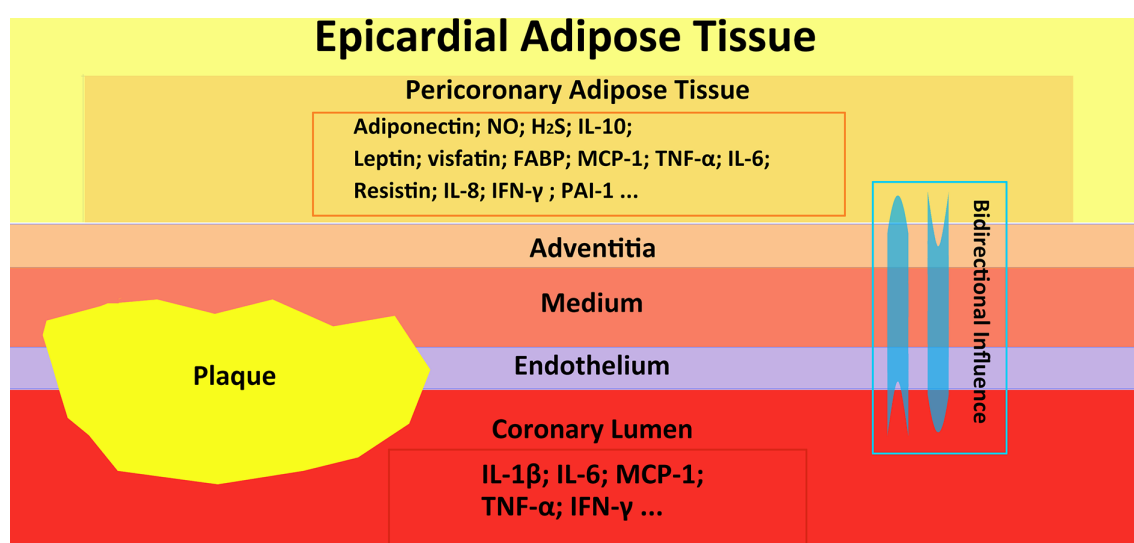
FROM EAT TO PCAT

Currently, there are no published recommendations for the standardization of EAT measurements.¹⁷ Some studies analyzed EAT linear thickness on transthoracic echocardiography, CT oMRI.^{18,19} EAT 3D volume quantification on cardiac CT is considered the most accurate measurement with the most literature

describing its value.¹⁷ Nevertheless, EAT volume as measure of cardiac inflammation has some major limitations. Systemic influences, such as obesity and diabetes, as well as medications and even season can affect EAT and EAT volume.²⁰ These systemic influences may cause differences between populations, or reflect temporary systemic variations, instead of coronary inflammation. The need of a more specific imaging marker, related to coronary inflammation, has recently turned attention to PCAT. PCAT is defined as the adipose tissue within the EAT depot that surrounds the coronary arteries,²¹ and has therefore the closest interaction with the adjacent coronary arteries,²² see Figure 1. Recent studies have shown that there is a bidirectional, biochemical communication between the coronary arterial wall and PCAT.²³ When PCAT becomes dysfunctional it can produce biologically active factors that induce endothelial dysfunction and inflammation, leading to the progression of atherosclerosis.²⁴ Vice versa, signals originating from the coronary wall can affect PCAT in a paracrine manner and lead to decreased perivascular lipid accumulation, with decreased lipophilic content and smaller, undifferentiated, lipid-poor adipocytes.²⁵ These factors result in volume and attenuation difference of the PCAT depot, which can be evaluated using coronary CT angiography (CCTA).²⁶

Although PCAT is included in the EAT depot, they have different pathophysiological effects and clinical significance. Compared to EAT, PCAT, in closer proximity to the coronary arteries, consists of a higher percentage of pre-adipocytes which are smaller in size with increased adipogenic gene expression compared to mature adipocytes. Inflammatory factors involved in the coronary atherosclerotic process prevent pre-adipocytes to mature into adipocytes in PCAT by paracrine effects.²⁶ This suggests that PCAT is more influenced by the paracrine inflammatory signals from the coronary arteries than autocrine signals released from the fat depot itself, whereas EAT captures both paracrine and autocrine signals.²⁶

Figure 1. This figure shows the epicardial adipose tissue, pericoronary adipose tissue, and coronary artery with plaque. Besides that, the interaction of inflammatory factors among EAT, PCAT and coronary artery is shown. FABP, fatty acid binding protein; H₂S, hydrogen sulfide; IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protein-1; NO, nitric oxide; PAI, plasminogen activator inhibitor; TNF, tumor necrosis factor.



PCAT MEASUREMENT METHODOLOGIES

Several measurement methods for CT evaluation of PCAT have been reported in literature: thickness, volume and attenuation, the last one being the most commonly used.²⁷ Most studies define PCAT as adipose tissue with a 3 mm width around the coronary artery wall, usually the right coronary artery (RCA). There are different approaches to define the length and location of PCAT measurements. Below, we will describe the methodologies of PCAT from current literature.

PCAT THICKNESS

Previously, PCAT has been measured as thickness of the adipose tissue around the coronary artery. The most common way to measure PCAT thickness is by calculating the maximum EAT width around the proximal coronary artery in cross-sectional CT images. The limited number of CCTA studies on PCAT thickness on axial views or multiplanar reformats showed good reproducibility, and reported improved metabolic syndrome and atherosclerosis diagnosis in CAD patients.^{24,26} PCAT thickness measurement is a straightforward and fast approach. However, PCAT thickness contains less information than other PCAT variables, and sometimes it is difficult to visually identify and distinguish PCAT and EAT thickness.

PCAT VOLUME

PCAT volume is rarely used and subject to controversy since it is hard to define the measurement range of PCAT volume. There are several ways to calculate PCAT volume. One way is to calculate the volume by using the original method of PCAT_{MA} segmentation, so the volume of the 3 mm around the coronary arteries in CCTA.²⁸ Another way is manually tracing the region containing PCAT in axial images perpendicular to the center line of the coronary artery, and subsequently summing every slice to create one volumetric measurement in CCTA.²⁹ A third way is to manually define a region of interest according to coronary segments, and use the 3D reconstructions to calculate PCAT volume in non-contrast cardiac CT.³⁰ A recent study showed that RCA-based PCAT volume on contrast and non-contrast images is highly correlated.²⁸ PCAT volume provides additional 3D information of PCAT compared to thickness. However, PCAT volume measurements have not been standardized and differences in measurement approached as described above could lead to different results. There is controversy about the association of PCAT volume with CAD, and outcomes of the few available studies show conflicting results.^{26,30}

PCAT MEAN ATTENUATION

Nowadays, the most widely used PCAT measurement method is the mean attenuation of PCAT (PCAT_{MA}). Here, the HU values of voxels in surrounding adipose tissue (defined as -190 to -30HU) perpendicular to the center line of the coronary artery in 3D reconstruction are averaged.²⁶ Usually, the adipose tissue around the proximal coronary artery is measured with 40 mm length and 3 mm width, leaving a 1 mm gap around the coronary artery wall to avoid blooming effects of contrast medium.

PCAT_{MA} is an indirect measure of adipocyte size and lipid content, reflecting inflammation status. In contrast to PCAT

volume, the role of PCAT_{MA} in coronary inflammation has been proven in pathophysiological studies with histological samples.²⁶, with relation to vulnerable lesions. Moreover, PCAT_{MA} measurements have higher inter- and intrareader agreement, compared to PCAT thickness or volume.^{28,31,32} However, one study showed that variation in contrast intensity of CCTA images affects PCAT_{MA} assessment and that lumen-normalization might be a requirement for accurate PCAT_{MA} measurements.³³ Per patient, per vessel or per lesion PCAT_{MA} measurements have been proposed depending on the application of PCAT (Table 1 for overview).

PATIENT-BASED MEASUREMENTS

Most recent studies have focused on PCAT_{MA} of the RCA as a patient-based biomarker. Patient-based PCAT_{MA} measurement has preference for the evaluation of relationships with patient-level parameters and for patient-based prognostic purposes. In a landmark study by Antonopoulos et al., RCA-based PCAT_{MA} was measured.²⁶ The origin point of the measurement was located 10 mm from ostium of the RCA, see Figure 2. A study by Kanaji et al. used the average PCAT_{MA} of all three main coronary arteries with 40 mm measured length and width equivalent to the vessel wall as a patient-based measure instead of the RCA only.³⁴ Few studies have investigated the relationship of PCAT_{MA} with patient-based demographic factors such as age or sex. One study by Ma et al in patients without CAD showed that PCAT_{MA} was significantly higher in males than in females.³² A study by Yuvaraj et al. also showed that PCAT_{MA} is significantly higher in males than in females independent of the presence of high-risk plaque.³⁵ However, this study showed age has no significant effect on PCAT_{MA} while the study by Ma et al. showed that age does have a significant, albeit small, effect.³²

VESSEL-BASED MEASUREMENTS

Although patient-based measurements are useful for identifying patient-level disease status and overall risk prediction, many CAD parameters such as stenosis degree and plaque burden are vessel-based. In addition, invasive coronary interventions are vessel-specific.^{36,37} For these associations, vessel-based PCAT_{MA} could be more appropriate and potentially more accurate (Figure 2C and D). Transitioning from patient-based measurements, predominantly using the RCA, to vessel-based measurements using the RCA, left anterior descending artery (LAD) and left circumflex (LCx), requires some methodological changes in order to enable PCAT_{MA} measurement for all three coronaries. The measurement length of 40 mm may cause some issues in proximal LAD and LCx evaluation due to limited length and the presence of side branches. Also, the width requires some adjustments because the presence of veins and myocardium in close vicinity to the coronary arteries may cause artifacts. Finally, because of the different anatomy of coronary arteries, it is important to define and standardize anatomical start and end points of the measurement per coronary.

Ma et al proposed a 10 mm length and 1 mm width, using the original RCA measurement starting point.³² This adjusted approach can avoid interference from the myocardium and veins, and is applicable for all three coronaries, see Figure 2C

Table 1. PCAT evaluation methods

PCAT measurements	Measured vessels	Start point	Length	Width	Gap between vessel wall
Patient-based	Original PCAT; RCA. Average of LAD, LCX and RCA	RCA: 10 mm from ostium LAD and LCX: left bifurcation point	40 mm	3 mm 1 mm	1 mm
Vessel-based	RCA LAD LCX	RCA: 10 mm from ostium LAD and LCX: left bifurcation point LAD: 10 mm from bifurcation	40 mm 10 mm 5 mm	3 mm 1 mm	1 mm
Lesion-specific	RCA LAD LCX	Beginning point of the lesion centered around lesion mid-point	10 mm Lesion-length	3 mm 1 mm	1 mm

LAD, left anterior descending artery; LCX, left circumflex artery; PCAT, pericoronary adipose tissue; RCA, right coronary artery.

and D. In addition, using comparable lengths and width for each coronary makes measurements more comparable. A study by Balcer et al.³⁰ used an even shorter measurement length of 5 mm in order to measure PCAT_{MA} on a per segment level. They showed that PCAT_{MA} was lower in distal segments compared to proximal segments. This indicates that measurement location can influence the PCAT_{MA} value, emphasizing the need for standardized measurement location for vessel-based analysis. For RCA measurements, the most common approach starts 10 mm from the ostium while for LAD and LCX, most studies set the starting point at the bifurcation point of the left coronary artery. One study used 5 mm from the bifurcation as starting point for LAD and LCX measurements.³⁰

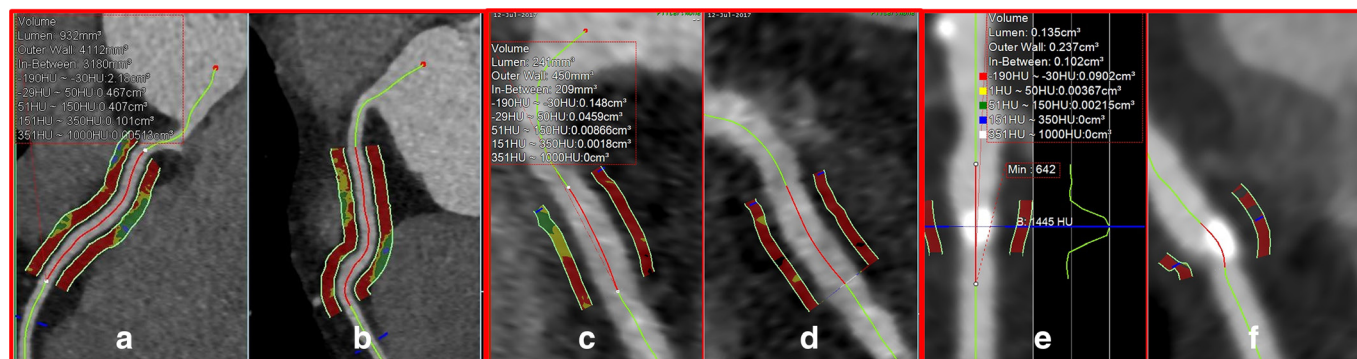
LESION-BASED MEASUREMENTS

Some studies used lesion-specific methods to investigate specific lesion-related features such as high-risk plaque (HRP) features, plaque composition and hemodynamic significance. Lesion-specific measurement can be of interest specifically when trying to identify plaques at risk of rupture or to identify lesions that will benefit from intervention.³⁸ Lesion-based measurements can be performed in different ways, mostly by adjusting measurement lengths, see **Figure 2E & 2F**. The most common approach is to take a PCAT measurement length equivalent to the length of the lesion. However, this causes the lengths of PCAT_{MA} measurements to differ, making comparison between measurements difficult. Another approach is to use a standard measurement length of 10 mm length that covers the lesion. If the lesion is longer than 10 mm, the measurement length could be centered on the mid-point of the lesion. This method uses a uniform measurement length, however in longer lesions information may be incomplete.³⁹

ARTIFICIAL INTELLIGENCE AND RADIOMICS

With the increasing interest in PCAT and the simultaneous progress in artificial intelligence (AI) and radiomics in the field of radiology, it comes as no surprise that AI and radiomics technology is increasingly used to assess PCAT_{MA}.⁴⁰ A detailed overview of the use of AI is given a review by Zhang et al outlining the latest progress of image segmentation, quantification, and application in evaluating cardiac adipose tissue.⁴⁰ In a direct AI approach, mostly convolutional neural networks (CNN) are investigated for segmenting the fat depot and subsequently calculating volume and/or attenuation. No published study so far uses this method for PCAT specifically, but it has been used for EAT.⁴¹ Another approach uses radiomics to identify PCAT-specific features with a subsequent machine learning approach to create a classifier to identify the outcomes defined.^{42,43} The main study using radiomics and AI for PCAT was performed by Oikonomou et al showing that an AI-powered fat radiomic profile not only identifies inflammatory differences but also improves cardiac risk prediction.⁴⁴ Radiomic analysis could extract more information from PCAT apart from PCAT_{MA}. This could potentially improve the risk prediction by PCAT measures while AI-based approaches reduce manual labor resulting by reducing processing time and variability, which could increase the clinical applicability of PCAT analysis.

Figure 2. Different measurement approaches for PCAT. (A, B) show the patient-level PCAT measurement. The indicated measurement is made for the RCA with 40 mm length and 3 mm width with 1 mm gap from the coronary lumen. (C, D) show an example of vessel-level PCAT measurement. The measurement is here depicted for RCA with 10 mm length, 1 mm width and 1 mm gap. (E, F) show a lesion-specific PCAT measurement, here across a plaque in the LAD. The measured length is the same as the length of the plaque, while the measured width is 1 mm with 1 mm gap. LAD, left anterior descending; PCAT, pericoronary adipose tissue; RCA, right coronary artery.



PCAT EVALUATION: IMAGING TECHNOLOGY

Commonly used tube voltage in CCTA

The currently most recognized PCAT measurement approach is CCTA-derived PCAT_{MA}. The proof-of-concept studies of PCAT_{MA} were performed on 120 kVp CCTA scans.²⁶ One of the main focuses in CCTA is to lower radiation dose according to the guiding principle of radiation safety, as low as reasonably achievable (ALARA), while maintaining coronary evaluability.⁴⁵ There is a trend of CCTA performed at lower kVp levels. Depending on CT scanner technology, kVp can be lowered to 70 or 80 kVp.⁴⁶ Ma et al, investigating the effect of kVp levels on PCAT_{MA} in patients without CAD, showed that PCAT_{MA} is significantly lower at lower kVp levels (70 kVp: -95.6 HU ± 9.6 vs 120 kVp: -79.3 HU ± 6.8).³² Two other studies confirmed these results, using dual layer spectral CT systems that enable image reconstruction at different keV levels. They showed that PCAT_{MA} measurements at 120 kVp were higher than in 40 keV images in patients with and without CAD. They also suggested that PCAT_{MA} acquired at 40 keV is more closely related to CAD with a higher AUC for identifying significant stenosis compared to 120 keV scans (0.811 vs 0.731).^{47,48} With the new photon counting detector CT scanner (PCD-CT), a phantom validation study comparing different energy level from 55 to 80 keV was performed. Results confirm that also with PCD-CT systems, there were significant differences in PCAT_{MA} between different energy levels.⁴⁹ All of these results indicate that for evaluating PCAT_{MA}, the kVp level and scan parameters should be considered, especially when quantitative comparisons are made between different scans or with the use of thresholds. Moreover, different spectral characteristics between CT systems may also limit comparisons.

Non-contrast cardiac CT

Non-contrast cardiac CT is commonly used to quantify coronary calcium. This acquisition is performed without the use of iodine contrast, and at very low radiation dose.^{50,51} These acquisitions are often made earlier at the disease process, and can be used for screening purposes. Adding an early-stage CAD-related biomarker such as PCAT to the traditional calcium score evaluation might improve early identification of patients at risk. Almeida

et al, comparing PCAT measurements on contrast-enhanced and non-contrast CT, concluded that PCAT volume showed particularly strong correlation while mean attenuation showed medium correlation.²⁸ Balcer et al. studied PCAT volume and attenuation around the proximal and mid segments of the main coronary arteries on non-contrast CT.³⁰ They showed that PCAT volume but not attenuation was strongly and independently correlated to culprit lesions.³⁰ These studies suggest that non-contrast studies are more suitable for PCAT volume than for attenuation analysis. Further studies of PCAT in non-contrast CT are needed, and better measurement methods of PCAT in non-contrast CT need to be developed.

PCAT AS A CAD BIOMARKER

PCAT correlation with CAD imaging markers

CCTA studies have demonstrated the incremental diagnostic and prognostic value of evaluating plaque features and composition over stenosis severity alone.^{52,53} Recently, several, mostly cross-sectional and small-sized studies showed that PCAT_{MA} is correlated with stenosis severity, plaque burden and HRP presence. See Table 2 for an overview of these studies and the measurement methods they used.

Ma et al investigated lesion-specific PCAT_{MA} in 165 patients and showed a minimal but significant difference between lesions with a minimal (<25%) and severe stenosis (>70%) (-98.3 HU vs -96.2 HU, $p = 0.037$).³⁹ Sugiyama et al found in 540 patients that RCA stenoses >50% on ICA have significantly higher PCAT_{MA} compared to patients with a < 50% stenosis (-70.17 HU ± 8.05 vs -73.07 HU ± 8.51, $p < 0.001$).⁶⁵ In 2018, Goeller et al. analyzed PCAT_{MA} around every coronary lesion in matched ACS ($n = 19$) and stable CAD ($n = 16$) patients.⁶⁴ They showed that PCAT_{MA} was increased around high-burden lesions compared to low-burden ones, within the same patient, both in the ACS group (-69.1 HU vs -74.8 HU; $p = 0.01$) and stable CAD group (-69.1 HU vs -76.4 HU, $p = 0.01$). Furthermore, the same group found a positive correlation between changes in non-calcified plaque (NCP) burden in the RCA and changes in RCA PCAT_{MA} ($r =$

Table 2. List of studies reporting the correlation of PCAT_{MA} with imaging markers of CAD severity

First author	Year	Study type	Measurement method	Patients	Main findings
Nakajima ⁵⁴	2022	Retrospective cohort study	Patient-based, vessel-based (proximal 40 mm of all coronary arteries) and lesion-based	198 patients presenting with NSTEMI who underwent CCTA prior to intervention	Plaque rupture is associated with higher PCAT _{MA} than plaque erosion both at the culprit plaque level and at the culprit vessel level. The mean PCAT _{MA} of all three coronary arteries is significantly higher in patients with plaque rupture than in plaque erosion.
Yan ⁵⁵	2022	Retrospective cohort study	Vessel-based (40 mm segments of the 3 coronary vessels, RCA starting 10 mm distal to the ostium, LAD and LCX starting at LM bifurcation)	247 patients with suspected or known CAD who underwent CCTA (with derived FFRCT) and invasive FFR	PCAT _{MA} predicts ischemia independently of plaque characteristics. The use of a PCAT _{MA} threshold improves discrimination and reclassification abilities of CT visual stenosis assessment compared with stenosis assessment alone. The diagnostic performance of these two methods combined is comparable with FFRCT.
Chen ⁵⁶	2021	Retrospective case-control study	Lesion-based	104 patients with chest pain and at least 1 non-calcified plaque on coronary CT divided in two groups: first group with at least one high risk plaque (44 patients), control group with non-high-risk plaques (60 patients)	PCAT _{MA} around high-risk plaques is higher compared to low-risk plaques.
Pasqualetto ⁵⁷	2021	Retrospective cohort study	Patient-based (proximal 10–50 mm of RCA and proximal 40 mm of LAD)	202 patients with suspected ACS who underwent pharmacological dipyridamole SE and CCTA within a short interval (<3 months)	PCAT _{MA} is related to coronary microvascular dysfunction detected by pharmacological dipyridamole stress-echocardiography, in particular in patients without obstructive CAD.
Pergola ⁵⁸	2021	Retrospective case-control study	Patient-based (proximal 10–50 mm of RCA)	38 patients divided in 3 groups based on CMR findings: myocarditis, ¹⁵ MINOCA ¹⁴ and TTS. ⁹ 12 patients with atypical chest pain who underwent CCTA in the control group.	PCAT _{MA} is significantly lower in healthy controls compared to patients with myocarditis, MINOCA and TTS. 8 days after acute event, there is no differences in PCAT _{MA} values between patients with MINOCA and controls.
Yuvaraj ³⁵	2021	Retrospective case-control study	Patient-based (proximal 10–50 mm of RCA) and lesion-based	41 CAD patients with HRP matched to 41 CAD patients without HRP	PCAT _{MA} value is higher in stable CAD patients with high-risk plaques compared to those without.
Ma ³⁹	2021	Retrospective case-control	Vessel-based (proximal 10 mm of LAD, LCX and RCA) Lesion-specific (10 mm in middle of lesion)	165 symptomatic patients with 70 kVp CCTA (93 patients with CAD and 72 patients without CAD)	Lesion-specific PCAT _{MA} is increased in non-calcified and mixed plaque than calcified plaque, and in minimal stenosis compared to severe.
Goeller ⁵⁹	2020	Retrospective case-control study	Patient-based (proximal 10–50 mm of RCA)	300 symptomatic patients with suspected CAD from three ethnic groups (100 in each group)	PCAT _{MA} is increased in patients with any plaque in the coronary tree compared to patients without plaque. PCAT _{MA} is correlated with total plaque volume and total plaque burden.
Hoshino ⁶⁰	2020	Retrospective cohort study	Patient-based (proximal 40 mm of LAD)	187 patients with intermediate stenosis of the LAD who underwent CCTA and invasive FFR	PCAT _{MA} is associated with CCTA-derived lumen stenosis and plaque size and with functional ischemia as evaluated by FFR.
Lin ⁴³	2020	Prospective case-control study	Patient-based (proximal 10–50 mm of RCA) and lesion-based	60 prospectively recruited patients with MI who underwent CCTA prior to invasive angiography, matched to patients with stable CAD ⁶¹ and controls with no CAD ⁶¹	PCAT _{MA} independently distinguishes MI from stable CAD and no CAD. Patients with MI have a higher PCAT _{MA} compared with patients with stable CAD and controls.
Yu ³⁸	2020	Retrospective cohort study	Lesion-based	167 patients with stable angina who underwent CCTA and invasive FFR measurement 2 weeks within	PCAT _{MA} is significantly higher for flow-limiting lesions than for non-flow-limiting lesions. PCAT _{MA} and total plaque volume provide incremental value to diameter stenosis for identifying hemodynamically significant lesions.
Gaibazzi ⁶²	2019	Retrospective case-control study	Patient-based and vessel-based (40 mm segments of the 3 coronary vessels, RCA starting 10 mm distal to the ostium, LAD and LCX starting at LM bifurcation)	106 patients with MINOCA and Tako-Tsubo Syndrome, who had CCTA and cardiac MRI matched to 106 control subjects with atypical chest pain who had a negative CCTA	In MINOCA and Tako-Tsubo Syndrome, mean PCAT _{MA} demonstrates higher values compared with controls.
Goeller ⁶³	2019	Retrospective cohort study	Vessel-based (proximal 10–50 mm of RCA)	111 consecutive symptomatic patients with suspected or known CAD and serial CCTA	PCAT _{MA} is related to the progression of plaque burden and helps identifying patients at increased risk of high-risk plaque progression.
Goeller ⁶⁴	2018	Retrospective case-control study	Lesion-based	19 patients with ACS matched to 16 controls with stable CAD	PCAT _{MA} is higher around culprit lesions compared with non-culprit lesions of patients with ACS and the lesions of matched controls.

PCAT_{MA}: pericoronary adipose tissue mean attenuation; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; NSTEMI: Non-ST-Elevation Myocardial Infarction; CCTA: Coronary Computed Tomography Angiography; FFR: Fractional Flow Reserve; FFRCT: Fractional Flow Reserve measured with Computed Tomography; CAD: coronary artery disease; MI: Myocardial Infarction; MINOCA: Myocardial Infarction with Non-obstructive Coronary Arteries; ACS: Acute Coronary Syndrome

0.55, $p < 0.001$),⁶³ and between RCA-based PCAT_{MA} and total volume and burden of RCA-based NCP ($r > 0.39$, $p < 0.001$).⁵⁹

Multiple studies have demonstrated that CCTA is able to detect plaque features associated with ACS risk.^{58,61} Yuvaraj et al matched 41 patients with stable CAD presenting with HRP on CCTA to 41 patients without HRP. They found that RCA-based PCAT_{MA} was higher in patients with HRP than in patients without ($-80.7\text{HU} \pm 6.50$ vs $-84.2\text{HU} \pm 8.09$, $p = 0.03$).⁶⁶ PCAT_{MA} was also higher in patients with subsequent ACS compared to those without in the whole population ($-78.0\text{HU} \pm 7.3$ vs $-83.3\text{HU} \pm 7.3$, $p = 0.02$), and in patients with HRP only ($-76.8\text{HU} \pm 5.7$ vs $-82.0\text{HU} \pm 6.3$, $p = 0.03$). Chen et al investigated the correlation between PCAT_{MA} and HRP features in 101 patients using spectral CT analyzing 220 plaques of which 48 had HRP features.⁵⁶ They found that PCAT_{MA} around HRP was higher than around non-HRP, especially when using 40 keV images ($-119.87\text{HU} \pm 22.74$ [HRP] vs $-153.76\text{HU} \pm 24.97$ [non-HRP], $p < 0.001$). The use of spectral imaging may be interesting considering that in most other studies the differences between different PCAT_{MA} groups are below 10 HU, making this imaging marker hard to use in clinical practice for individual patients.

Regarding the functional significance of coronary artery stenosis, fractional flow reserve (FFR) derived from invasive coronary angiography (ICA) is the gold-standard for guiding revascularization.⁶⁷ Functional measures have shown to be a better predictor of outcome than anatomical assessment of CAD.⁶⁸ Hoshino et al showed in 187 stable patients with intermediate LAD stenosis evaluated by FFR that PCAT_{MA} was associated with CCTA-derived lumen stenosis and FFR-based functional ischemia.⁶⁰ A study by Yan et al involving 247 patients, suggested that vessel-based PCAT_{MA} may predict ischemia identified by FFR, independently of plaque characteristics. The use of a PCAT_{MA} threshold ($\geq -71.9\text{HU}$) improved discrimination and reclassification abilities of visual stenosis assessment. A combination of PCAT with stenosis severity assessment reached comparable performance as FFRCT (AUC 0.772 vs 0.762, $p = 0.771$).⁵⁵ Another study also suggested that PCAT_{MA} may be higher in flow-limiting lesions (FFR ≤ 0.8). Lin et al showed that PCAT_{MA} independently distinguishes patients with myocardial infarction (MI) from stable CAD and no CAD (60 subjects for each group). Patients with MI had a higher PCAT_{MA} ($-82.3\text{HU} \pm 5.5$) than patients with stable CAD ($-90.6\text{HU} \pm 5.7$, $p < 0.001$) and controls ($-95.8\text{HU} \pm 6.2$, $p < 0.001$).⁴³

PCAT_{MA} may also have a role in patients without obstructive lesions but with coronary microvascular dysfunction (CMD).⁶⁹ CMD is one of the most recognized causes of myocardial infarction with non-obstructive CAD ($\leq 50\%$ diameter stenosis in major coronary arteries). CMD has been reported in about 50% of patients with chronic coronary syndromes, and up to 20% of those with ACS, in the absence of obstructive coronary lesions.⁷⁰ Pasqualetto and colleagues found a direct relationship between PCAT_{MA} and CMD measured with pharmacological dipyridamolestress-echocardiography, in particular in patients without obstructive CAD.⁵⁷ This suggests that PCAT_{MA} may be

related to microvascular dysfunction as well as macrovascular CAD.^{57,71}

Gaibazzi et al showed that in MINOCA and Tako-Tsubo Syndrome patients, PCAT_{MA} is increased compared to controls (106 patients in each group), possibly due to differences in coronary artery inflammation.⁶² However, a preliminary report from Pergola et al involving 50 patients showed no differences in PCAT_{MA} values between patients with MINOCA and controls, 8 days after an acute event. This may reflect the disappearance of coronary inflammation after MI. Larger studies are needed to identify the potential value of PCAT_{MA} in this subset of patients.

RISK STRATIFICATION AND PROGNOSTICATION USING PCAT

Current cardiac risk stratification relies on traditional clinical risk factors such as age, sex, race, body mass index, hyperlipidemia, hypertension,⁷² and imaging biomarkers such as the coronary calcium score (CCS) measured using CT.⁷³ However, coronary calcification represents a non-reversible process that does not regress in response to appropriate medical treatment, limiting its value in secondary prevention.⁷⁴ On the other hand, inflammation has an important role in both atherogenesis and atherosclerotic plaque rupture leading to ACS.^{13,75} Therefore, detection of the inflammatory coronary risk could guide more timely preventive measures in patient care and serve as an early-stage prognosticative marker, see Table 3.

Oikonomou et al investigated patient-based PCAT_{MA} and its correlation to clinical outcomes in 3912 patients. They showed that high PCAT_{MA} ($\geq -70.1\text{HU}$) could predict all-cause and cardiac mortality better than clinical risk factors and state-of-the-art interpretation of CCTA (HR 9.04, 95% CI: 3.35–24.40, $p < 0.0001$ for cardiac mortality; 2.55, 1.65–3.92, $p < 0.0001$ for all-cause mortality).⁸¹ In a study by Hoshino et al including 220 consecutive patients with intermediate stenosis, the authors showed that a PCAT_{MA} $\geq -73.1\text{HU}$ was related to an increased risk of major adverse cardiac events (MACE) (multivariate HR 3.11, 95% CI: 1.40–6.94, $p = 0.005$). Goeller et al defined a similar cut-off value of -73.5HU for PCAT_{MA} as independent predictor of MACE (HR 2.01, $p = 0.044$).⁷⁷

Oikonomou et al used a cloud-based quantitative software that calculates vessel-based PCAT_{MA}, and incorporates those values into a risk prediction algorithm together with traditional cardiovascular risk factors and information extracted from CCTA-based plaque analysis. The result was a vessel-specific coronary inflammation score that correlated with the 8 year risk for a fatal cardiac event (ΔC statistic of 0.085, $p = 0.01$ for the US Cohort and ΔC of 0.149, $p < 0.001$ in the European cohort).⁸⁰

Some studies focused on the relationship between PCAT_{MA} and outcome in specific high-risk subgroups. Ichikawa et al analyzed 333 patients with Type 2 diabetes, finding that high LAD-derived PCAT_{MA} predicted MACE.⁷⁶ Left ventricular hypertrophy (LVH) is a powerful predictor for cardiac disease prognosis. Hirano et al investigated 114 CAD patients with intermediate or severe stenosis on CCTA and invasive physiological tests. They

Table 3. List of studies reporting the role of PCAT_{MA} in prognostication and risk stratification

First author	Year	Study type	Measurement method	Patients	Main findings
Ichikawa ⁷⁶	2022	Prospective cohort study	Patient based (proximal 10–50 mm of RCA and proximal 40 mm of LAD)	333 patients with Type 2 diabetes mellitus undergoing clinically indicated CCTA	LAD PCAT _{MA} > -70.7 HU can significantly predict cardiovascular events in T2DM patients.
Goeller ⁷⁷	2021	Prospective cohort study	Patient based (proximal 10–50 mm of RCA)	293 patients who underwent CCTA because of atypical chest pain and blood sample to analyze serum levels of atherosclerosis-relevant inflammatory mediators	RCA PCAT _{MA} ≥ -73.5 HU is an independent predictor of MACE and shows a weak association with serum levels of atherosclerosis-relevant inflammatory biomarkers.
Hirano ⁷⁸	2021	Prospective cohort study	Patient-based (40 mm segments of the 3 coronary vessels, RCA starting 10 mm distal to the ostium, LAD and LCX starting at LM bifurcation)	114 CAD patients who underwent CCTA and invasive angiography and invasive functional measurements showing intermediate or severe stenosis	PCAT _{MA} is independently and significantly associated with LV mass index in patients with functionally significant epicardial stenosis and preserved systolic function.
Hoshino ⁷⁹	2021	Retrospective cohort study	Patient-based (proximal 40 mm of LAD)	220 consecutive patients with intermediate stenosis who underwent CCTA within 90 days of FFR	Patients with LADPCAT _{MA} ≥ -73.1 HU have an increased risk of MACE.
Kanaji ³⁴	2021	Retrospective cohort study	Vessel-based (40 mm segments of the three coronary vessels, RCA starting 10 mm distal to the ostium, LAD and LCX starting at LM bifurcation)	131 patients who underwent CCTA for suspected CAD, showing an intermediate-severe coronary stenosis, followed by phase-contrast MRI prior to PCI within 60 days	PCAT _{MA} is significantly associated with CFR independently of epicardial stenosis severity evaluated by FFR in CAD patients with a single lesion and preserved systolic function.
Oikonomou ⁸⁰	2021	Software training and validation	Patient-based (40 mm segments of the 3 coronary vessels, RCA starting 10 mm distal to the ostium, LAD and LCX starting at LM bifurcation)	3912 consecutive patients undergoing CCTA as part of clinical care in the USA (<i>n</i> = 2040, training cohort) and Europe (<i>n</i> = 1872, validation cohort).	CT cloud-based quantitative software that calculates PCAT _{MA} and, together with traditional cardiovascular risk factors and information extracted from plaque analysis, gives a vessel-specific coronary inflammation score which correlated with the risk for a fatal cardiac event in the next 8 years.
Kanaji ³⁶	2020	Retrospective cohort study	Patient-based (average PCAT _{MA} of LAD, LCX and RCA, 40 mm segments of the 3 coronary vessels, RCA starting 10 mm distal to the ostium, LAD and LCX starting at LM bifurcation)	116 patients with suspected first NSTEMI who underwent CCTA and subsequent successful PCI and CMR	Measured PCAT _{MA} before urgent percutaneous coronary intervention (PCI) was significantly related to lower CFR acquired with magnetic resonance at one-month post-PCI
Oikonomou ⁸¹	2018	Retrospective multicohort study	Patient-based (40 mm segments of the 3 coronary vessels, RCA starting 10 mm distal to the ostium, LAD and LCX starting at LM bifurcation). Statistical analysis performed only with RCA PCAT _{MA} .	3912 consecutive patients who underwent clinically indicated CCTA in two different institutes. 1872 patients in the first cohort (derivation cohort), 2040 patients in the second cohort (validation cohort).	RCA PCAT _{MA} ≥ -70.1 HU predicts all-cause and cardiac mortality beyond current risk stratification approaches, including measurement of coronary calcium and CCTA evaluation.

PCAT_{MA}: pericoronary adipose tissue mean attenuation; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; CCTA: Coronary Computed Tomography Angiography; FFR: Fractional Flow Reserve; CAD: coronary artery disease; MI: Myocardial Infarction; ACS: Acute Coronary Syndrome; CMR: Cardiac Magnetic Resonance; PCI: Percutaneous Coronary Intervention; CFR: Coronary Flow Reserve; MACE: Major Adverse Cardiovascular Events

found an independent relationship between PCAT_{MA} and LV mass index in patients with functionally significant CAD and preserved systolic function.⁷⁸

Coronary flow reserve (CFR) is the ratio of myocardial blood flow at stress to myocardial blood flow at rest. The presence of significant stenosis changes this parameter, making it an outcome predictor in patients with CAD. Kanaji et al. performed a retrospective cohort study involving 116 patients with non-ST segment elevation MI and successful coronary intervention and cardiac MRI in addition to CCTA imaging. They showed that PCAT_{MA} measured before urgent PCI was related to lower CFR based on cardiac MRI at 1-month post-PCI.³⁶ The same

author demonstrated a relationship between PCAT_{MA} and CFR independent of FFR in CAD patients with a single lesion and preserved systolic function.³⁴

CONCLUSION

CT-based PCAT analysis enables non-invasive evaluation of coronary inflammation, which is an indicator of cardiac disease, with PCAT_{MA} emerging as the most valuable measurement. Multiple studies have found a relationship between PCAT_{MA} and presence and severity of CAD and risk of cardiac events. Integrating PCAT_{MA} into modern coronary CTA interpretation may in the future help in the identification of individuals at risk of MACE, who might be candidates for more

intensive treatment. This review shows that there are still limitations and gaps of knowledge in the literature regarding PCAT evaluation. One of the main limitations this review points out is the variation in measurement approaches. In order to move forward, the measurement methodology should be standardized, considering influences such as age, sex, lumen-normalization, and tube voltage. Although PCAT_{MA} is currently mostly acquired in CCTA images, non-contrast cardiac CT-derived PCAT_{MA} may be a potential direction for evaluation at an early disease stage. Moreover, whether PCAT volume is relevant needs further exploration. Multicenter and prospective studies are needed to find cut-off values of PCAT_{MA} for diagnostic and prognostic purposes. Finally, so far, PCAT_{MA} merely shows associations on group level with limited HU differences (around 3–10 HU). Whether PCAT_{MA},

in view of physiological variations, measurement variations, and small absolute differences, can have value for individual patients, will need to be determined.

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