ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Exploring the interplay between epicardial fat, coronary artery calcium score, and nonalcoholic fatty liver disease through non-ECG-gated chest computed tomography: A cross-sectional study

Golnaz Moradi[1] ⓘ　|　Aisen Abed[1]　|　Diana Zarei[2] ⓘ　|　Haleh Ashraf[3]　|　Hoda Asefi[1]

[1]Department of Radiology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran

[2]Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Tehran University of Medical Sciences, Tehran, Iran

[3]Cardiac Primary Prevention Research Center (CPPRC), Cardiovascular Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran

Correspondence
Golnaz Moradi, Department of Radiology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran.
Email: Golnazz.moradi@gmail.com

Abstract

Background and Aims: This study examines the relationships between epicardial adipose tissue (EAT), nonalcoholic fatty liver disease (NAFLD), and coronary artery calcium score (CACS) using non-ECG-gated CT scans. It aims to determine the effectiveness of EAT measurements and NAFLD as predictors for coronary artery disease (CAD).

Methods: This cross-sectional study was conducted at a specialized center, focusing on individuals who underwent non-ECG-gated chest CT scans without contrast. We evaluated EAT thickness and density in three areas: the right atrioventricular groove, the free wall of the right ventricle, and the central area of the right anterior interventricular groove. Additionally, we measured CACS and determined the presence of NAFLD by comparing liver-to-spleen density ratios. Statistical analyses, including regression models, were performed using SPSS (version 26).

Results: In this study, we enrolled 365 participants, including 203 males with an average age of 47 ± 17.93 years. EAT thickness was 6.28 ± 1.62 mm, and EAT density was -96.07 ± 12.47 Hounsfield units (HU). The mean CACS was 22.27 ± 79.01, and the mean liver density was 50.01 ± 10.76 HU. A significant positive correlation was observed between EAT thickness and CACS ($r = 0.208$, $p < 0.001$). EAT density showed a significant negative correlation with CACS ($r = -0.155$, $p = 0.003$). No correlation was found between NAFLD and CACS. Univariate logistic regression analysis identified significant predictors of increased CACS, including EAT thickness (OR: 1.803), EAT density (OR: 0.671), diabetes mellitus (DM) (OR: 5.921), and hypertension (HTN) (OR: 7.414). Multivariate analysis confirmed the significance of EAT thickness (OR: 0.682), DM (OR: 3.66), and HTN (OR: 2.79) as predictors of elevated CACS.

Conclusion: Our findings demonstrate that increased EAT thickness and decreased density are associated with higher CACS. Also, both DM and HTN significantly contribute to increased CACS. These results support the inclusion of EAT measurements in cardiovascular risk assessment models to enhance diagnostic accuracy.

1 | INTRODUCTION

Coronary artery disease (CAD) is a major global health challenge and the leading cause of death and disability worldwide, responsible for about 20% of all deaths annually.[1,2] Epicardial adipose tissue (EAT), located between the myocardium and the visceral epicardium, plays a dual role in its interaction with the adjacent myocardium.[3] EAT can be beneficial due to its brown fat-like thermogenic function, but it can also be harmful by releasing proinflammatory and pro-fibrotic cytokines.[4] This unique anatomical position of EAT is closely linked to the development of CAD.[5] As atherosclerosis advances, the accumulation of calcium in the arteries intensifies. Consequently, measuring coronary artery calcium score (CACS) emerges as a promising method for assessing cardiovascular risk.[6]

Current advancements in cardiac imaging, particularly coronary computed tomography angiography (CCTA), have underscored the importance of assessing EAT volume.[7] This evaluation has shown a significant correlation with the presence and severity of coronary artery stenosis, even in asymptomatic individuals. Additionally, it aids in identifying high-risk atherosclerotic plaques. This approach underscores the potential of EAT characteristics as predictive markers for cardiovascular issues, extending their utility beyond conventional risk factors.[8,9] Recent investigations have confirmed an inverse association between EAT density and the risk of cardiovascular diseases. This positions EAT density as a distinct prognostic parameter for cardiovascular health in both genders.[10] On the other hand, the prevalence of nonalcoholic fatty liver disease (NAFLD) has surged in parallel with rising obesity rates.[11] Furthermore, cardiovascular diseases, particularly CAD, have emerged as a leading cause of mortality among individuals with NAFLD.[12]

Cardiac imaging modalities like echocardiography, cardiac magnetic resonance imaging (MRI), and cardiac computed tomography (CT) are used for noninvasive assessment of EAT. However, there is still no consensus on the best method for accurately measuring this type of fat.[13] Non-ECG-gated chest CT scans without contrast offer distinct advantages, including reduced radiation exposure and the elimination of the need for contrast agents. These scans also enable the calculation of CACS and provide the opportunity to assess metabolic indicators.[14]

Despite advances, the relationship between EAT measurements and NAFLD with CACS remains poorly studied. Furthermore, many studies rely on CCTA, which is not cost-effective and widely accessible.[10]

This study aims to investigate these associations using non-ECG-gated chest CT scans without contrast. This methodology provides a noninvasive and cost-effective approach, aiming to deliver a comprehensive analysis of EAT density, EAT thickness, NAFLD, and their relationships with CACS. Ultimately, this study endeavors to elucidate the intricate mechanisms underlying cardiovascular diseases.

2 | MATERIALS AND METHODS

2.1 | Study population

This single-center, cross-sectional study was conducted in 2021 at a university-affiliated hospital. The inclusion criteria were patients aged 18 and older who had non-ECG-gated, non-contrast chest CT scans and provided informed consent. Exclusion criteria included individuals with a history of prior heart surgeries or coronary interventions, chronic liver diseases, and heavy alcohol use. Additionally, to ensure the accuracy and reliability of our findings, we excluded 85 cases with missing data. This approach was chosen to avoid potential biases that could arise from imputation methods, thereby ensuring robust and credible findings.

2.2 | Data collection

We evaluated factors including the thickness and density of EAT, NAFLD, and CACS, along with demographic and clinical data. Patients filled out a custom-designed form with their demographic and clinical details at the time of admission. We divided the study population into two groups: those > 47 years and those ≤47 years, based on the mean age of our cohort, which was 47. This classification allows for a balanced comparison and detailed analysis of cardiovascular risk factors around the average age of our participants. Moreover, middle age is a critical period for the onset of many cardiovascular risk factors.[15]

2.3 | Measurements

In this study, a Philips Ingenuity Flex CT scanner was used to obtain high-resolution, thin-slice images of the thoracic region. The scan settings included a slice thickness of 1.5 mm. The tube voltage was set at 120 kVp for standard-sized patients, while for obese patients, it was increased to 140 kVp to account for the additional body mass. The average tube current across all scans was 70 mAs. The rotation time was 0.5 s, with a pitch value of 1.438. The collimation was set at 16 × 1.5 mm. The field of view (FOV) was adjusted for each patient to

ensure comprehensive coverage of the area of interest. As no contrast agents were used, there were no enhancement protocols. DoseRight technology was employed to minimize radiation exposure, and the dose-length product (DLP) was recorded for each scan. DoseRight technology was utilized to minimize radiation exposure, and the DLP was documented for each scan. Two board-certified radiologists, each with over 8 years of specialized experience, manually assessed all images. In cases of disagreements, a third expert radiologist provided the final evaluation. All image analyses were conducted using the MarcoPACS system for accurate and efficient interpretation.

2.3.1 | Quantification of epicardial fat thickness and density

EAT thickness was manually measured using an axial scan at three designated locations: the atrioventricular groove at the mid-section of the right coronary artery, the midpoint of the right ventricular free wall, and the mid-ventricular septum. The average of these measurements was recorded as the EAT thickness. The maximum EAT thickness was assessed by measuring from the visceral epicardium to the myocardium's outer edge, aligning the measurement perpendicular to the surface of the heart. Furthermore, we quantified the attenuation of epicardial fat by placing a circular region of interest (ROI) at these three points, and the average density value obtained was recorded as the EAT density. All measurements were performed on magnified images to accommodate the small dimensions of the EAT.

2.3.2 | Quantification of liver density

The application of non-contrast CT scans is instrumental in diagnosing and evaluating the presence and severity of hepatic steatosis. A liver density measurement below 40 Hounsfield units (HU) indicates hepatic steatosis. To assess liver density, we took measurements in three regions: two in the right lobe and one in the left lobe, each spanning an area of 100 mm². The average of these measurements was then used for analysis.

2.3.3 | Quantification of CACS

For the quantification of CACS, we used the Agatston method.[16] This involves calculating the score by multiplying the area of the calcified plaque (with a density greater than 130 HU) by a specific density factor. The area is determined by multiplying the maximum length and width of the plaque, measured perpendicularly. The density factor is assigned based on the highest HU value of the plaque: a factor of 1 for HU values between 130 and 199, 2 for values between 200 and 299, 3 for values between 300 and 399, and 4 for values of 400 or higher. The cumulative plaque scores were then calculated, and all measurements were taken from magnified images.

2.3.4 | Statistical analysis

The data analysis was conducted using SPSS version 26 (IBM SPSS Statistics for Windows, Version 26.0.: IBM Corp.). Descriptive statistics, including means and standard deviations, were employed to summarize quantitative variables, while frequencies and percentages were used for qualitative variables. To compare the two groups, a t-test was conducted. Relationships between variables were assessed using Pearson's correlation coefficient. Logistic regression analysis was performed to examine the independent associations among variables in predicting outcomes. A significance level of $p < 0.05$ was established for all statistical tests.

3 | RESULTS

3.1 | Study population

In this study, we initially evaluated 450 cases, ultimately 365 cases with fully completed forms were included. The mean age of the participants was 47 ± 17.93 years, ranging from 18 to 96. Among these patients, 203 (55.6%) were male, 53 had diabetes mellitus (DM), and 67 had hypertension (HTN). Detailed characteristics of the study population are summarized in Table 1.

3.2 | CACS, EAT thickness, and density

The mean CACS was 22.27 ± 79.01, with 72.3% (264 patients) having a CACS of zero. The average thickness of EAT was 6.28 ± 1.62 mm, and the mean EAT density was -96.07 ± 12.47 HU. Table 2 provides detailed information on CACS, EAT thickness, and density across various subgroups.

Significant correlations were observed between age, DM, and HTN with CACS. Patients older than 47 years had an average CACS of 50.68 ± 114.5, compared to an average CACS of 0.82 ± 4.76 in younger patients ($p < 0.001$). Those with DM had an average CACS of 70.38 ± 145.27, while patients without DM had an average CACS of 14.10 ± 57.59 ($p < 0.001$). Similarly, patients with HTN had an average CACS of 71.41 ± 127.74, compared to 11.22 ± 57.95 in those without HTN ($p < 0.001$). Age and BMI demonstrated significant associations with EAT thickness. Patients aged over 47 years exhibited an average EAT thickness of 7.04 ± 1.71 mm, compared to 5.7 ± 1.26 mm in younger patients ($p = 0.003$). Furthermore, individuals with a BMI of 30 or higher had an average EAT thickness of 6.92 ± 1.32 mm, while those with a BMI under 18.5 had an average EAT thickness of 4.37 ± 1.25 mm ($p < 0.001$).

Table 3 presents the correlation between EAT thickness and EAT density with CACS across various subgroups. The correlation analysis revealed a significant positive correlation between EAT thickness and CACS, with a correlation coefficient of 0.208 ($p < 0.001$). This indicates that as EAT thickness increases, CACS tends to increase as well. Additionally, this correlation remained significant when analyzed

TABLE 1 Characteristics of patients undergoing non-contrast, non-ECG-gated chest CT scans.

Variable		Mean ± SD (range)/N (%)
Age (year)		47 ± 17.3 (18–96)
Age (year)	≤47	208 (57%)
	>47	157 (43%)
Sex	Male	203 (55.6%)
	Female	162 (44.4%)
BMI (kg/m²)		26.58 ± 4.25 (16.06–42.42)
BMI (kg/m²)	<18.5	7 (1.9%)
	18.5–24.9	129 (35.3%)
	25–29.9	162 (44.4%)
	≥30	67 (18.4%)
DM		53 (14.5%)
HTN		67 (18.4%)
Smoker		59 (16.8%)
Cigarette consumption (pack/year)		13.60 ± 19.24 (0–100)
NAFLD		36 (9.9%)
Liver density		50.01 ± 10.76 (−10.6 to 73)
EAT thickness		6.28 ± 1.62 (1.66–14.33)
EAT density		−96.07 ± 12.47 (−112.4 to −62)
CACS		22.27 ± 79.01 (0–596)
CACS	0	264 (72.3%)
	>0	101 (27.7%)

Abbreviations: BMI, body mass index; CACS, coronary artery calcium score; DM, diabetes mellitus; EAT, epicardial adipose tissue; HTN, hypertension; N, number; NAFLD, nonalcoholic fatty liver disease; SD, standard deviation.

within subgroups based on sex and BMI (all $p < 0.05$). In contrast, EAT density demonstrated a significant negative correlation with CACS, with a correlation coefficient of −0.155 ($p = 0.003$). This suggests that higher EAT density is associated with lower CACS values. This negative correlation was particularly notable in females ($r = −0.258$, $p = 0.001$) and patients over 47 years ($r = −0.243$, $p = 0.002$). The correlation was significant across all BMI groups except for those with a BMI between 25 and 29.9, where the correlation was not significant ($r = −0.136$, $p = 0.084$). For more detailed information regarding the correlations of EAT characteristics with CACS in different subgroups, please refer to Table 3.

In the present study, 36 participants were diagnosed with NAFLD. The liver density was quantified as 50.01 ± 10.76 HU, ranging from −10.6 to 73 HU. Patients with NAFLD exhibited a higher EAT thickness, averaging 7.12 ± 1.72 mm, compared to 6.18 ± 1.57 mm in those without NAFLD. However, this difference was not statistically significant, with a p-value of 0.410. Additionally, patients with NAFLD demonstrated a lower average EAT density,

measuring −98.11 ± 6.03 HU, compared to −95.85 ± 12.96 HU in those without NAFLD; however, this difference was not statistically significant ($p = 0.353$). Analysis of the relationship between liver density and CACS revealed a correlation coefficient of 0.016, indicating no significant association ($p = 0.761$).

3.3 | Logistic regression findings

Univariate logistic regression analysis revealed that EAT thickness, EAT density, DM, and HTN had odds ratios (OR) of 1.803, 0.671, 5.921, and 7.414, respectively, all with $p < 0.001$, indicating their statistical significance in predicting CACS (0/ > 0). Furthermore, multivariate regression analysis underscored the significance of EAT density (OR = 0.682, $p < 0.001$), DM (OR = 3.66, $p = 0.005$), and HTN (OR = 2.79, $p = 0.015$) in predicting elevated CACS. The OR of 0.68 for EAT density in the multivariate analysis demonstrates an inverse relationship with CACS, suggesting that higher EAT density is associated with a reduced likelihood of increased CACS. All these variables remained statistically significant in predicting CACS, as detailed in Table 4.

4 | DISCUSSION

Our study provides valuable insights into the relationships between CACS, EAT measurements, and associated clinical factors in patients undergoing non-contrast, non-ECG-gated chest CT scans. Among 365 included patients, we found a mean CACS of 22.27 ± 79.01, with 72.3% of patients having a CACS of zero. Patients over 47 years old, as well as those with DM and HTN, exhibited significantly higher CACS values. The average EAT thickness was 6.28 ± 1.62 mm, and it showed a positive association with both age and BMI. Furthermore, EAT thickness was significantly correlated with CACS ($r = 0.208$, $p < 0.001$), indicating that increased EAT thickness is linked to higher CACS. Conversely, EAT density, which averaged −96.07 ± 12.47 HU, demonstrated an inverse correlation with CACS ($r = −0.155$, $p = 0.003$), suggesting that higher EAT density may offer protection against coronary artery calcification. The correlation between EAT measurements and CACS was more pronounced in females. EAT characteristics, along with DM and HTN, were significant predictors of CACS. Additionally, our analysis found no significant correlation between CACS, EAT thickness, or density with NAFLD. These findings highlight the importance of considering EAT characteristics in cardiovascular risk assessments.

Recent studies have identified EAT as a dynamic organ involved in cardiovascular physiology and pathology. EAT releases free fatty acids and inflammatory molecules, playing a critical role in cardiovascular health.[17] It has consistently been associated with coronary artery calcification and cardiovascular conditions.[18,19] Cardiac CT scans have demonstrated effectiveness in precisely assessing EAT characteristics, offering three-dimensional high-resolution visualization. This capability positions EAT measurements as valuable indicators for predicting CACS and assessing the risk of cardiac diseases.[20,21]

TABLE 2 Coronary artery calcium score and epicardial adipose tissue measurements in patients undergoing non-contrast, non-ECG-gated chest CT scans.

Variables		CACS Mean ± SD	p Value	EAT thickness Mean ± SD	p Value	EAT density Mean ± SD	p Value
Sex	Male = 203	23.85 ± 86.96	0.54	6.31 ± 1.57	0.21	−96.12 ± 15.43	0.3
	Female = 162	20.29 ± 67.96		6.23 ± 1.66		−96.01 ± 7.23	
Age, year	≤47 (N = 208)	0.82 ± 4.76	<0.001	5.7 ± 1.26	0.003	−93.32 ± 15.17	0.120
	>47 (N = 157)	50.68 ± 114.5		7.04 ± 1.71		−99.72 ± 5.78	
BMI	<18.5 (N = 7)	10.43 ± 20.48	0.153	4.37 ± 1.25	<0.001	−92.47 ± 10.32	0.806
	18.5–24.9 (N = 129)	35.07 ± 111.03		5.78 ± 1.61		−95.65 ± 7.73	
	25–29.9 (N = 162)	15.72 ± 56.47		6.48 ± 1.57		−96.26 ± 16.62	
	≥30 (N = 67)	14.7 ± 46.8		6.92 ± 1.32		−96.78 ± 7.37	
NAFLD	Yes = 36	9.24 ± 39.78	0.078	7.12 ± 1.72	0.410	−98.11 ± 6.03	0.353
	No = 329	23.70 ± 82.09		6.18 ± 1.57		−95.85 ± 12.96	
DM	Yes = 53	70.38 ± 145.27	<0.001	7.25 ± 1.61	0.466	−99.70 ± 5.63	0.256
	No = 312	14.10 ± 57.59		6.11 ± 1.55		−95.45 ± 13.18	
HTN	Yes = 67	71.41 ± 127.74	<0.001	7.35 ± 1.68	0.170	−100.78 ± 5	0.194
	No = 298	11.22 ± 57.95		6.03 ± 1.5		−95.01 ± 13.36	
Smoker	Yes = 67	11.07 ± 37.25	0.535	6.12 ± 1.29	0.061	−97.27 ± 7.51	0.909
	No = 298	23.06 ± 79.53		6.31 ± 1.68		−95.78 ± 13.39	

Abbreviations: BMI, body mass index; CACS, coronary artery calcium score; DM, diabetes mellitus; EAT, epicardial adipose tissue; HTN, hypertension; N, number; NAFLD, nonalcoholic fatty liver disease; SD, standard deviation.

TABLE 3 Association between coronary artery calcium score and epicardial fat characteristics in patients undergoing non-contrast, non-ECG-gated chest CT scans across different subgroups.

CACS Subgroups		Mean ± SD	EAT thickness Mean ± SD	Correlation (r)	p Value	EAT density Mean ± SD	Correlation (r)	p Value
Age, year	≤47 (N = 208)	0.82 ± 4.76	5.70 ± 1.26	0.085	0.223	−93.32 ± 15.17	−0.122	0.078
	>47 (N = 157)	50.68 ± 114.5	7.05 ± 1.71	0.117	0.145	−99.73 ± 5.79	−0.243	0.002
Sex	Male (N = 203)	23.85 ± 86.96	6.32 ± 1.58	0.174	0.013	−96.13 ± 15.43	−0.129	0.066
	Female (N = 162)	20.29 ± 67.96	6.23 ± 1.67	0.265	0.001	−96.01 ± 7.24	−0.258	0.001
BMI	<18.5 (N = 7)	10.43 ± 20.48	4.38 ± 1.25	0.789	0.035	−92.47 ± 10.32	−0.760	0.047
	18.5-24.9 (N = 129)	35.07 ± 111.03	5.78 ± 1.61	0.184	0.037	−95.58 ± 7.7	−0.243	0.005
	25-29.9 (N = 162)	15.72 ± 56.47	6.48 ± 1.57	0.353	<0.001	−96.3 ± 16.7	−0.136	0.084
	≥30 (N = 67)	14.7 ± 46.8	6.92 ± 1.32	0.361	0.003	−96.8 ± 7.37	−0.360	0.003

Abbreviations: BMI, body mass index; CACS, coronary artery calcium score; EAT, epicardial adipose tissue; N, number; SD, standard deviation.

Our findings suggest that both the quantity and quality of EAT are crucial in modulating CAD risk. This underscores the vital need to include EAT metrics in risk stratification models, in conjunction with traditional cardiovascular risk factors. These results align with previous studies, such as those by Goeller et al.[10] and Mohammadzadeh et al.,[22] which also employed non-contrast CT scans for their assessments. Furthermore, research by Mahabadi et al. involving patients without diagnosed cardiac conditions demonstrated a significant association between the volume of

EAT and CACS.[23] The consistency of these findings across multiple studies strengthens the evidence supporting EAT measurements as reliable indicators for early cardiovascular risk assessment. A strong observed association in this study between BMI and EAT thickness (p < 0.001) is consistent with existing research linking visceral obesity to increased EAT thickness and coronary calcification.[24]

This correlation underscores the impact of obesity on cardio-vascular health, as individuals with higher BMI exhibited increased

TABLE 4 Regression analysis for predicting coronary artery calcium score.

Variable		Univariate model		Multivariate model	
		OR (95% CI)	p Value	OR (95% CI)	p Value
Imaging findings	EAT thickness	1.803 (1.514–2.147)	<0.001	1.046 (0.836–1.309)	0.695
	EAT density	0.671 (0.614–0.733)	<0.001	0.682 (0.619–0.750)	<0.001
Comorbidities	DM	5.921 (3.194–10.97)	<0.001	3.66 (1.48–9.024)	0.005
	HTN	7.414 (4.168–13.187)	<0.001	2.79 (1.223–6.359)	0.015

Abbreviations: CI, confidence interval; DM, diabetes mellitus; EAT, epicardial adipose tissue; HTN, hypertension; OR, odds ratio.

EAT thickness and lower EAT density. Weight reduction in obese individuals has been shown to decrease EAT thickness, highlighting the importance of weight management in mitigating cardiovascular risks.[25] Additionally, this study revealed that older individuals exhibited elevated CACS, increased EAT thickness, and decreased EAT density. These observations indicate the importance of age and specific attributes of EAT in assessing cardiovascular risk.

Although our study found no significant correlation between NAFLD and CACS, EAT thickness, or density, patients with NAFLD exhibited higher EAT thickness and lower EAT density. This lack of significance may be due to the underrepresentation of NAFLD patients in our study. Other research, such as that by Kim et al.,[26] has demonstrated a correlation between NAFLD and coronary calcification, particularly in nonobese male subjects.

DM and HTN are substantial predictors of CACS, confirmed by both univariate and multivariate regression analyses. These findings are consistent with previous studies highlighting the prognostic significance of DM in atherosclerosis development, attributed to increased connective tissue growth, elevated glycoprotein levels, and enhanced plaque calcification.[27,28] Similarly, HTN has been associated with increased EAT thickness, as observed in a study conducted by Dicker et al.[29]

The findings derived from our investigation demonstrate a significant correlation between the morphological characteristics of EAT, specifically its density and thickness, and the degree of calcification within the coronary arteries. These findings indicate that EAT parameters, such as thickness and density, could be valuable in assessing the risk and severity of CAD. Moreover, the imaging technique that was employed in this study is noted for offering significant advantages; it provides a noninvasive, cost-effective, and practical method for assessing coronary artery health. This prognostic approach holds promise for early identification of CAD before critical complications arise, facilitating timely and targeted clinical interventions. Thus, integrating EAT measurements into standard cardiac CT scan evaluations could prove extremely advantageous.

Several limitations of this study warrant consideration. First, the cross-sectional design enables the identification of correlations but does not allow for the investigation of causal relationships. Second, the absence of inflammatory biomarker evaluations limits our ability

to provide supplementary evidence for the causal link between EAT and CACS. Third, the measurement of EAT thickness and density was performed using a single methodological approach. Additionally, by focusing exclusively on variables such as EAT characteristics, NAFLD, and CACS, other potentially influential factors may have been overlooked, introducing potential bias. Future research should aim to address these limitations by employing longitudinal designs to explore causality, incorporating inflammatory biomarkers for a more comprehensive understanding, using multiple imaging modalities for EAT assessment, and including a broader array of variables to provide a more holistic evaluation of cardiovascular risk factors.

5 | CONCLUSION

This study delineates robust correlations between EAT thickness and density with CACS. Our study reveals that increased EAT thickness is consistently associated with elevated CACS, whereas EAT density exhibits a negative correlation. Moreover, our findings identify DM and HTN as substantial contributors to increased CACS, whereas NAFLD does not demonstrate a significant relationship. Based on these results, the characteristics of EAT emerge as critical indicators for cardiovascular risk assessment. It is imperative for future research to explore the integration of EAT metrics into conventional cardiovascular risk assessment frameworks to refine their prognostic efficacy.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Golnaz Moradi had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICS STATEMENT

This study was approved by the Research Ethics Committees of Sina Hospital, Tehran University of Medical Sciences (TUMS) under the ID: IR.TUMS.SINAHOSPITAL.REC.1400.052. Patients' private information was kept confidential, with no identifying details disclosed. The study was conducted in accordance with the principles outlined in the Helsinki Declaration.

TRANSPARENCY STATEMENT

The lead author, Golnaz Moradi, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

ORCID

Golnaz Moradi 🔟 http://orcid.org/0000-0002-1112-459X
Diana Zarei 🔟 http://orcid.org/0000-0001-5468-9235

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