



Epicardial and pericardial fat analysis on CT images and artificial intelligence: a literature review

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Abstract: The present review summarizes the available evidence on artificial intelligence (AI) algorithms aimed to the segmentation of epicardial and pericardial adipose tissues on computed tomography (CT) images. Body composition imaging is a novel concept based on quantitative analysis of body tissues. Manual segmentation of medical images allows to obtain quantitative and qualitative data on several tissues including epicardial and pericardial fat. However, since manual segmentation requires a considerable amount of time, the analysis of adipose tissue compartments based on AI has been proposed as an automatic, reliable, accurate and fast tool. The literature research was performed on March 2021 using MEDLINE PubMed Central and “adipose tissue artificial intelligence”, “adipose tissue deep learning” or “adipose tissue machine learning” as keywords for articles search. Relevant articles concerning epicardial adipose tissue, pericardial adipose tissue and AI were selected. The evaluation of adipose tissue compartments can provide additional information on the pathogenesis and prognosis of several diseases, including cardiovascular. AI can assist physicians to obtain important information, possibly improving the patient’s quality of life and identifying patients at risk of developing variable disorders.

Keywords: Obesity; artificial intelligence (AI); adipose tissue; cardiac computed tomography (cardiac CT); metabolic syndrome (MetS)

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Introduction

The compartments of adipose tissue surrounding the heart are metabolically active organs. In recent years, a relationship has been demonstrated between epicardial adipose tissue (EAT) and heart diseases including coronary artery disease, heart failure with preserved ejection fraction, and atrial fibrillation (1-3). Obesity could cause unbalanced adipogenesis in EAT resulting in secretion of proinflammatory cytokines. Furthermore, the paracrine activity of the adipose tissue seems to be affected by other changes of hormonal status such as diabetes mellitus or menopause (4-7).

The metabolic syndrome (MetS) comprised of obesity, hyperglycemia, hypertension and atherogenic dyslipidemia, can lead to proinflammatory state and is a risk factor for cardiovascular diseases (*Figure 1*) (8). Moreover, the accumulation of visceral adipose tissue associated with MetS, non-alcoholic fatty liver disease (NAFLD) and EAT has been advocated as biomarker of cardiometabolic risk (6,9-11).

Computed tomography (CT) and magnetic resonance imaging (MRI) allow for non-invasive quantification of adipose tissue depots, including pericardial fat (12-17). However, quantification of pericardial adipose tissue depots is rarely performed outside research setting. Indeed, while CT is in the literature the most validated and reproducible technique for fat quantification, given the higher spatial resolution compared to MRI (18), many practical challenges remain.

When quantification is performed, manual segmentation of epicardial fat volume (EFV) quantification is today the method of choice (18). Nevertheless, this approach requires a laborious stepwise manual segmentation of relevant anatomical structures, being therefore operator-dependent and time-consuming, not suitable for routine clinical practice (18). Therefore, development of computer-assisted tools aimed at tissue segmentation and quantification is of paramount importance to improve consistency of results and reduce processing times (18).

In this context, artificial intelligence (AI) solutions, including machine learning and deep learning, has been recently proposed as solution to obtain fast, automatic, and reliable measures of abdominal adipose tissue on CT and MRI (19-24).

Machine learning is a group of techniques allowing to extrapolate or classify models through computer learning (19-24). These algorithms have the potential to offer

robust and feasible solutions to quantify adipose tissue compartments of the human body, including epicardial and pericardial fat, possibly enhancing, in an opportunistic fashion, the value of images acquired for other purposes.

The present literature review will be focused on AI supervised methods for epicardial and pericardial fat analysis using CT Images. Neither other imaging modalities (such as ultrasound or MRI) nor other adipose tissue compartments (such as paracardial adipose tissue) will be addressed in detail.

The aim of this paper is to provide an overview of the available evidence on AI algorithms proposed for the segmentation and quantification of epicardial and pericardial adipose tissues on CT images.

We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dx.doi.org/10.21037/qims-21-945>).

Anatomy and physiology

The adipose tissue surrounding the heart is divided into several compartments (*Figures 2,3*). EAT is the adipose tissue localized between the myocardium and the visceral layer of the pericardium. The contiguity between epicardial fat and myocardium is an important anatomical feature, given the epicardial tissue distinct properties. Within the EAT there is the pericoronary adipose tissue (PCAT), consisting of adipose tissue located in a radial distance to the external wall of the vessel equal to the diameter of the coronary vessel (25). PCAT is contiguous with the adventitial layer in large vessels, while adipocytes are present in vascular wall of small vessels and microvessels (3). The pericardial adipose tissue is located outside the EAT. It is lined internally by the visceral layer (located between the EAT and the pericardial adipose tissue) and externally by the parietal layer, located between the pericardial adipose tissue and the paracardial adipose tissue. Hence, from the inner to the outer layer this anatomy can be summarized with the following scheme: ((((((heart) perivascular adipose tissue) EAT) [pericardial adipose tissue = PCAT + EAT + pericardial adipose tissue] pericardial sac) paracardial adipose tissue) mediastinum).

EAT covers 80% of cardiac surface, with a greater concentration in the atrioventricular sulci, interventricular sulci and around the epicardial coronary arteries (26,27). Epicardial adipocytes are smaller in size than adipocytes of the subcutaneous and visceral adipose tissue. EAT also contains immune, stromal, inflammatory, nodal, and nerve tissue cells (4,28) (*Figures 2,3*).

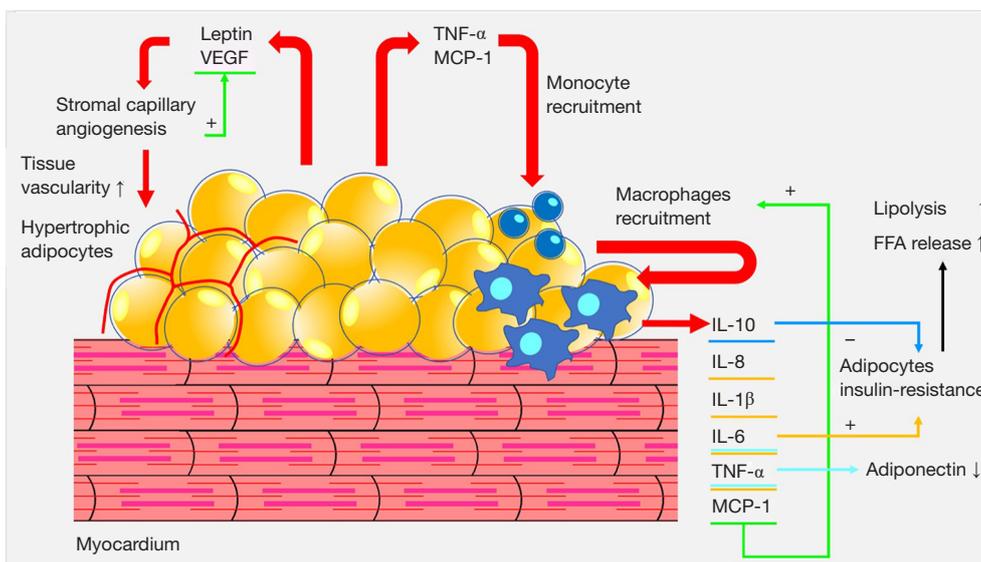


Figure 1 Pathophysiology of hypertrophic epicardial adipocytes. In obese subjects, triglycerides accumulation in adipocytes makes them hypertrophic. This result in a cellular and molecular inflammatory cascade with both positive and negative feedbacks involving VEGF and MCP-1. The mechanism determines macrophages accumulation with release of cytokines and relative local insulin-resistance with acceleration of lipolysis and release of FFA and reduction of adiponectin levels, and the increase in vascularization due to the increase in leptin and VEGF. VEGF, vascular endothelial growth factor; TNF- α , tumor necrosis factor α ; MCP-1, monocyte chemoattractant protein-1; IL-10, interleukin-10; IL-8, interleukin-8; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; FFA, free fatty acids.

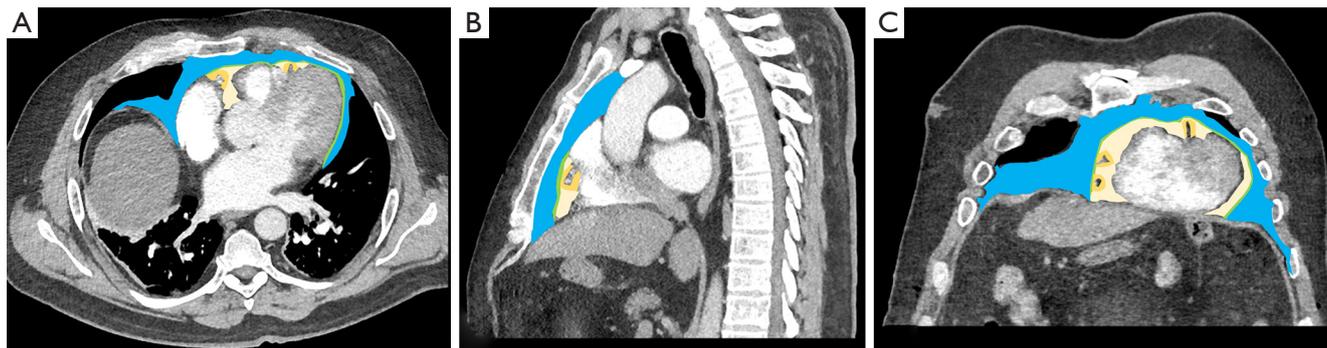


Figure 2 Thoracic CT on axial (A), sagittal (B) and coronal (C) planes. See regions of interest (ROIs) of PCAT (light orange ROI), EAT (light yellow ROI), pericardial adipose tissue (green ROI) and paracardial adipose tissue (light blue ROI). CT, computed tomography; PCAT, pericoronary adipose tissue; EAT, epicardial adipose tissue.

There are several known physiological functions of EAT related to cardiac physiology. It holds a protective function for the heart and a support for the coronary arteries against the torsion caused by the arterial pulse and cardiac contraction (29). Moreover, EAT derives from the same (splanchnopleuric) mesoderm as brown adipose tissue and omental fat cells.

It is also a barrier against pathogens through immune

activity, protects against hypothermia thanks to the activity of adipocytes that have brown or beige characteristics, adipocytes typically involved in thermogenesis, and regulates the energy supply to the myocardium through lipolytic and lipogenic activities (30,31).

Furthermore, it is now known that EAT is an endocrine organ having a unique secretome. In fact, it exerts a paracrine and vasocrine activity on the myocardium and

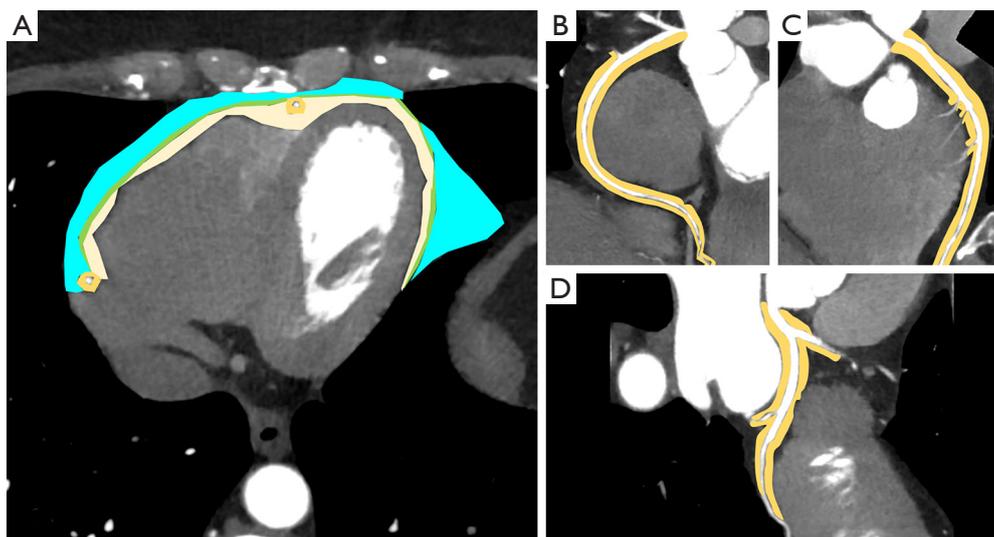


Figure 3 Coronary CT on axial plane (A) shows regions of interest (ROIs) of PCAT (light orange ROI), EAT (light yellow ROI), pericardial adipose tissue (green ROI) and paracardial adipose tissue (light blue ROI). Curved plane reconstructions of right coronary artery (B), left anterior descending artery (C) and circumflex artery (D), with highlighted perivascular adipose tissue (light orange ROI). CT, computed tomography; PCAT, pericoronary adipose tissue; EAT, epicardial adipose tissue.

coronary arteries through the release of adipokines with vasodilator, antioxidant, antifibrotic and anti-inflammatory activities (11,32). Indeed, EAT and pericardial adipose tissue correlate with several markers of oxidative stress, inflammation, and vascular dysfunction, underlining the importance of pericardial adipose tissue segmentation in addition to the other compartments (33).

Taken together, these arguments underline that adipose tissue surrounding the heart is of anatomical and physiological paramount importance.

AI

Machine learning

Machine learning is based in algorithms that enable computers to learn and predict, possibly improving according to experience (19). These sophisticated algorithms operate on large-scale heterogeneous data sets with the aim of discovering helpful patterns that would be hard or impossible to detect even for well-trained individuals (34).

Machine learning is subdivided into three categories according to the level of human supervision: supervised, unsupervised and reinforcement learning (19).

In supervised machine learning, training is supervised.

In this category the outputs are labeled by human experts, while the algorithm associates the inputs to the outputs. In unsupervised machine learning, the computer finds hidden structures of data and separates it into groups. The first subcategory provides data labels to the algorithm, while the second does not (19). In reinforcement machine learning, interactions with the environment provide computer learning that receives negative or positive reinforcement feedback (19).

These approaches can have profound implications for the diagnosis and treatment of diseases (34). The collection of specific data such as genomic testing for personalized cancer therapies, high-resolution two- (2D) and three-dimensional (3D) anatomical imaging or histological analyses, provide basis for future medicine based on early and precise diagnoses, personalized treatments and improve health assessment (34,35).

Artificial neural networks

Artificial neural networks are mathematical and statistical models that process information through elements called neurons connected to each other by multiple connections (i.e., nodes and edges), with a structure inspired by the biological nervous system (19). This network is made up of input layers, hidden layers, and an output layer. Through

these three levels the information is respectively entered, processed, and issued (19,36). This type of network can be achieved by three categories of learning: supervised, partially supervised, or unsupervised (19).

Deep learning

Deep learning consists of a subset of neural network algorithms in which there are several hidden levels. The different deep learning models are 1D convolutional neural networks (CNNs) in DL framework, such as pytorch and tensorflow, 2D model or 3D model. These two models are fully connected neural network and CNNs respectively, being the latter learning model the most used technique in medical imaging analyses.

Deep learning applies a different learning method of raw data than machine learning, in fact, the computational models of deep learning are composed by multiple processing layers that learn data representation with multiple levels of abstraction (21).

Deep learning also differs from artificial neural networks according to the number of hidden layers, connections, and ability to learn significative abstractions of the inputs. Indeed, artificial neural networks consist of three layers and are trained to gain supervised representations that are improved for specific assignments (37). The deep learning system instead receives data from an underlying layer and creates a representation of the observed models by improving a local unsupervised criterion (38). A characteristic of deep learning is that these layers of features are learned from the data using a learning procedure (39).

Methods

The literature research was carried out on March 2021 using MEDLINE PubMed Central. Only articles written in English, without limits of time span, were included. The keywords used for articles search were: “adipose tissue artificial intelligence”, “adipose tissue deep learning” or “adipose tissue machine learning”. Relevant articles related to EAT, pericardial adipose tissue and AI were selected also from the reference list of each identified article.

The title and abstract of all the articles of potential interest to our topic were screened, without any specific exclusion criteria. After this screening we filtered the literature search and selected 11 appropriate original articles for further review.

The articles investigating EAT, pericardial adipose tissue

together with mediastinal adipose tissue were included in this manuscript, focusing our analysis on the former two.

AI: epicardial and pericardial adipose tissues

In recent years, several research studies investigated the automatic segmentation of EAT on CT (*Figures 2,3*) using machine learning and deep learning algorithms. Most of these studies showed a level of evidence of 3. The major characteristics of studies are summarized in *Tables 1,2*.

A common path across studies is that AI-derived algorithms are often validated using the Dice similarity coefficient. This indicator is a statistical method that is used to reliably measure the similarity between two sets of data (*Figure 4*). Another indicator commonly applied is the accuracy, a fraction of true positive and true negative predicted instances among all instances (51) (*Figure 4*).

One of the first studies assessing a technique for the segmentation of the fat surrounding the heart compartments was reported by Rodrigues *et al.* (40). They divided the adipose tissue surrounding the heart into two compartments: the EAT (internal compartment) and the mediastinal adipose tissue (external compartment). The authors proposed an intersubjective registration consisting of multiple steps and based on the creation of an atlas that is subsequently moved over any cardiac CT image with range of Hounsfield unit (HU) of interest. Consequently, the similarity score was calculated and confirmation by heuristic method was added to reinforce the chosen position. For training the algorithm, a series of reliable data was provided, obtained from the manual segmentation of adipose tissue compartments of 10 male and 10 female patients. The model of automatic segmentation proposed by Rodrigues *et al.* showed a mean epicardial and mediastinal adipose tissue quantification accuracy of 98.4% and a mean true positive rate of 96.2%. Furthermore, for to the quantification of EAT, the model demonstrated a rate of successful automatic segmentations of 100%, a Dice score of 97.9%, and a true positive rate of 98.3% (40). However, this study was performed with an atlas-based, and not AI-based, method.

Rodrigues *et al.* proposed another method of epicardial, and mediastinal adipose tissue segmentation based on regression algorithms (41). The authors analyzed images according to the quantity of red pixels (i.e., epicardial fat), green pixels (i.e., mediastinal fat), blue pixels (i.e., pericardium), gray pixels (i.e., areas of interest to be segmented), black pixels (i.e., areas not to be segmented),

Table 1 Summary of CT comparative studies with proposed algorithms and results of EAT and pericardial adipose tissue compartments

Authors	AI category	Adipose tissue compartments	Algorithm	Accuracy	Number of patients	Dice score	Level of evidence*
Rodrigues <i>et al.</i> [2015] (40)	Machine learning	EAT, mediastinal adipose tissue	J84Graft	99.00%	20	96.80%	3
			Random Forest	98.90%			
			REPTree	98.90%			
			J84	98.90%			
			SimpleCart	98.90%			
			SMO	98.30%			
			RandomTree	97.50%			
			RBFNetwork	96.80%			
			Spegasos	96.80%			
			DecisionStump	96.80%			
			HyperPipes	94.80%			
			NaiveBayes	86.00%			
Rodrigues <i>et al.</i> [2017] (41)	Machine learning	EAT, mediastinal adipose tissue	Rotation Forest +	–	20	–	3
			MLP Regressor	98.70%			
			RBF Regressor	98.60%			
			MLP Regressor	98.50%			
			SMO Regressor	98.50%			
			Rotation Forest +	–			
			Random Forest	98.20%			
			Additive Regressor + Random Forest	98.10%			
			k-NN/IBk	98.00%			
			Random Forest	97.60%			
			M5P	96.90%			
			Alternating	–			
			Model Tree	96.90%			
			M5 Rules	96.80%			
			Linear Regression	95.30%			
			Extra Tree	95.10%			
			LeastMedSq	94.90%			
			Elastic Net	94.90%			
REP Tree	94.30%						
Random Tree	93.40%						

Table 1 (continued)

Table 1 (continued)

Authors	AI category	Adipose tissue compartments	Algorithm	Accuracy	Number of patients	Dice score	Level of evidence*
Priya <i>et al.</i> [2019] (42)	Machine learning	EAT, mediastinal adipose tissue, pericardial adipose tissue	Proposed methodology	EAT 98.5%	20	EAT 98.7%	3
				Mediastinal adipose tissue 98.4%		Mediastinal adipose tissue 98.2%	
				Pericardial adipose tissue 96.4%		Pericardial adipose tissue 98.5%	
Commandeur <i>et al.</i> [2018] (43)	Deep learning	EAT, thoracic adipose tissue	ConvNets	EAT 82.3%; thoracic adipose tissue 90.5%	250	95.3%±0.5% obtained for a threshold $t_s = 53.1\% \pm 5.1\%$	3
Commandeur <i>et al.</i> [2019] (44)	Deep learning	EAT	ConvNets	–	70	87.30%	3
Bandekar <i>et al.</i> [2006] (45)	Machine learning	Pericardial adipose tissue	Fuzzy affinity-based framework	Pericardial adipose tissue 99.13%±0.38%	23	–	3

*, SIGN100: Scottish Intercollegiate Guidelines Network 2019. CT, computed tomography; AI, artificial intelligence; EAT, epicardial adipose tissue.

the quantity of scan images and the index of the slice to be segmented. For the prediction of mediastinal adipose tissue, they reported a correlation coefficient of 0.9876, calculated with Rotation Forest algorithm with Multilayer Perceptron (MLP) Regressor, with a relative absolute error of 14.4% (root relative squared error of 15.7%) (41).

Priya *et al.* proposed an accurate method of adipose tissue segmentation using a Fruitfly Algorithm based on Modified region growing algorithm applied on CT images (42). Ground truth images of fat depots was provided as input to the neural network classifier, trained to distinguish a fat-infested image from a non-fat one image. Each pixel of the image was classified as epicardial or mediastinal. Finally, the segmented image was used as a source to distinguish epicardial or mediastinal adipose tissue based on the interpolation between pixels. This segmentation methodology based on the optimal neural network showed excellent results presenting with a Dice cross-correlation of 98.7 for epicardial fat, 98.2 for mediastinal fat and 98.5 for pericardium (42).

Moreover, Commandeur *et al.* proposed a deep learning method for the quantification of EAT and thoracic adipose tissue on coronary calcium scoring CT scans based on CNN ConvNets (43). The segmentation of the adipose tissue was performed on axial slices, provided as input in a

first network Net1. Then, the hidden convolutional unit was used to define the thoracic mask and differentiate pericardial and epicardial masks. A second Net2 network detected the pericardium. The epicardial mask obtained from Net1 was used to perform a radial sampling and modify the input CT slice from Cartesian coordinates to cylindrical coordinates. The transformed input was then supplied to Net2 which resulted in an output probability map of the pericardial sac. Finally, post-processing including HU threshold values (e.g., -190, -30 HU) to remove non-fat pixels and median filtering, provided binary images for quantification of adipose tissue. The authors reported a strong correlation between automatic and manual segmentation, with Dice scores of 0.924 and 0.945 for EAT and thoracic adipose tissue volumes, respectively (43).

Subsequently, Commandeur *et al.* conducted a multicenter study aimed to the quantification of EAT on non-contrast calcium-scoring CT scans using deep learning method from multiple cohorts, scanners, and protocols (n=850) (44). This deep learning model was implemented by using CNN with the TensorFlow framework, version 1.10.1 (<http://www.tensorflow.org>), and the Keras library, version 2.2.2 (<https://keras.io>). Using this network, the lower and upper limits of the heart are recognized, and the pericardium is segmented. The EAT is quantified through

Table 2 Summary of CT clinical studies with relative correlations with EAT and others adipose tissue compartments

Authors	AI category	Algorithm and/or software	Adipose tissue compartments	Data	Correlation	Number of patients	Results	Level of evidence*
Kroll et al. [2021] (46)	Deep learning	U-Net 3D	EAT	EAT Volume EAT Attenuation	Calcium artery score	966	r=0.18 r=-0.09	3
Eisenberg et al. [2020] (47)	Deep learning	Fully automated DL algorithm incorporated into QFAT research software (version 2.0)	Paracardial adipose tissue Visceral adipose tissue Intermuscular adipose tissue Subcutaneous adipose tissue	EAT	Major adverse cardiovascular events	2,068	P<0.01	1
Oikonomou et al. [2019] (48)	Machine learning	Aquarius Workstation V4.4.11-13, TeraRecon Inc., Foster City, CA, USA for basic segmentation and CaRI-HEART proprietary algorithms Caristo Diagnostics Ltd, Oxford, UK	Perivascular adipose tissue	Fat attenuation index Fat radiomic profile	Inflammation Vascularity	167, 1,575, 44	See Figure 4 for inflammation, vascularity and fibrosis	1, 3, 3
Lin et al. [2021] (49)	Deep learning	QFAT v2.0, CSMC, Los Angeles, CA, USA	EAT NAFLD	EAT volume EAT attenuation Hepatic attenuation	Fibrosis Major adverse cardiovascular events Perivascular changes related to acute myocardial infarction	2,068	P<0.001 P<0.001 P<0.001	2
Tamarappoo et al. [2021] (50)	Deep learning	QFAT v2.0, CSMC, Los Angeles, CA, USA	EAT	EAT volume EAT attenuation	Major adverse cardiovascular events Long-term risk prediction for cardiac events	1,069	P<0.0001 P=0.002	1

*, SIGN100: Scottish Intercollegiate Guidelines Network 2019. CT, computed tomography; AI, artificial intelligence; EAT, epicardial adipose tissue; NAFLD, non-alcoholic fatty liver disease.

$$\text{Dice similarity coefficient} = \frac{2 * \text{area of overlap}}{\text{Total area of ROIs}}$$

$$\text{Accuracy} = \frac{\text{True positive} + \text{true negative}}{\text{True positive} + \text{true negative} + \text{false positive} + \text{false negative}}$$

Figure 4 Mathematical formulas of the Dice similarity index and accuracy.

three axial sections: the classification and segmentation section and the previous and subsequent sections. In addition, post-processing consisting of median filtering and the HU threshold for adipose tissue is applied. This study reported high correlation between deep learning quantification and manual segmentations of two experienced tracers ($r=0.973$ and $r=0.979$; $P<0.001$). Furthermore, a strong correlation was also demonstrated between deep learning EAT progression and manual EAT progression in 70 patients ($r=0.905$; $P<0.001$) (44).

Fully automatic deep learning method was adopted by Eisenberg *et al.* to quantify EAT volume and attenuation measures (HU) from non-contrast coronary CT to predict major adverse cardiovascular events, considered as myocardial infarction, late revascularization (>180 days) and cardiac death (47). Interestingly, they showed a correlation of major adverse cardiovascular events with the increased EAT volumes [hazard ratio, 1.03 (95% CI: 1.01–1.04), $P<0.01$] and with decreased EAT mitigation measures [hazard ratio, 0.83 (95% CI: 0.72–0.96); $P=0.01$]. Moreover, EAT volume correlated with serum levels of C-reactive protein, D-dimer, adiponectin, myoglobin, plasminogen activator inhibitor-1 and myeloperoxidase ($P<0.01$). These serum biomarkers together with interleukin-6, endothelial cell-selective adhesion molecule and matrix metalloproteinase-9 showed an inverse correlation with EAT attenuation ($P<0.05$). This study robustly demonstrated how fully automated deep learning analysis of EAT volume and EAT attenuation can provide important clinical information in asymptomatic patients (47).

Kroll *et al.* examined a method for fully automatic quantification of epicardial and paracardial adipose tissues for possible use in cardiovascular risk assessment (46). A deep learning network was used for quantification of adipose tissue from coronary CT in 966 patients with intermediate Framingham risk scores. The deep learning architecture used was an evolution of the system described by Koitka *et al.* (52). The body was segmented into semantic regions using a multi-resolution U-Net 3D network. HU thresholds ranging from –190 to –30 and –29 to –150 were

used to segment adipose tissue (subcutaneous adipose tissue, visceral adipose tissue, intermuscular adipose tissue, EAT and paracardial adipose tissue, respectively) and muscle tissue. The Dice score on the test set showed the following values: subcutaneous tissue, 0.97; muscle, 0.96; thoracic cavity, 0.98; mediastinum, 0.90 and pericardium, 0.96. The results of this study showed no correlation between the volume and density of EAT and paracardial adipose tissue with the coronary artery calcium score. EAT and pericardial adipose tissue volume and attenuation were not significantly correlated with Agatston score: EAT volume $r=0.19$, EAT attenuation $r=-0.09$, pericardial adipose tissue volume $r=0.25$ and pericardial adipose tissue attenuation $r=-0.14$. Because EAT and pericardial adipose tissue did not show a significant correlation when compared with coronary artery calcium, these parameters should not be used as a surrogate marker for coronary artery calcium.

No cut-off scores were identified in EAT and pericardial adipose tissue features for high-risk coronary artery disease (46).

Bandekar *et al.* presented another method for the automatic quantification and classification of pericardial adipose tissue (45). The study performed on 23 subjects was divided into two phases: training phase and deployment phase. Using a training dataset in the first phase, object-specific distributions (fat, non-fat, background classes) were estimated. The second phase consisted of multiple steps mainly to remove artifacts, automatically detect the body contour to process data within the contour, segment and label the different organs/tissues. The results of this study were compared with manual segmentation and showed a mean accuracy for pericardial adipose tissue of $99.13\% \pm 0.38\%$, a mean true negative rate of $99.28\% \pm 0.33\%$ and a mean true positive rate of $85.63\% \pm 7.42\%$ (45).

Oikonomou *et al.* analyzed the radiomic profile of the perivascular adipose tissue using coronary CT through a machine learning-derived radiotranscriptomic signature (48). The authors performed a fundamental work composed by three different analyses:

❖ Study 1: in this study, 167 patients performed

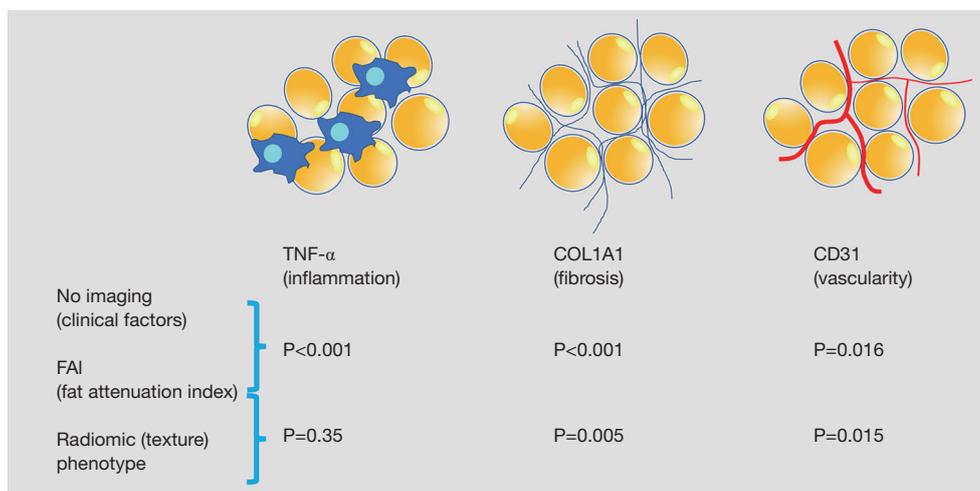


Figure 5 Comparison of nested linear regression models with relative gene expression as the dependent variable and clinical risk factors, FAI and radiomic (texture) phenotype.

coronary CT and underwent cardiac surgery. Adipose tissue biopsies were performed during surgery to look for a relationship between the expression of genes that characterized inflammation, fibrosis, and vascularity and radiotranscriptomic evaluation. Gene expression was evaluated by tumor necrosis factor α (TNF- α) for inflammation, COL1A1 for fibrosis and endothelial-marker platelet and endothelial cell adhesion marker CD31 (PECAM1) for vascularity.

- ❖ Study 2: then, a case-control study was designed to distinguish the perivascular adipose tissue of individuals with increased risk for major adverse cardiac events and compare it with radiotranscriptomic signature of inflammation, fibrosis, and vascularity. The groups consisted of patients with a major adverse cardiac event within 5 years and patients who had no cardiac events in the same period. The radiomic signature of high-risk perivascular adipose tissue [fat radiomic profile (FRP)] was trained and validated by scans randomly divided into training/internal validation (80%) and an external validation set (20%), to discriminate high-risk cases from low-risk cases. Consequently, FRP was explored in 1,575 patients to verify if it could add value in cardiac risk prediction beyond traditional risk factors.
- ❖ Study 3: finally, a prospective evaluation was performed to assess the ability of FRP to monitor

perivascular changes related to acute myocardial infarction. Forty-four patients with coronary CT performed 96 hours before and 6 months after the ischemic event were evaluated. A total of 843 radiomic features were calculated for each adipose tissue segmentation using the Slicer Radiomics extension which incorporates the Pyradiomics library into 3D Slicer (v.4.9.0-2017-12-18 r26813).

The results of the three studies are summarized below:

- ❖ Study 1: the fat attenuation index (FAI) was a performing metric for the evaluation of adipose tissue inflammation. The radiomic plot showed a comparable or greater performance than FAI in detecting fibrosis and vascularity, but not inflammation, suggesting that adipose tissue phenotyping constitutes a non-invasive model for detecting fibrosis and microvascular remodeling of the adipose tissue (*Figure 5*).
- ❖ Study 2: radiomic phenotyping of perivascular adipose tissue produced 1,686 radiomic features (843 features around each vessel). The stability analysis identified 1,391 features with an intra-class correlation coefficient of 0.9. In the case-control evaluation the univariable receiver operating characteristic (ROC) analysis highlighted a total of 22, 86 and 241 of the 1,391 stable radiomic characteristics discriminating cases with major adverse cardiac events from non-major adverse cardiac events ($P<0.001$, $P<0.01$, and $P<0.05$,

respectively). Moreover, FRP showed association with the adjusted risk of major adverse cardiac events [per 0.01 increments: adjusted hazard ratio (HR) 1.12 (95% CI: 1.08–1.15), $P < 0.001$].

- ❖ Study 3: higher FRP (i.e., adverse perivascular adipose tissue remodeling) values were found in 44 acute myocardial infarction patients undergoing coronary CT within 96 hours of admission compared to 44 matched controls undergoing coronary CT. Dynamic changes in perivascular FAI around the right coronary artery were seen at 6 months. Furthermore, in a subclass of 10 patients with ST elevation myocardial infarction these changes were pronounced in the region adjacent to the culprit lesion (50). These studies applied an atlas-based segmentation and not AI-based segmentation.

Recently, Lin *et al.* evaluated the association of MetS with CT-derived cardiometabolic biomarker (NAFLD and EAT) with long-term risk of major adverse cardiovascular events in asymptomatic subjects (49). Volumetry and attenuation of EAT were measured using a fully automated deep learning algorithm included into research software (QFAT v2.0, CSMC, Los Angeles, CA, USA). The final population consisted of 2,068 participants. Subjects with MetS had a higher prevalence of NAFLD (26.0% *vs.* 9.9%), a greater amount of EAT (114.1 *vs.* 73.7 cm³), and low attenuation values of EAT (−76.9 *vs.* −73.4 HU, all $P < 0.001$) compared to subjects without MetS. At 14±3 years, major adverse cardiovascular events occurred in 10.8% of subjects. Multivariable Cox analysis highlighted that NAFLD was predictive for major adverse cardiovascular events independent of EAT measures, coronary artery calcium score and MetS [HR 1.78 (95% CI: 1.21–2.61), $P = 0.003$]. The addition of the EAT volume significantly improved the reclassification for major adverse cardiovascular events (22% over atherosclerotic cardiovascular disease risk score; 17% over atherosclerotic cardiovascular disease risk score plus coronary artery calcium score) (50).

Lastly, Tamarappoo *et al.* proposed a machine learning model integrating quantitative CT measures, clinical risk factors, and circulating biomarkers to provide a better long-term prediction of cardiac events than current risk assessment. As in the study by Lin *et al.*, EAT was quantified by non-contrast CT using a fully automated deep learning algorithm (QFAT version 2.0, CSMC, Los Angeles, CA). The results of this study demonstrated a statistically significant difference between calcium artery score, EAT

volume and EAT attenuation between patients without and with cardiac events ($P < 0.0001$, $P < 0.0001$ and $P = 0.002$ respectively) (50).

Taken together, studies on the topic underline that investigating adipose tissue surrounding the heart with AI-based methods can be a robust and reliable approach, offering novel metrics that should be further tested to understand whether they can contribute to improve the current cardiovascular risk-assessment, follow-up, and treatments monitoring.

AI and body composition on cardiovascular imaging: perspectives

Non-invasive cardiac imaging using CT and MR has significantly evolved in the last decade, delivering anatomical and functional information at increasing superior levels. This is at least partially due to technological advances pairing advanced imaging methods with software solutions to extract more information from acquired images. As such, AI has already led to the introduction of potential new biomarkers like perivascular fat infiltration (48). This shows the potential of software techniques to extract from every CT or MRI scan “hidden” data regarding tissue characteristics that can be measured, including muscle mass and density, visceral and subcutaneous fat, liver fat, and vascular calcifications (53,54). Moreover, advanced analysis of medical images might provide insights into the interplay between functional phenotypes and genetic fingerprints in health and disease. In this respect AI solutions, such as machine learning and deep learning, can be helpful for researchers and physicians to improve classic disease definitions, genomic discovery, deep phenotyping, predict outcomes more precisely, and enhance our understanding of genetic and environmental basis of several disorders, including cardiovascular, with a potential positive impact on patient-tailored drug development (55).

There is growing interest in applying AI solutions in the context of opportunistic use of imaging data, to make this application feasible, fast, reproducible, and reliable across patients. It is likely that soon the value of epicardial and pericardial fat analysis on CT images will be empowered by AI, possibly becoming a clinical routine approach.

Conclusions

AI is a revolutionary innovation allowing for quantitative and qualitative analysis of EAT and pericardial adipose

tissue. These algorithms enable researchers and physicians to obtain important data at minimal or no additional cost to the healthcare system and almost no additional workload to physicians. The current literature showed that investigating adipose tissue surrounding the heart with AI-based methods can be a feasible, robust and reliable approach to obtain novel metrics that will be used in clinical practice. Information including quantitative and qualitative data of EAT and pericardial adipose tissue can have an impact on cardiovascular disorders, possibly enhancing risk stratification, pathogenesis understanding, prediction of clinical outcomes and overall morbidity and mortality. Application of AI to cardiovascular images might help to prevent future adverse events, and support predictive and precision medicine strategies to improve patients' quality of life.

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Footnote

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