RESEARCH ARTICLE

Epicardial adipose tissue is a promising imaging biomarker of subclinical atherosclerosis

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ABSTRACT

Introduction: Identifying markers to discriminate high and low-risk individuals better is essential. Coronary Calcium Score (CAC) is an established marker of subclinical atherosclerosis. Epicardial Adipose Tissue (EAT), a new imaging biomarker, has shown considerable interest in the scientific community.

Purpose: Study the impact of EAT volume in discrimination and reclassification of cardiovascular events when added to CAC score. Investigate whether EAT volume is a good prognosis marker in an asymptomatic population.

Methods: A cohort of 1024 individuals without coronary disease were selected and followed prospectively during an extended period. CAC score was evaluated by cardiac tomography. Quantification of EAT was performed through a semi-automated technique (TeraRecon Aquarius Workstation). Pearson's or Spearman's correlations identified EAT-associated parameters. Harrel C-statistics assessed the discriminative ability for events. Categorical free Net Reclassification Improvement (cfNRI) and Integrated Discrimination Index (IDI) reclassified the individuals. Kaplan-Meier evaluated cardiovascular disease prognosis, and Cox regression identified variables independently associated with cardiovascular events.

Results: EAT volume was significantly correlated with age, body mass index, non-high-density lipoprotein (HDL) cholesterol, triglycerides, systolic and diastolic blood pressure, and inversely with HDL cholesterol. CAC score and EAT had a C-Statistic of 0.737 (0.651 - 0.823) and 0.662 (0.564-0.760), respectively. When EAT was added to CAC, it increased to 0.777 (0.681 - 0.873) and 60% of the participants were better reclassified (NRI=60%). Higher EAT volume displayed the worst prognosis (p=0.006) and was associated, independently, with cardiovascular events, even after adjusting for risk factors and CAC score (p=0.021).

Conclusions: EAT may be an essential imaging marker of subclinical atherosclerosis and a potential therapeutic target for primary prevention. Reducing EAT volume with adequate measures (physical exercise, proper diet, pharmacological interventions) could decrease atherosclerosis and improve outcomes.

Introduction

Epicardial adipose tissue (EAT) is a type of fat tissue located between the myocardium and the visceral layer of the epicardium (Fig.1).
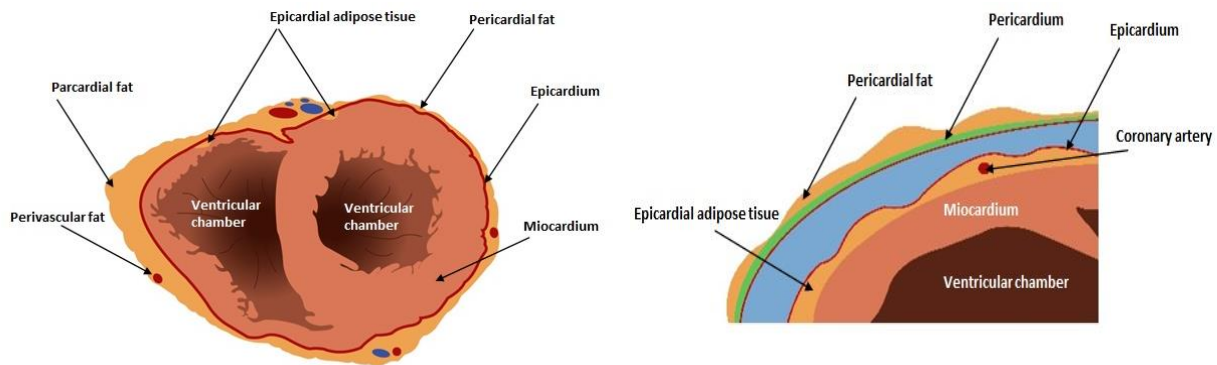

Fig. 1 Fat tissue bordering the heart

It has a common embryologic origin with the visceral fat depot and is considered the heart's visceral fat deposit in the body[1]. It should not be confounded with pericardial fat, as they have different embryologic sources and blood supply[2]. EAT is not isolated from the myocardium and vessels by muscular fascia. It plays a role in cardiovascular physiology and pathophysiology through its direct contact with the myocardium and coronary arteries by a shared microcirculation. EAT is now accepted as a metabolically active tissue producing and secreting multiple bioactive molecules, such as adipokines, cytokines, and growth factors which could be secreted to the myocardium and the coronary arteries via paracrine or vasocrine[3]. It also supplies energy by retaining a local reservoir that stores and releases fatty acids (FAs) as an energy substrate. EAT could release FAs directly to the myocardium when high energy is required, keeping it as request declines. If FAs remain in excess may produce cardio-lipotoxicity[4-6].

EAT plays several essential roles in heart function, and its dysfunction or excessive accumulation is associated with cardiovascular diseases such as atherosclerosis, coronary disease, arrhythmias, and heart failure[7].

Under normal physiological conditions, EAT has anti-inflammatory and immune-modulatory functions that help to protect the heart from inflammation and injury. Secreting adiponectin sustains the myocardium causing FAs combustion, and conferring protective activities against hypertrophy stimulus for the cardiac myocytes, inflammation, and fibrosis, protecting the myocardium and coronary arteries[8]. However, opposite to this defensive behaviour in pathological states such as obesity, type 2 diabetes, and others, EAT can become inflamed and provide cardiac inflammation and dysfunction[9].

Echocardiography, computed cardiac tomography, and magnetic resonance imaging have assessed EAT volume.

Nevertheless, differences among methodologies limit the equivalence between these modalities and a uniform standardized method for EAT quantification is still required, combined with average range values for this variable[10].

EAT is recently considered a robust independent predictor of future coronary events. In a current review, it was highlighted as a promising target organ for developing new drugs to improve cardiovascular prognosis[11].

The coronary artery calcium (CAC) score measures the amount of calcium in the walls of the coronary arteries, which can indicate the presence and extent of atherosclerosis (plaque buildup) in these arteries, revealing the lifetime aggregate effect of risk factors, genetic and environmental. Reflects the total calcium burden in the coronary artery, being a marker that provides relevant prognostic information to predict the probability of Coronary Artery Disease (CAD) in asymptomatic people[12]. The score is obtained using non-contrast computed tomography (CT). Previous studies have proved that CAC score is a strong independent predictor of CAD. It may be implemented in both sexes, middle-aged and senior classes, different ethnicities, and individuals with and without diabetes, playing an essential role in reclassifying individuals from intermediate to high risk allowing good decision-making without significant adverse effects[13-14]. Nonetheless, EAT's composition evaluation might be crucial in developing high-risk plaque behaviour, increasing the risk for Major Adverse Coronary Events (MACE). New

software versions quantify EAT density and volume when applicable to the no-contrast CT image. When EAT density was included, low-density EAT values were more significantly associated with plaque instability and MACE than higher EAT Volume. Individuals with a high CAC score and more advanced atherosclerosis showed a significantly lower EAT density than those with early atherosclerosis. However, this measure is most useful in arteries with low CAC scores (<100), higher EAT volume and low plaque density, as these very unstable boards can trigger serious events[15].

Nowadays, investigation has shown a strong independent association between EAT and CAC score, suggesting that EAT may play a role in subclinical atherosclerosis[16].

With this study, firstly, we aim to evaluate the relationship between EAT with CAC score and other cardiovascular risk factors. Secondly, we want to study whether EAT volume adds value to the CAC score in discriminating and reclassifying future cardiovascular events (MACE). Finally, we intend to investigate if EAT may be a predictive marker of prognosis, independent of the CAC score, in our asymptomatic population.

2. MATERIAL AND METHODS

2.1 Study Design and Participants
A prospective work was performed on 1024 subjects (mean age 51.6±8.2, 75.6% male) from the control population of the GENEMACOR study. This "ongoing" long-term

study investigates genetic and environmental factors affecting CAD in Madeira Archipelago[17]. Data were retrieved from the image retained in a standardized file of the Department of Cardiology's Archive and Communication Service. All participants, born and residents of Madeira, were called for a face-to-face appointment, gave their written informed consent to enter the study, and all demographic and clinical data, as well as traditional risk factors, were registered. Blood was collected for subsequent biochemical analysis, as designated elsewhere[18]. The participants delivered their written consent to participate in the study and were followed up between 2004 and 2022. The study protocol is in conformity with the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee and Institutional Board of our Central Hospital (50/2012).

2.2 Assessment of Epicardial Adipose Tissue volume and coronary artery calcium score

One operator independently measured the EAT using a quantitative semi-automated method on the TeraRecon Aquarius Workstation (version 4.4.7, TeraRecon, Inc., San Mateo, CA, USA). The technique involved measuring a single slice of EAT at the level of the left main coronary artery that had previously been validated (Fig.2). This method was found to be an effective and practical way to estimate total EAT volume, which is clinically relevant for prognostic purposes[19]. Before imaging, heart rate control and quality optimization were achieved using metoprolol and nitroglycerine. The imaging was performed using a 64-slice TOSHIBA CT scan. A non-contrast-enhanced, prospective ECG-triggered image acquisition was performed at the 70% phase with specific settings (collimation ¼ 64 × 0.625 mm; gantry rotation ¼ 350 ms; tube current ¼ 400–800 mA; tube voltage ¼ 120 kV), and images were reconstructed with a slice thickness of 3 mm. The Pericardial outline was manually traced at the ostium level of the left main coronary artery. The volume of tissue within the outlined boundary (ROI) with an attenuation of -250 to -30 HU was calculated in cm^3. This process was repeated for each patient/CT (as shown in the figure). The same imaging acquisitions were used to quantify the CAC score using the Agatson score algorithm. The distribution of CAC score by age and gender was done using Hoff's nomogram[20]. According to this nomogram, in the present study, two categories were created: CAC ≤ 100 and Percentile < 50 for gender and age; and CAC > 100 or Percentile ≥ 50 for gender and age.
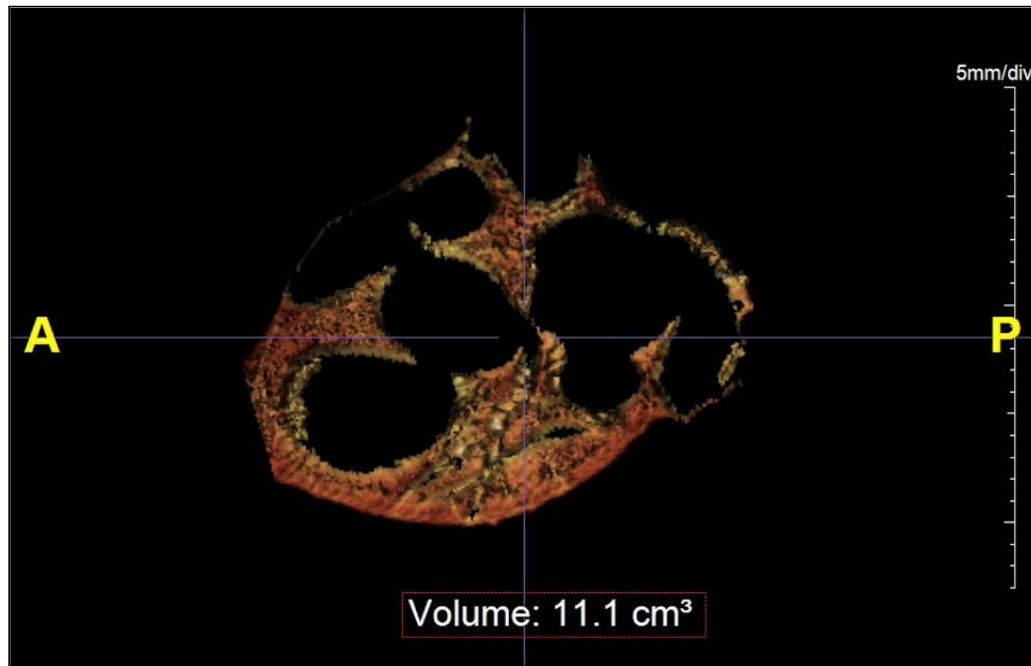
Fig. 2 - Epicardial Adipose Tissue (EAT) volume estimation from a single 3 mm slice at the level of the left main coronary, using a range of attenuation of- 250 to -30H U-TeraRecon Aquarius Workstation

2.3 Outcomes

Asymptomatic participants may have atherosclerosis manifestations during the follow-up period, including myocardial infarction, unstable and stable angina, cardiac failure, ischemic stroke, cardiovascular death or death from any other cause. The follow-up examinations were done every two to three years to supervise myocardial ischemia, incident heart failure, ischemic stroke and other harmful events until December 2022 (5.6±4.5 years).

2.4 Statistical analysis

Continuous variables are presented as means (±SD) or medians (Min-Max), as appropriate, and categorical variables showed frequencies and proportions. Student's t-test (or Mann-Whitney) compared continuous data, and the $\chi 2$ test compared categorical variables. EAT volume was determined and correlated with CAC score and other cardiovascular risk factors using linear Pearson or Spearman correlation coefficient, as indicated. Harrell C-statistics assessed the event's risk discrimination, and the event's reclassification was evaluated with categorical-free Net Reclassification Index (cfNRI) and Integrated Discrimination Index (IDI).

By Kaplan-Meier´s method, we assessed EAT volume on the individual's survival probability, with MACE or overall events, during an extended follow-up period.

Finally, we performed Cox proportional hazards models to estimate whether EAT is independently associated with MACE, even when adjusted for traditional risk factors and CAC score. Consequently, four EAT models were estimated: firstly unadjusted, with the EAT volume alone; secondly, adjusted to age and gender; thirdly, adjusted for traditional

risk factors (systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), fibrinogen, C reactive protein (CRP) and leukocytes) and lastly with conventional risk factors plus CAC score. A second Cox Hazard model (adjusted for traditional risk factors) was performed to investigate the impact of the combined interaction of CAC and EAT volume in the asymptomatic population prognosis.

3. RESULTS

3.1 Study population and baseline characteristics

A total of 1024 individuals without CAD were included in the study. Twenty-nine (3%) suffered MACE, and 995 (97%) did not. MACE included: Acute Coronary Syndrome, Percutaneous Transluminal Coronary Angioplasty, Coronary Artery Bypass Graft, Heart Failure, Ischemic Stroke and Cardiovascular Death.

The study population and baseline characteristics are described in Table 1.

Concerning traditional risk factors, patients with MACE were older (p<0.0001) and presented higher SBP (p=0.009) and DBP (p=0.030). They had increased type 2 diabetes (p<0.0001), BMI (p=0.046) and Pulse Wave Velocity (PWV) (p=0.010). They also displayed higher levels of leucocytes (p=0.002), fibrinogen (p=0.044) and CRP values (p=0.002).

EAT volume was highest in the population with events (p=0.001). Of the individuals in the EAT third tercile, 62.1% had MACE vs 32.3% with no MACE (p=0.001). Finally, the elevated CAC score (>100) presented a significantly higher percentage in the events group (65.5% vs 25.2%, p<0.0001).

The remaining variables did not show significant differences between subjects with and without MACE (Table 1).

Table 1 Overall characteristics of the population

Variables	Total (n=1024)	MACE (n=29)	No MACE (n=995)	P-value
Age, years	58.3 ± 8.4	64.6 ± 8.1	58.1 ± 8.3	<0.0001
Male sex, n (%)	774 (75.6)	22 (75.9)	752 (75.6)	0.972
Physical inactivity, n (%)	432 (42.2)	10 (34.5)	422 (42.4)	0.394
Smoking status, n (%)	232 (22.7)	9 (31.0)	223 (22.4)	0.274
Hypertension, n (%)	510 (49.8)	19 (65.5)	491 (49.3)	0.086
SBP, mmHg	135.4 ± 18.1	144.0 ± 18.9	135.1 ± 18.0	0.009
DBP, mmHg	83.7 ± 11.1	88.1 ± 12.3	83.4 ± 11.1	0.030
Dyslipidemia, n (%)	699 (68.3)	23 (79.3)	676 (67.9)	0.195
Diabetes, n (%)	126 (12.3)	10 (34.5)	116 (11.7)	<0.0001
Alcohol abuse, n (%)	448 (43.8)	16 (55.2)	432 (43.4)	0.208
CV family history, n (%)	123 (12.0)	2 (6.9)	121 (12.2)	0.390
BMI, Kg/m^2	28.1 ± 4.4	29.7 ± 4.6	28.0 ± 4.4	0.046
PWV, m/s	8.2 ± 1.8	9.4 ± 2.4	8.1 ± 1.7	0.010
Total cholesterol, mg/dl	204.0 (101.0 – 361.0)	199.0 (133.0 – 292.0)	204.0 (101.0 – 361.0)	0.453
LDL-c, mg/dl	126.1 (9.6 – 582.0)	123.6 (43.6 – 222.8)	126.2 (9.6 – 582.0)	0.503
HDL-c cholesterol, mg/dl	49.0 (22.0 – 100.0)	46.3 (29.5 – 73.0)	49.0 (22.0 – 100.0)	0.271
Non-HDL cholesterol	154.0 (55.0 – 322.0)	149.7 (94.0 – 247.2)	154.0 (55.0 – 322.0)	0.631
Triglycerides, mg/dl	112.0 (4.9 – 1631.0)	137.0 (41.0 – 404.0)	112.0 (4.9 – 1361.0)	0.148
Cr. Clearance*, n (%)	28 (2.7)	1 (3.4)	27 (2.7)	0.811
Creatinine, mg/dl	1.0 (0.5 – 1.6)	0.9 (0.6 – 1.5)	1.0 (0.5 – 1.6)	0.759
Fibrinogen, mg/dl	369.0 (175.0 – 705.0)	380.0 (276.0 – 582.0)	368.0 (175.0 – 705.0)	0.044
Leucocytes, 10^3/µl	6.6 (2.9 – 14.1)	7.3 (5.3 – 11.0)	6.5 (2.9 – 14.1)	0.002
CRP, mg/L	2.7 (0.1 – 645.0)	4.9 (0.4 – 359.4)	2.7 (0.1 – 645.0)	0.002
EAT Volume, cm^3	6.0 ± 2.6	7.4 ± 2.5	5.9 ± 2.6	0.001
EAT 3rd tercile, n (%)	339 (33.1)	18 (62.1)	321 (32.3)	0.001
CAC>100, n (%)	270 (26.4)	19 (65.5)	251 (25.2)	<0.0001

MACE – Major Adverse Cardiovascular Events; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; CV – Cardiovascular; BMI – Body mass index; PWV – Pulse wave velocity; LDL – Low-density lipoprotein; HDL – High-density lipoprotein; Cr. – Creatinine; *Cockroft-Gault<60ml/min.; CRP – C Reactive Protein; EAT – Epicardial Adipose Tissue; CAC – Coronary Artery Calcium; Continuous data presented as mean ± SD or median (min-max); Statistically significant for p<0.05

3.2 Correlation of Epicardial Adipose Tissue volume with quantitative data

Age, BMI, non-HDL cholesterol, systolic and diastolic blood pressure, CAC score, and triglycerides were positively associated with EAT volume. Conversely, HDL cholesterol was negatively correlated (Table 2).

Table 2 - Correlation of Epicardial Adipose Tissue volume with quantitative data

Variables	R	P-value
Age	0.261	<0.0001
BMI	0.579	<0.0001
Total cholesterol	0.010	0.759
LDL-cholesterol	-0.002	0.958
HDL-cholesterol	-0.181	<0.0001
Non-HDL	0.069	0.027
Triglycerides	0.234	<0.0001
Fibrinogen	0.053	0.087
Leucocytes	0.106	0.001
SBP	0.297	<0.0001
DBP	0.281	<0.0001
CAC score	0.231	<0.0001

BMI – Body mass index; LDL – Low-density lipoprotein; HDL – High-density lipoprotein; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; CAC – Coronary Artery Calcium; Statistically significant for p<0.05

3.3 Correlation among Epicardial Adipose Tissue volume with categorical risk factors

Gender, obesity, hypertension, dyslipidemia, CAC score >100 and type 2 diabetes are significantly associated to EAT. Smoking status did not associate with EAT volume (Fig.3).
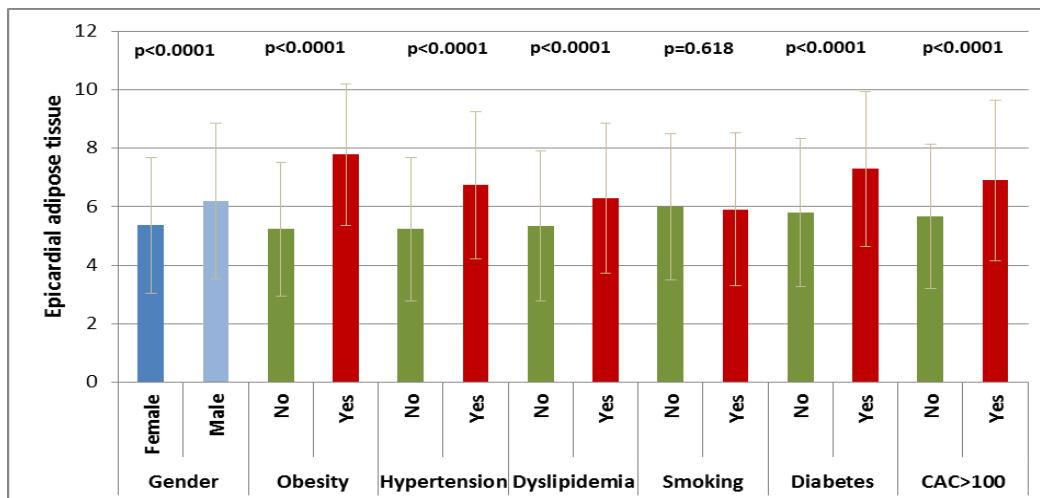

Fig. 3 – Epicardial Adipose Tissue volume according to cardiovascular risk factors. Data are presented as mean ± SD.

3.4 Evaluation of Epicardial adipose tissue ability on MACE discrimination and reclassification

Harrell's C-statistics and cfNRI were used to evaluate the MACE discrimination and the subject group reclassification. Results showed that EAT volume third tercile and CAC score >100 individually presented a C-statistics estimate of 0.662 and 0.737, respectively. However, when EAT was included in the CAC score model, C-statistic significantly increased to 0.777 (p=0.011). Likewise, a better reclassification was observed when EAT was added to CAC, with a cfNRI of 60% (p=0.001) and an IDI of 0.009 (p=0.033).

Table 3 - Evaluation of the incremental value of Epicardial Adipose Tissue added to the Coronary Artery Calcium model

	Estimate	95% CI	P-value
EAT C-statistic	0.662	0.564 - 0.760	-
CAC C-statistic	0.737	0.651 - 0.823	-
CAC + EAT C-statistic	0.777	0.681 - 0.873	-
ΔC-statistic	0.040	-	0.011
cfNRI, %	59.6	23.8 - 95.4	0.001
IDI	0.009	0.001 - 0.018	0.033

EAT – Epicardial Adipose Tissue; CAC – Coronary Artery Calcium score; ΔC – The change of C-statistic value when EAT was added; cfNRI – categorical-free Net Reclassification Index; IDI - Integrated Discrimination Index.

3.5 Survival analysis

3.5.1 Kaplan-Meier estimator

Survival analysis was performed with EAT volume over an extended follow-up period for MACE and overall events (Fig. 4A and B).

At 18 years of follow-up, the MACE-free survival time for the EAT volume for the first, second and third terciles was 97.0%, 94.9% and 79.3%, respectively (p=0.006) (Fig.4A).

Concerning the overall events (MACE plus death from any other cause), the events-free survival time also decreased per each EAT tercile (Fig. 4B). However, the third tercile of EAT had the most significant survival reduction (p=0.001).

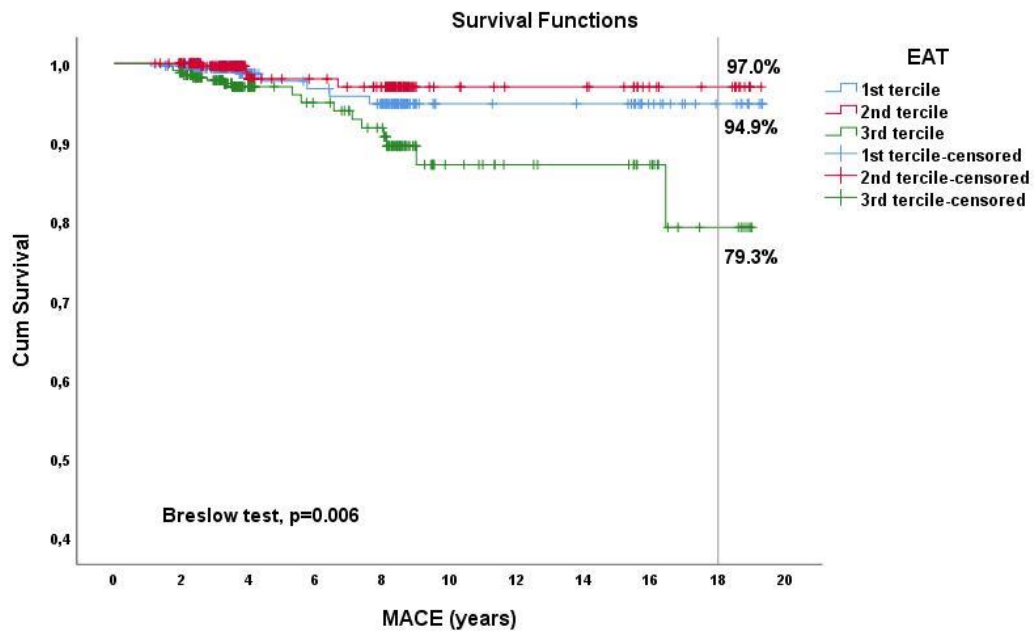**Fig. 4A** - This plot displays MACE-free survival time according to the EAT volume
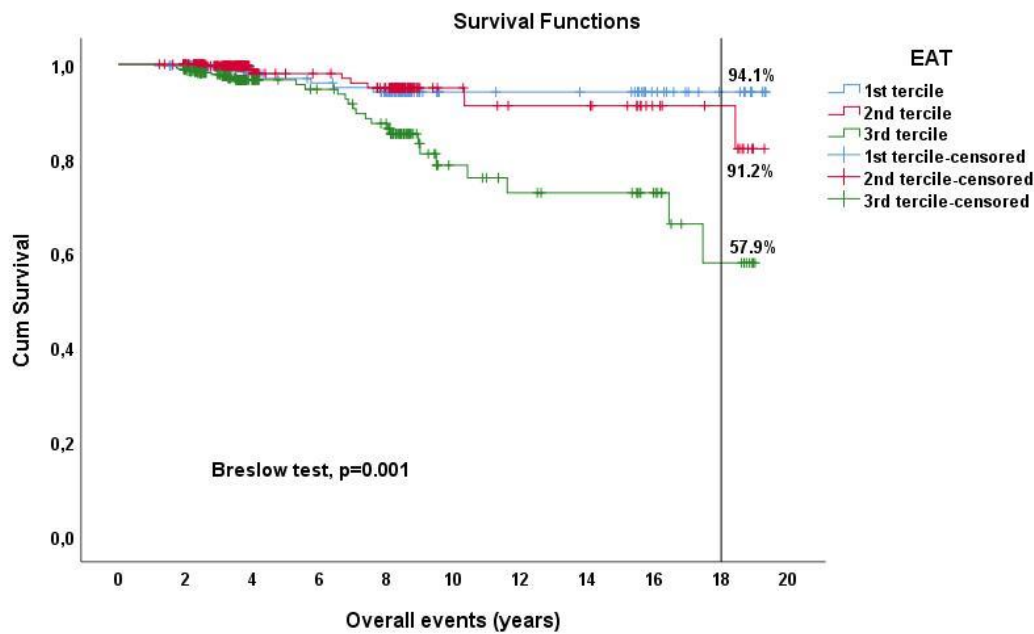

Fig. 4B – Overall events (n=44) free survival time according to the EAT volume

3.5.2 Cox regression analysis EAT volume on MACE risk occurrence (four successive models)

Four EAT models were created: model 1, unadjusted with the EAT volume alone; model 2, adjusted to age and gender; model 3, adjusted to age, gender and traditional risk factors; and model 4, adjusted to age, gender, traditional risk factors and CAC score.

When traditional risk factors were added to model 2, the EAT hazard ratio (HR) decreased from 3.382 to 2.433, with diastolic blood pressure and leucocyte count remaining in the equation. Likewise, when CAC was included in model 3, the HR was 2.466, remaining CAC score and leucocyte count as independently associated with MACE (Table 4).

Table 4 - Different EAT Hazard ratios for the models used in Cox regression analysis

Model (EAT volume)	Hazard ratio (95% CI)	P-value
1 – Unadjusted	3.382 (1.596 – 7.164)	0.001
2 - + age and sex-adjusted	3.382 (1.596 – 7.164)	0.001
3 - + Traditional risk factors*	2.433 (1.122 – 5.274)	0.024
4 - + CAC score (>100)	2.466 (1.148 – 5.298)	0.021

EAT – Epicardial Adipose Tissue; CAC – Coronary Artery Calcium.

*Traditional risk factors included systolic blood pressure, diastolic blood pressure, body mass index, fibrinogen, leucocytes and C reactive protein.

Combined interaction effects of CAC score and EAT on MACE risk occurrence

The combined interaction effects of CAC and EAT on MACE risk occurrence were performed with four combinations: CAC≤100 and EAT<third tercile (reference); CAC≤100 and EAT third tercile; CAC>100 and EAT<third tercile; CAC>100 and EATthird tercile. The

model was adjusted to the traditional and biochemical risk factors.

When CAC was ≤100 and EAT third tercile, the HR was 2.51; CAC>100 and EAT<third tercile, the HR raised to 3.47; CAC>100 and EAT third tercile, the HR increased to 8.47.
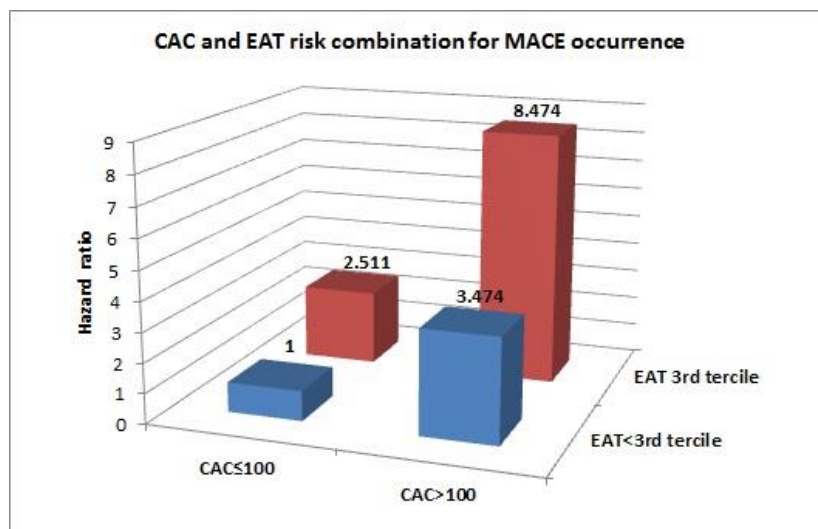

Fig. 5 – The combined interaction effects of CAC score and EAT on MACE risk occurrence.

4. DISCUSSION

Due to the increasing usage of coronary CT and new simplified imaging methods, the CAC score measured from non-contrast CT has regularly been added to traditional risk factors for predicting future cardiovascular events[21-22]. EAT volume, easily quantified from non-contrast cardiac CT, provides additional information regarding the "activity" of atherosclerosis in asymptomatic individuals. Dysfunctional EAT has been outlined as a source of inflammatory intermediaries associated with advancing coronary atherosclerosis through its direct contact with the adventitia of the underlying coronary arteries. It remains unidentified whether increased EAT volume is only restricted to subjects with more advanced atherosclerosis or could be observed in subjects with early coronary atherosclerosis (usually asymptomatic)[23].

In our work, we performed a prospective study to investigate the impact of EAT volume when added to the CAC score or on its own for events prediction, discrimination, and reclassification of the coronary risk in an asymptomatic population from Madeira Island.

We showed that the highest EAT volume (third tercile) was significantly associated with a CAC score>100 as well as with many risk factors for CV disease (age, male sex, hypertension, obesity, type 2 diabetes, BMI, non-HDL cholesterol, triglycerides, SBP, DBP, among others). In an "apparently" normal population followed over a long-time, we proved that EAT volume assessment could improve event risk stratification (future events discrimination and individuals' reclassification)

with a better estimate for cardiovascular and non-cardiovascular outcomes. Although the CAC score is a more powerful prognostic predictor than the EAT volume, we confirmed that EAT is complementary to CAC score and, when together, improves the discrimination for future events and the reclassification of risk groups. After survival analysis, the prognostic evaluation of EAT showed that a higher value was associated with a shorter event-free survival time after an extended follow-up (18 years). After multivariable Cox analysis, adjusted for CAC and other atherosclerotic risk factors, EAT volume (third tercile) remained in the equation as independently associated with MACE. Moreover, the combined interaction effects of CAC>100 with higher EAT volume increased exponentially the MACE risk (HR=8.47) (Fig. 5).

James Spearman et al. performed a meta-analysis to review the growing literature evaluating EAT's prognostic value systematically[24]. The results of their analysis indicate a need to standardize the quantitative evaluation of EAT. Considering all limitations of the meta-analysis studies, they conclude that EAT quantification significantly predicts clinical outcomes and provides incremental prognostic value over traditional cardiovascular risk factors and CAC scoring. EAT quantification can offer patients and their healthcare providers a more accurate outcome risk estimate. EAT volume quantification is an 'add-on' to the CAC score and may benefit asymptomatic patients for whom coronary CT angiography is not recommended.

Several studies also stated a direct relationship between EAT volume and CAC score. Iwasaki et al. confirmed increased CAC in patients with EAT volume>100 cm^3 than those with low EAT volume[25]. Their results showed that EAT was associated with coronary atherosclerosis and rose sharply in patients with significant coronary artery stenosis and those with severe coronary artery calcification. The authors concluded that EAT might be helpful, in addition to CAC score and coronary angiography, to detect patients at risk for CAD.

Heinz Nixdorf Recall Study also supports our findings. In this study, epicardial fat is correlated with fatal and nonfatal coronary events in the general population, independent of traditional cardiovascular risk factors, complementing the CT CAC score information[26].

The assessment of the EAT by CT in the past represented a complicated process, restricting its clinical applicability. However, as Commandeur and colleagues have shown, implementing new methods has changed the time-consuming EAT volume approach[27]. Artificial intelligence and convolutional neural networks make EAT a reliable and time-saving tool for assessing cardiovascular risk representing a clinically helpful and readily available instrument. Nonetheless, EAT's composition evaluation might be essential for determining high-risk plaque behaviour, increasing the risk for MACE. The new software versions already quantify EAT density and volume. When EAT density was included, low values were more heart significantly associated with plaque instability and MACE than higher EAT volume. Low EAT density was associated with an increased risk of readmission in patients with failure preserved ejection fraction (HFpEF)[28]. This finding agrees with a large population-based prospective study, which showed that low EAT density was significantly associated with MACE risk in asymptomatic individuals[29].

In the post-COVID-19 era, recent research showed the importance of EAT volume quantification in prognosis of this deadly infection. The SARS-CoV-2 could induce myocardial damage and other CV complications involving acute myocarditis, pulmonary embolism, or heart failure[30]. The exact process of heart injury in the sequence of SARS-CoV-2 infection is not entirely understood. Still, a high EAT volume and low EAT density in CT images could indicate myocardial harm, as it generally arises in severe and critical COVID-19 patients. Specific cardiovascular problems are asymptomatic during acute infection but may occur in post-COVID-19 disorder. Wei et al. proved that, in a group of 400 patients with confirmed COVID-19, patients with myocardial damage had a history of primary hypertension, type 2 diabetes, dyslipidemia, or cardiovascular disease[31]. They stated elevated plasma concentrations of Interleukin 6 as a marker of a greater risk of adverse complications in-hospital, such as mortality, mechanical ventilation, or admission to an intensive care unit. A CT image performed on admission showed that these patients also had a high EAT volume and low EAT density. This association is a strong independent predictor for myocardial damage in patients with

COVID-19[31]. Importantly, EAT may be a container of severe acute respiratory syndrome SARS-CoV-2 and an amplifier of COVID-19-related heart syndrome. In another study by Leandro Slipczuk et al., including patients admitted with proven COVID-19, the cluster with a mixture of CAC≥400 and EAT≥98 had the highest mortality[32]. CAC and EAT measured from chest CT were solid independent predictors of inpatient mortality from COVID-19 in this high-risk cohort.

Strengths

The long 18-year follow-up period of our study is, from our perspective, the strongest attribute in confirming the predictive value of EAT in the population's prognostic evaluation. Likewise, the fact that it was conducted in a single Centre enabled the quick identification of participants in case of need, minimizing any losses to follow-up. All fatal or nonfatal occurrences were noted. Our study proved, for the first time in Madeira, as far as we are aware, that this new marker may be crucial in the primary prevention of the asymptomatic population.

Limitations

Firstly, we should not assume that our population is representative of the Madeira Island population since it is composed of the GENEMACOR study control group. The participants had therefore been matched to a population suffering from coronary heart disease by age and gender, so there is a higher percentage of males (75%) than expected in the normal population.

In addition, despite including over 1000 subjects, the number of MACE remained small (n=29),

which may weaken the statistical analysis, even if significant results were obtained.

Furthermore, due to the limitations of the software used, we were able to measure the EAT volume but not its density, and this data is, therefore, lacking.

It is known that changes in lifestyle, such as diet, physical exercise, bariatric surgery, and pharmacological intervention, can modulate EAT volume. Still, unfortunately, we have not been able to investigate the impact of the changes, as mentioned earlier.

Finally, our study population was Caucasian, and thus our conclusions cannot be safely applied to other ethnic groups.

CONCLUSIONS

Epicardial fat is associated with cardiovascular events in the general population, regardless of conventional cardiovascular risk factors and CAC score. Our results confirmed that the EAT complemented the information received from the CAC score and could improve the value of non-contrast cardiac CT scans. We showed that EAT was independently associated with early cardiovascular manifestations of subclinical atherosclerosis in an asymptomatic population.

Therefore, EAT may be a reliable non-invasive primary prevention marker and could be used to improve risk stratification and early assessment of cardiovascular prognosis. The anatomical proximity of EAT and adjacent vascular and myocardial tissues may provide, in the future, an opportunity for appropriate measures through lifestyle changes or pharmacological intervention.

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Conflicts of interest:

None

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