THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2025.89896
Med Bull Sisli Etfal Hosp 2025;59(2):218-225

Original Research

Prognostic Value of Epicardial Fat Volume Quantification Related to Coronary Artery Calcium Score and Degree of Stenosis on Coronary CT Angiography

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Abstract

Objectives: Epicardial fatty tissue volume (EFV) is regarded as an important parameter in the evaluation of coronary artery disease (CAD). The aim of our study was to investigate the prognostic value of EFV measurements related to age, gender, coronary artery calcium score (CCS) and CAD severity through coronary computed tomography angiography (CCTA).

Methods: We retrospectively evaluated a total of consecutive 688 patients who were either asymptomatic but had a positive family history or had typical or atypical symptoms suggesting the presence of CAD. They all underwent CCTA examination with multiplanar reformat (MPR), maximal intensity projection (MIP), and myocardial three-dimensional (3D) volume rendering (VRT) images were obtained. We calculated CCS, coronary artery plaque stenosis degrees, the number of main coronary arteries involved and the EFVs for each patient. Finally, the relationship between the EFVs and all other parameters was analyzed by performing the Pearson and Spearman correlation analysis.

Results: We found a statistically significant difference between the genders of the patients where males presented higher EFVs than females (p=0.001, p<0.01). The correlation between the presence of CAD and the number of main vessels involved with EFVs was also statistically significantly higher in the analysis performed with the student t-test (p=0.001, p<0.01). There was a statistically significant but weak positive correlation between the ages of the patients (r=0.271, p=0.001, p<0.01), calculated total CCSs (r=0.149, p=0.001, p<0.01) and the degree of vessel stenosis determined based on coronary artery disease reporting and data system (CAD RADS) (r=0.347, p=0.001, p<0.01) and their EFV measurements.

Conclusion: We assume that the quantification of EFV performed by the CCTA technique is a potential novel method and hence, can guide clinicians in predicting the presence and severity of CAD.

Keywords: Coronary artery calcification, coronary artery disease, coronary artery stenosis, coronary computed tomography angiography, epicardial fat volume

Please cite this article as "Halefoglu AM, Yanc U, Belen E. Prognostic Value of Epicardial Fat Volume Quantification Related to Coronary Artery Calcium Score and Degree of Stenosis on Coronary CT Angiography. Med Bull Sisli Etfal Hosp 2025;59(2):218-225".

Coronary artery disease (CAD) is one of the leading causes of death and disability all over the world and also in our country. Epicardial fat tissue (EFT) is a metabolically active fat storage tissue lying down beneath the pericardium and in recent years, a significant association has been shown between EFV and coronary artery plaque stenosis, coronary artery calcium score (CCS), myocardial ischemia and major cardiac events.[1]

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Submitted Date: December 03, 2024 **Revised Date:** January 13, 2025 **Accepted Date:** January 26, 2025 **Available Online Date:** July 02, 2025

Although EFV may be measured by various imaging techniques, coronary computed tomography angiography (CCTA), due to its capability of providing multiplanar reformat (MPR) and volumetric images with high spatial resolution and reproducibility, should be the preferred technique and therefore is increasingly gaining a major role in predicting the severity of CAD and major cardiac events.[2]

In our study, we investigated the relationship between EFV quantified on CCTA and the age, gender, CCS, coronary artery plaque stenosis and the number of main coronary artery involvement parameters in a relatively large patient cohort.

Methods

Patient Selection

Our retrospective evaluation covered 688 consecutive patients. They were either asymptomatic but with a positive family history or had typical or atypical symptoms indicative of CAD and all underwent CCTA between February 2022 and September 2023.The study was approved by our Hospital Institutional Research Ethics Committee and written informed consents were waived. In our study, Declaration of Helsinki criteria were applied. Exclusion criteria included prior coronary stenting or bypass surgery and a history of myocardial infarction.

CCTA Protocol

The patients were advised to give up caffeine consumption a couple of days before the examination. Prior to examination, blood creatine levels were controlled. Optimal heart rate was provided, otherwise intravenous metoprolol was administered.

CCTAs of the patients were performed via a 64-slice multidetector CT (Siemens Somatom Definition Edge CT) by using heart-rate-dependent electrocardiographic (ECG) gating. Imaging parameters were; Field of view: 178 mm, Matrix size: 512x512, tube current: 188 mAs, tube voltage: 120 kV, Pitch: 0.17, Rotation time: 0.28 sec., Delay time: 3 sec., Scan time: 8.58 min., CTDI volume: 28mGy.

Images were obtained both before and after the intravenous administration of an iodine contrast agent. First, non-contrast CT (NCCT) images were acquired, extending from the carina down to the diaphragm level using 1 mm slice thickness and 0.75 or 1 increment factor during a single breath hold. On CCTA examination, a 70-80 ml iodine contrast agent (opaxol 350/100 ml or kopaq 350/100 ml) followed by 40 ml saline at an injection rate of 6 ml/sec was intravenously administered into the right median antecubital vein. Then, ECG-gating angiographic phase images were obtained during a single breath hold via automatic triggering when the opacification of the ascending aorta reached 120 HU. Finally, the acquired angiographic data was reconstructed with a 0.5 mm slice thickness at the appropriate diastolic phase, using three different kernels (BR 32, 38, 46). Thus axial, multiplanar reformat (MPR) and curved MPR, maximal intensity projection (MIP) and three-dimensional (3D) volume rendering (VRT) myocardial reconstructions were obtained (Fig. 1 a-c).

EFV Measurements

EFV measurements were performed on NCCT images using a dedicated, semi-automatic, validated segmentation software on the post-processing workstation (Siemens Syngovia). These measurements were obtained during the diastolic phase. Two abdominal radiologists determined pericardial boundaries on axial cardiac images with a consensus on starting at the pulmonary valve level and ending at the outermost inferior cardiac apex level. In this process, following the pericardium detection, approximately 20-30 contour points were placed manually

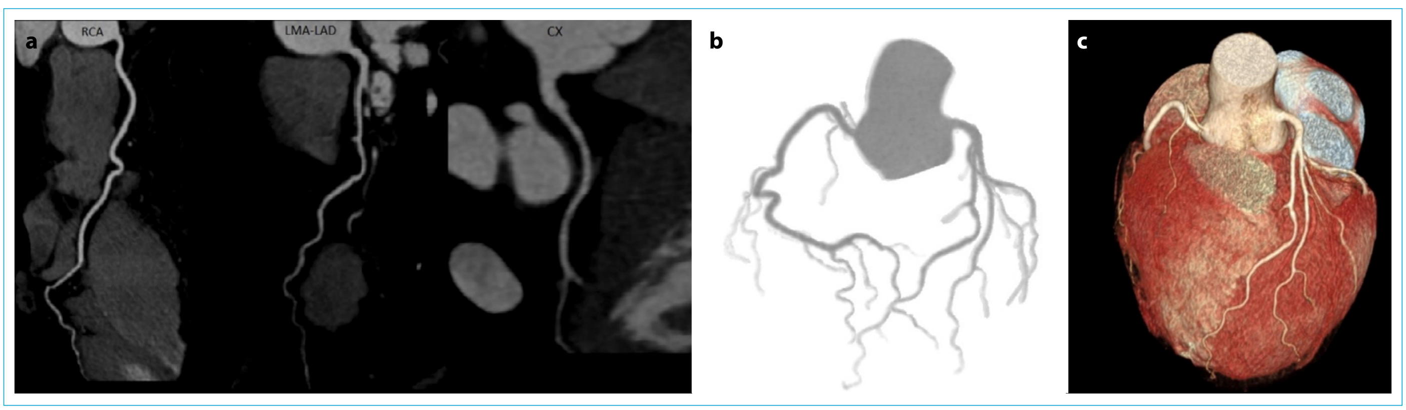

Figure 1. (a) Right main coronary artery (RCA), left main coronary artery (LMCA), left anterior descending artery (LAD) and left circumflex artery (LCx), curved MPR images. **(b)** VRT angiographic image. **(c)** Myocardium 3D VRT image.

on the pericardium at each axial image from the upper slice to the lowest one. As a result, a smooth pericardial contour was automatically generated. The EFV quantification was then automatically calculated using a segmentation algorithm based on the density threshold values, taking into account Hounsfield units (HU) ranging from -30 HU to -190 HU representative of fat tissue (Fig. 2 a-g). Here, the EFV is reported as cm^3 and the upper limit is regarded as 125 cm^3.[3]

CCS Quantification

Each set of NCCT cardiac axial images was evaluated in order to calculate CCS via a dedicated, semi-automatic software, enabling segmentation for detecting dense areas covering ≥ 3 pixels and showing >130 HU density, which were regarded as hyperattenuated lesions (CaScore, Siemens Medical Solutions).

A sum of total calcified plaque scores involving all main coronary arteries, (i.e. total CCS) was calculated by means of Agatston method. CCSs were classified into 4 groups: (Group 0:0, Group 1:1-99, Group 2:100-299, Group 3:>300).

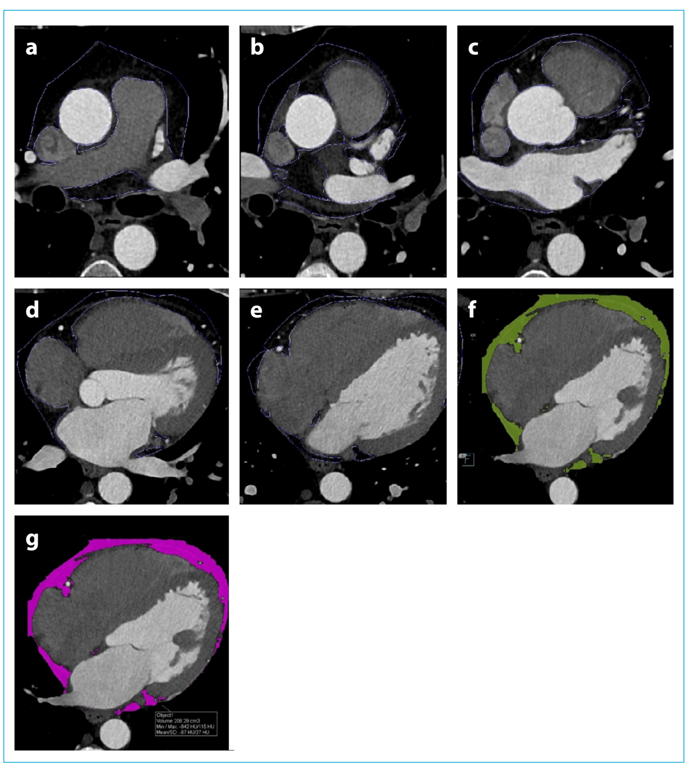

Figure 2. (a-e) EFV measurement technique. The pericardium boundaries were detected from the upper to the bottom slice and approximately 20-30 counter points were manually placed on all of the none-contrast axial cardiac images. **(f)** Then, a smooth pericardial contour was automatically obtained. **(g)** Finally, after adjusting the threshold values consisting of fat tissue, EFV quantification was calculated via a segmentation algorithm.

CCTA Analysis

According to the Society of Cardiac Computed Tomography (SSCT) guidelines, coronary artery stenosis is classified into four groups: minimal (<25%), mild (25-49%), moderate (50-69%) and severe (70-99%) stenoses.[4]

Coronary artery disease reporting and data system (CAD-RADS) is a scoring system that standardizes reporting in CCTA. This system gives a score between 1 and 5 depending on the severity of coronary artery stenosis. (0: no stenosis, 5: total occlusion).[5]

Two abdominal radiologists (A.M.H., 27 and U.Y., 4 years of experience, respectively) carried out plaque assessments on axial, MPR, curve MPR and MIP coronary artery images. Plaque-type classification was based on the presence of calcification and divided into calcified (only containing calcium) and non-calcified (calcium-free) types. Coronary artery stenosis was manually calculated based on the luminal diameter ratio, taking into account maximal stenotic segment and normal diameter healthy proximal or distal vessels.[6] According to the degree of stenosis, CAD-RADS scoring system was used for classification.

We also determined the number of main coronary arteries involved in terms of stenosis and classified patients into five groups based on four main coronary arteries (i.e. right main coronary artery (RCA), left main coronary artery (LMCA), left anterior descending artery (LAD) and left circumflex artery (LCx)) evaluated in the study.

Statistical Analysis

In evaluating the findings obtained in the study, NCSS (Number Cruncher Statistical System) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA) program was utilized for statistical analysis. The quantitative variables of the data were evaluated with mean, standard deviation, median, minimum and maximum values, and the qualitative variables were shown with descriptive statistical methods such as frequency and percentage. Shapiro-Wilks test and box plot graphics were used to evaluate the suitability of the data for normal distribution.

A Student t-test was used for the normally distributed quantitative evaluation of the two groups and a paired sample t-test was used for within-group evaluations. In comparisons of three groups or more, the oneway ANOVA test was used and the Bonferroni test was applied to determine the group causing the difference.

To evaluate the relationships between variables, Pearson or Spearman's correlation analysis was performed depending on the distribution.

The results were evaluated at the 95% confidence interval and the significance level was $p<0.05$.

Results

There were 688 patients in our study cohort consisting of 359 (52.2%) females and 329 (47.8%) males. Mean age was found to be 52.40±12.34, where median age was 52 and ages ranged between 29 and 93. Among these patients, 275 (40%) had hypertension and 172 (25%) had diabetes mellitus. All patients underwent CCTA in whom EFVs, CCSs, the presence or absence of CAD, CAD-RADS scores and the number of the main coronary artery vessels involved were determined.

EFV measurements of the patients ranged between 20.24 and 381.2 cm^3 and the average EFV was found to be 123.67±50.34 cm^3.

CCSs of the cases ranged between 0 and 3930 and the average score was 82.34±321.07. It was observed that 40.7% (n=280) of the patient cohort had CAD. CAD-RADS stenosis scores of the patients varied between 0 and 5, where the mean score was found to be 0.85±1.28. When these stenosis scores of the cases were classified; 59.3% (n=408) had a score of 0, 18.4% (n=127) 1, 7.7% (n=53) 2, 7.7% (n=53) 3, 6% (n=41) 4, and 0.9% (n=6) had 5 scores. The number of main coronary arteries involved was as follows; in 59.3% (n=408) of the patients 0; in 16.5% (n=114) 1, in 9.2% (n=63) 2, in 11.2% (n=77) 3 and in 3.8% (n=26) 4 arteries were detected. The above-mentioned demographic and clinical findings of the patients are summarized in Table 1.

EFV measurements of the males were found to be statistically significantly higher than the females (p=0.001, p<0.01). EFVs of the patients having CAD were found to be statistically significantly higher than those of the disease-free population (p=0.001, p<0.01). A statistically significant difference was found between the number of main coronary arteries involved and EFVs of the patients (p=0.001, p<0.01). As a result of pairwise comparisons performed to determine the source of the difference; The EFVs of the patients without an involved main coronary artery were significantly lower than those having involved arteries and there was a gradual increase between the number of arteries involved and EFVs (p=0.001, p=0.001, p=0.001, p=0.001, p<0.01). These findings are summarized in Table 2.

A weak positive, statistically significant relationship was detected between the ages of the patients and EFV measurements (r=0.271, p=0.001, p<0.01). A weak positive, statistically significant relationship was found between the CSCs and EFV measurements (r=0.149, p=0.001, p<0.01). Again, similarly, a weak but positive statistically significant relationship was found between the CAD RADS scores and EFV measurements (r=0.347, p=0.001, p<0.01). These findings are summarized in Table 3. Figure 3, Figure 4 and Figure 5 are representative cases.

Table 1. Distribution of descriptive features

	N (%)
Gender	
Female	359 (52.2)
Male	329 (47.8)
Age	
Mean±SD	52.40±12.34
Median (Min-Max)	52 (9-93)
EFT volume	
Mean±SD	123.67±50.34
Median (Min-Max)	116.5 (20.24-381.2)
Plaque burden (calcium score)	
Mean±SD	82.34±321.07
Median (Min-Max)	0 (0-3930)
Coronary artery disease	
Absent	408 (59.3)
Present	280 (40.7)
Stenosis (CAD RADS score)	
Mean±SD	0.85±1.28
Median (Min-Max)	0 (0-5)
0	408 (59.3)
1	127 (18.4)
2	53 (7.7)
3	53 (7.7)
4	41 (6.0)
5	6 (0.9)
Number of main coronary artery involved	
Absent	408 (59.3)
1 vessel	114 (16.5)
2 vessel	63 (9.2)
3 vessel	77 (11.2)
4 vessel	26 (3.8)

EFT: Epicardial fat tissue; CAD RADS: Coronary artery disease reporting and data system.

Discussion

EFT is a visceral adipose fat tissue encircling the myocardium and the visceral layer of the epicardium. It is a highly metabolically active tissue which secretes various inflammatory factors and therefore may act as an endocrine organ in the body.[7,8]

Recently, a significant correlation has been demonstrated between EFT and other various disease entities including CAC, coronary artery stenosis, myocardial ischemia, atrial fibrillation, diabetes and major adverse cardiovascular events (MACE).[1,9] Consequently, we may say that the non-invasive measurement of EFV can be investigated as a potential major prognostic factor underlying previously mentioned disease processes. EFV may be determined by various imaging techniques including CT, MRI, SPECT and

Table 2. Comparison of EFV measurements according to descriptive characteristics

	EFT volume		p
	Mean±SD	Median (Min-Max)	
Gender			
Female	107.95±41.04	104.2 (20.2-261.4)	[a]0.001**
Male	140.78±53.89	135.5 (28.9-381.2)	
Coronory artery disease			
Present	142.64±50.92	138.6 (41.5-381.2)	[a]0.001**
Absent	110.95±46.07	103.4 (20.2-269.1)	
Number of main coronary artery involved			
Absent	109.84±45.22	102.8 (20.2-246)	[b]0.001**
1	137.34±50.65	132.4 (41.5-273.1)	
2	138.87±51.65	133.5 (46.8-381.2)	
3	149.52±49.53	140 (60.9-309.3)	
4	165.69±48.46	157.1 (56.7-272.1)	

[a]Student-t Test; [b]One-Way ANOVA Test & Dunn-Bonferroni Test; **p<0,01.

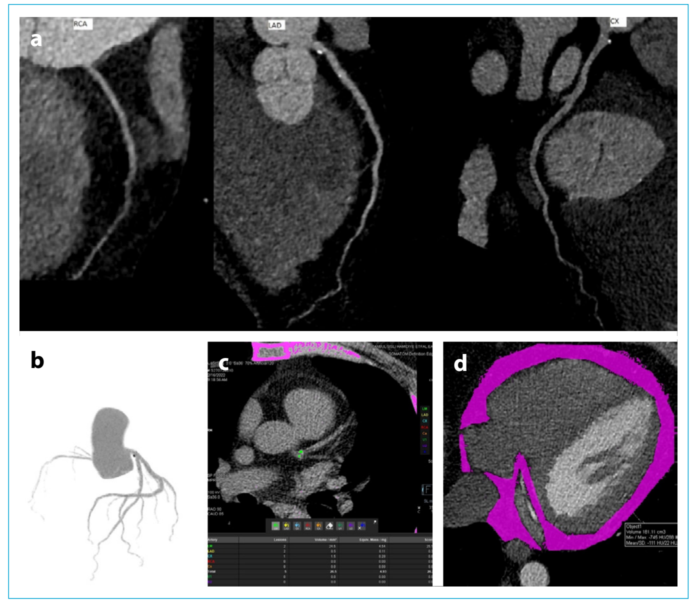

Figure 3. 46 year-old male patient. **(a)** LAD: 2, LCx: 1; calcific plaques are seen on curved MPR images. **(b)** VRT angiographic image, CAD RADS: 1. **(c)** CCS: 26.2, Agatston score: Group 1. **(d)** EFV: 181.11 cm^3.

Table 3. Relationship between EFV measurements and age, plaque burden and stenosis

	EFT volume	Age
Age		
†r	0.271	
p	0.001**	
Plaque burden (calcium score)		
‡r	0.149	0.241
p	0.001**	0.001**
Stenosis (CAD RADS score)		
‡r	0.347	0.452
p	0.001**	0.001**

p: Pearson's Correlation Test; r‡: Spearman's Correlation Test; **p<0.01; CAD RADS: Coronary artery disease reporting and data system.

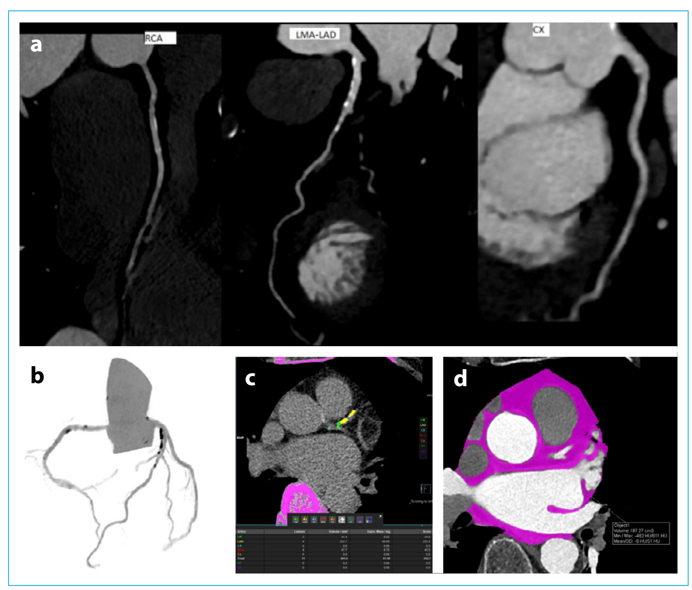

Figure 4. 64 year-old female patient. **(a)** RCA, LMCA, LAD; calcific plaques are avaliable on curved MPR images. **(b)** VRT angiographic image, CAD RADS: 3. **(c)** CCS: 342.7, Agatston score: Group 3. **(d)** EFV: 197.27 cm^3.

cardiac echo, based on either thickness or volume measurements.[10] In our study, EFV measurements were performed on consecutive non-contrast axial images of CCTA and the patients were thus not subjected to additional radiation exposure, because these quantitative measurements were only performed on the data set obtained from the previous routine examination.

A recently published meta-analysis performed by Wang et al.[11] including 21 studies and consisting of 1336 CAD and 1762 non-CAD patients revealed that a correlation was present between enlarged EFV and the occurrence of CAD. EFVs of CAD patients were shown to be larger compared to the non-CAD patients. An additional subgroup analysis showed that in severe CAD patients, both the thickness and volume of EFT were significantly larger than those of the mild and moderate group CAD patients. They concluded that extremely enlarged EFT volumes can play a role in the development of CAD and therefore could be considered as a prognostic factor and also a potential therapeutic target for CAD.[11]

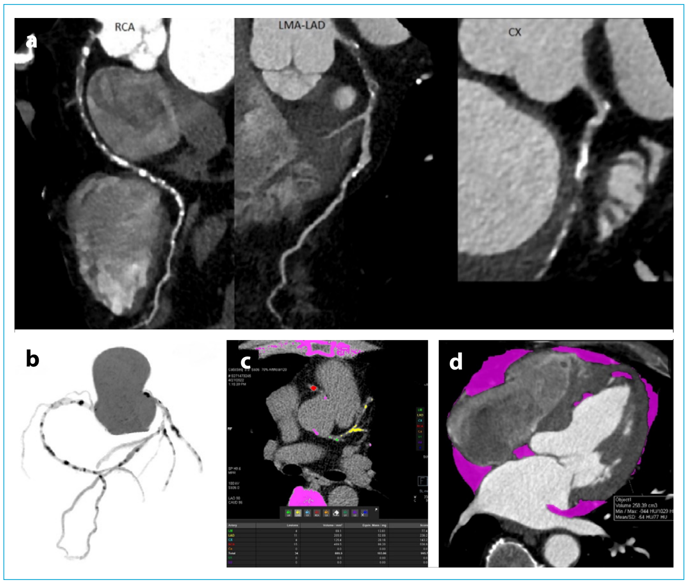

Figure 5. 65 year-old male patient. **(a)** RCA, LMCA, LAD, LCx: multiple, intensive calcific plaques are seen. **(b)** VRT angiographic image, CAD RADS: 5. **(c)** CCS: 995.7, Agatston score: Group 3. **(d)** EFV: 258.39 cm^3.

Wang et al.[12] demonstrated that an epicardial fat thickness measured along the left atrioventricular groove independently correlates to the severity of the CAD, supporting the study of Ueno et al.[13] who showed the relationship between EFV and chronic total coronary artery occlusions.

Rajani et al.[14] in their study revealed that in patients having calcified, partially calcified and non-calcified plaques, larger EFVs were detected. Furthermore, EFV has been proven to be associated with severe CAD (>70%) and is also independently associated with high-risk plaque features.[14]

Iwasaki et al.[15] determined the EFV of 197 patients who underwent a 64-slice multidetector CCTA and showed significantly higher EFVs in severe coronary artery stenosis patients (> 50%) compared to the non-stenotic ones.

Similar to these studies, we have also found a strong correlation between increased EFV and the development of CAD.

Spearman et al.[3] performed a systematic review investigating the incremental prognostic value of EFV measurements over CAC scoring and concluded that EFV measurements as an "add-on" to CAC scoring can be particularly useful for the asymptomatic patient group who do not need a CCTA. We obtained a positive but weak correlation between EFV and CCSs of our patient cohort.

Nerlekar et al.[16] reviewed a meta-analysis consisting of 9 studies and a total of 3772 patients. Herein, in 2 studies the EFT thickness and in the remaining 7 studies EFT volume measurements were performed. They obtained three important findings. First, larger EFVs showed a significant correlation with the occurrence of high-risk plaque (HRP) formation. Secondly, patients having HRPs demonstrated significantly larger EFVs compared to those without HRPs. Their third finding was that this correlation between EFT and the presence of HRPs was well demonstrated on volume measurements rather than the linear thickness methods.[16]

Mancio et al.[1] performed a systematic review and meta-analysis consisting of 70 published studies and comprising 41,534 patients. They found higher EFVs in patients presenting with CAC, coronary artery stenosis, myocardial ischemia and MACE. However, when they performed adjusted analysis, although an independent correlation was maintained for coronary artery stenosis, myocardial ischemia and MACE, it was not validated for CAC.[1] This result was also consistent with our study.

Milanese et al.[2] demonstrated a correlation between EFV and diabetes mellitus (DM), age, sex, body mass index (BMI), arterial hypertension, smoking and hypercholesterolemia on multivariate analysis.[2]

In a recently performed study by Weidlich et al.,[17] a significant correlation was shown between EFV and CAD-RADs scores of the patients indicating the importance of EFV in the development of CAD.

El Shahawy et al.[18] in their study revealed that 89.6% of patients presenting with higher EFV showed obstructive CAD, compared to 10.3% patients with non-obstructive CAD. They concluded that EFV was significantly higher in CAD patients, but also can be regarded as an important predictor for occurrence of multivessel coronary disease.[18] We also found a significant correlation between EFV and development of CAD with accompanying multivessel involvement.

Panda et al.[19] performed a retrospective study including 54 patients who underwent CT coronary angiogram using a multidetector row CT scanner. They demonstrated that quantification of EAT and pericardial adipose tissue (PAT) volume is useful in terms of revealing their relationship with the presence and severity of CAD.[19]

Yu et al.[20] showed a robust correlation between EFV and hemodynamically significant CAD and determined a cutoff value of 134.4 cm^3 for EFV in terms of alerting the risk of a hemodynamically significant CAD development.

In our study, consistent with the previous studies, a significant correlation was found between the EFVs of the patients and their gender, presence of CAD and the number of the main coronary arteries involved. Also, a statistically significant but a weak positive correlation was obtained between the EFVs and the patients' age, CCSs and the degree of coronary artery stenosis.

Our study had some limitations. First, it is a retrospectively designed study performed at a single center with a relatively limited population. Second, we could not obtain a complete clinical data from all of the patients. Third, the spatial resolution of CCTA may not be adequate in terms of detecting all coronary artery plaques. Fourth, we did not perform interobserver reliability but preferred a consensus way, which might have led to selection bias. Finally, we should state that further, larger cohort studies are needed to validate our results.

Conclusion

In conclusion, EFV measurements performed by CCTA could be a novel prognostic predictor in the diagnosis of CAD patients and may provide useful information about disease severity.

Disclosures

Ethics Committee Approval: The study was approved by the Sisli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (date: 04.07.2023, no: 2388).

Conflict of Interest: The authors declared no conflict of interest.

Funding Statement: The authors declared no financial support.

Authorship Contributions: Concept – A.M.H.; Design – A.M.H.; Supervision – A.M.H.; Materials – A.M.H., E.B.; Data Collection and/or Processing – U.Y., E.B.; Analysis and/or Interpretation – A.M.H., U.Y.; Literature Review – A.M.H., U.Y.; Writing – A.M.H.; Critical Review – A.M.H.

Use of AI for Writing Assistance: The authors declared that they did not use AI assisted technologies.

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