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Association between epicardial and pericadial fat thickness and coronary artery calcification severity in chronic kidney disease patients: A pilot study

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Abstract

BACKGROUND: This study aims to investigate the association between Coronary Artery Calcium (CAC) score and epicardial fat thickness (EFT) and pericardial fat thickness as indicators of inflammation in patients with chronic kidney disease (CKD).

METHODS: This cross-sectional study measured patients' CAC scores using dual-source cardiac CT, quantified with Agatston's score and dedicated Ca-Scoring software. Epicardial and pericardial fat thicknesses were assessed via echocardiography.

RESULTS: Thirty-one CKD patients participated in the study, with an average age of 54.45 ± 15.12 years. Of these, 22 were male (70.97%) and 9 were female (29.03%). Fifteen CKD patients (48.39%) had moderate to severe CAC scores. Patients with CKD exhibiting severe coronary calcification were found to be older (P = 0.003). A significant positive correlation was observed between epicardial fat thickness (r = 0.58, P < 0.001) and pericardial fat thickness (r = 0.56, P = 0.001) with CAC score. Multivariable analysis revealed that for each one-unit increase in EFT, the odds of having a moderate to severe CAC score were 2.88 times greater than those of a normal score (OR = 2.88, 95% CI = 1.04–7.96, P = 0.041). Similarly, a one-unit increase in pericardial fat thickness was associated with 1.51 times higher odds of a moderate to severe CAC score compared to a normal score (OR = 1.51, 95% CI = 0.93–2.46, P = 0.093).

CONCLUSION: The insights gained from this study advocate for a holistic approach to assessing cardiac function in patients with coronary calcification. By integrating echocardiographic analysis with traditional risk factor assessment, healthcare providers can gain a more comprehensive understanding of cardiovascular health, ultimately leading to better-targeted therapies to improve CKD patient outcomes.

Keywords: Chronic Kidney Disease; Coronary Artery Calcification; Epicardial Fat Thickness; Pericardial Fat Thickness; Echocardiography

Introduction

Cardiovascular events are the leading cause of death in patients with kidney failure on long-term hemodialysis[1]. The exact mechanisms and pathophysiological factors behind cardiovascular diseases in these patients remain unclear and complex[2]. Based on evidence, uremic toxins are known to induce vascular inflammation and endothelial dysfunction, which can increase the risk of atherosclerosis and other cardiovascular diseases[3]. Anemia, prevalent in chronic kidney disease (CKD) patients, leads to increased cardiac workload, contributing to ischemic events. Moreover, fluid overload can result in hypertension and additional cardiac strain, further exacerbating cardiovascular issues. Thus, the mechanisms behind cardiovascular disease (CVD) in CKD patients are multifactorial[2,3]. Various pathological pathways are implicated, including the activation of inflammatory processes[4-6].

Inflammation is frequently observed in patients with CKD undergoing hemodialysis, as well as in those with coronary artery disease (CAD), suggesting a potential cause-and-effect relationship between the two conditions[5,7]. Thus, CKD is increasingly recognized as a significant risk factor for CVD[5], with various studies highlighting the role of specific adipose tissues in this association[8,9].

Visceral adipose tissue, commonly known as epicardial adipose tissue (EAT), can release pro-inflammatory cytokines that contribute to inflammation. Before symptoms or clear signs of cardiovascular disease appear, early CAD may already be causing atherosclerotic lesions. These lesions can further provoke inflammation and stimulate EAT to produce various cytokines, including interleukin-1β, interleukin-6, the soluble interleukin-6 receptor, and tumor necrosis factor[10,11]. This process increases EAT volume and intensifies vascular inflammation, potentially leading to two outcomes: it may promote neoangiogenesis and the development of collateral blood vessels or trigger a self-perpetuating and uncontrolled inflammatory response that contributes to atherosclerosis and coronary artery calcification (CAC)[12].

Using similar mechanisms, increased EAT and its dysfunction may contribute to the onset of CAD[7]. EAT volume and radiodensity have recently been associated with serum inflammatory markers, subclinical atherosclerosis, and major cardiac events[13]. Recent studies have demonstrated a correlation between epicardial fat thickness and the severity of coronary atherosclerosis, as measured by the level of calcification in the coronary arteries[14-16].

Additionally, epicardial fat thickness (EFT) has been associated with several classic risk factors for heart disease, including arterial hypertension, hyperlipidemia, and particularly diabetes[17]. Similarly, pericardial fat thickness (PFT), which surrounds the heart, has been linked to adverse cardiovascular outcomes, such as increased vascular stiffness and myocardial dysfunction[18].

The metabolic components of EFT and PFT may also play a role in atherosclerosis and increased coronary plaque calcification; however, the precise mechanisms remain incompletely understood[19,20].

To accurately assess epicardial and pericardial fat thickness, imaging modalities play a pivotal role[21]. Magnetic resonance imaging (MRI) is considered the gold standard due to its ability to provide high-resolution images without radiation exposure, allowing for precise measurement of fat volumes[22]. Computed tomography (CT) is another effective method that offers rapid acquisition times and high accuracy in quantifying fat thickness but involves ionizing radiation[23]. Echocardiography, while more accessible and safer, may lack the precision of MRI and CT but remains a practical option in clinical settings[21]. Each imaging modality has its strengths, making them suitable for different clinical scenarios when assessing epicardial and pericardial fat thickness in CKD patients[21-23].

The proposed pilot study aims to investigate the association between epicardial and pericardial fat thickness and the severity of coronary artery calcification in patients with chronic kidney disease. Understanding this association could provide valuable insights into the pathophysiological mechanisms linking obesity, fat distribution, and cardiovascular risk in CKD populations. Clinically, this research may inform strategies for risk

stratification and management of cardiovascular complications in these high-risk patients.

Materials and Methods

Study design and participants

This cross-sectional study was conducted from August 17, 2022, to August 2023 at two educational hospitals (Imam Hossein Hospital and Labbafinejad Hospital), which are tertiary cardiovascular hospitals under the supervision of Shahid Beheshti University of Medical Sciences in Tehran, Iran. The inclusion criteria were patients aged 18 to 70 with renal failure, characterized by a glomerular filtration rate (GFR) of less than 45 ml/min per body surface area (stage 3b or higher) based on a 24-hour urinary creatinine clearance persisting for three months or more, irrespective of the cause. Exclusion criteria included any signs of acute infection within one month prior to study participation (such as acute respiratory infections, sepsis, or any viral, bacterial, parasitic, or fungal infections in organs); current cancer or liver disease; a diagnosed history of immune or rheumatic conditions; patients presenting with acute cardiac symptoms at the time of the study (unstable angina, ST-segment elevation myocardial infarction [STEMI], and non-ST-elevation myocardial infarction [NSTEMI]); and a lack of consent to participate in the study.

Ethical approval

All participants provided informed consent, both written and verbal, after a thorough explanation of the study's procedures. The study was conducted following the Declaration of Helsinki and received ethical approval from review board of the Ethics Committee of Shahid Beheshti University of Medical Sciences under the code IR.SBMU.RETECH.REC.1401.221.

Data gathering

Patient background information was gathered via clinical assessments and direct interviews. This data included gender, age, CKD duration, dialysis details, and medical history (e.g., smoking status, hypertension, diabetes, dyslipidemia, and cardiac and renal disease history). Additionally, anthropometric assessments were recorded.

Laboratory values—including complete blood count (CBC), lipid profiles, fasting blood sugar, HbA1c, thyroid and parathyroid hormones, urea, creatinine, albumin, C-reactive protein, serum 25(OH)D, serum calcium, and phosphorus—were obtained within the first 24 hours of admission.

Venous blood collection was performed in a sitting position after fasting for 12–14 hours, with a sample volume of 5 cc. All blood samples were analyzed using the Hitachi 704 auto-analyzer.

Due to the small sample size, the researchers opted to use Charlson's Comorbidity Index (CCI)[24], which encapsulates the overall effect of multiple comorbidities into a single score rather than evaluating each illness individually. Each comorbidity was weighted according to the system established by Mary Charlson[24]. These weights were then aggregated to create the CCI, reflecting a participant's comorbidity score.

Cardiac assessment's tools

All patients underwent a dual-source cardiac CT to determine their Coronary Artery Calcium (CAC) score, which was quantified using the Agatston scoring method and Ca-Scoring software by a radiologist. The Agatston score was categorized as follows[25]: a score of 0 indicates very low risk or normal coronary arteries; scores ranging from 1 to 99 suggest mild coronary artery calcification (CAC) with a slightly elevated CAD risk; scores between 100 and 299 indicate moderate CAC and a moderate increase in CAD risk; and scores above 300 reflect a moderate to severe increase in CAD risk.

An echocardiologist employed echocardiography to assess the thickness of epicardial and pericardial fat in patients. Using the Philips EPIQ CVx 7 Cardiovascular ultrasound system, each patient received a transthoracic echocardiogram at the hospital.

Epicardial fat thickness (EFT) was identified as a hypoechoic space between the outer wall of the myocardium and the visceral pericardium, measured on the free wall of the right ventricle in the parasternal long-axis view. Pericardial fat thickness was assessed as the

combined hypoechoic space outside the parietal pericardium and the epicardial fat adjacent to the right ventricular wall, visualized in the same parasternal long-axis view. Measurements were performed perpendicularly to the aortic annulus, ensuring accuracy by averaging values over three consecutive cardiac cycles at end-diastole, when cardiac dimensions are most stable.

Sampling method and sample size estimation

The sampling method used in this study was non-random and convenience sampling. Based on the assumptions of Tonbul HZ, et al.'s study[26], which considered a correlation coefficient between epicardial fat thickness and CAC score as 0.48 (r =0.48) among end-stage renal disease patients, with a type I error rate of 5% (α = 0.05) and a power of 80% (β = 0.2), the minimum estimated sample size was 31 using following formula:

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{\left(\frac{1}{2}\ln\frac{1+r}{1-r}\right)^2} + 3 = \frac{(1.96+0.84)^2}{\left(\frac{1}{2}\ln\frac{1+0.48}{1-0.48}\right)^2} + 3 \approx 31$$

Statistical analysis

Initially, the normality of quantitative variables was assessed using the Shapiro-Wilk test and Q-Q plot. Quantitative variables were described using means and standard deviations (SD), while categorical variables were reported as frequencies and percentages (%).

To compare the means of quantitative variables across the three calcium score risk groups, the researchers employed a one-way ANOVA test for normally distributed data and a Kruskal-Wallis test for non-normally distributed data. Additionally, post-hoc analysis using Dunn's test following the Kruskal-Wallis test was performed to identify which CAC categories differed from each other in terms of mean age.

Fisher's exact test was utilized to determine differences in the distribution of categorical variables. Spearman's rank correlation test was used to assess the correlation between two quantitative variables due to the non-normality of the CAC score. Finally, the intensity of correlation was interpreted as follows:

- **Strong correlation** for r ≥ 0.70
- **Medium correlation** for r = 0.4 – 0.7
- **Weak correlation** for r < 0.4

To investigate the association between epicardial and pericardial fat thickness and CAC score groups (normal, minimal/mild, and moderate/severe), while adjusting for probable confounding variables, an ordinal regression model was used at both univariate and multivariable levels.

In this statistical model, all probable confounding variables—including gender, age, body mass index, GFR value, CKD duration, dialysis treatment status, and Charlson's comorbidity index—were incorporated into the final multivariable model. The final multivariable models were fitted based on the lowest model's log likelihood. Additionally, model results were presented based on the odds ratio (OR).

Statistical analyses were performed using a two-tailed approach, with a 95% confidence interval and a significance threshold set at P < 0.05. STATA version 14 software was utilized for data analysis.

Results

Description of the study's population based on CAC score groups

Table 1 presents the descriptive and demographic information of patients with CKD based on CAC score severity. The study included 31 patients with an average age of 54.45 years (SD = 15.12, age range = 20–70 years). Among them, 22 patients were male (70.97%) and 9 were female (29.03%). Of the 31 CKD patients, 15 had moderate to severe CAC scores.

The mean body mass index (BMI) for all participants was 25.58 ± 4.65 kg/m². The average GFR among the patients was 23.62 ± 13.96 mL/min. CKD stage distribution was as follows: 13 patients (41.94%) in Stage 3b, 7 patients (22.58%) in Stage 4, and 11 patients (35.48%) in Stage 5.

The most common underlying condition was hypertension, affecting 64.52% (n = 20) of the population, followed by diabetes at 41.94% (n = 13)

Table 1. Description of demographic characteristics, medical and drugs' history of CKD patients between coronary artery calcium score groups

Factors	Total (n=31)	Normal (n=8)	Minimal/Mild (n=8)	Moderate to severe (n=15)	P-value
General information					
Age	54.45 ± 15.12	37.62 ± 17.11	57.62 ± 8.74 [c]	61.73 ± 8.99 [c]	0.003 [a]
Gender					
Female	9 (29.03)	2 (25.00)	4 (50.00)	3 (20.00)	0.355 [d]
Male	22 (70.97)	6 (75.00)	4 (50.00)	12 (80.00)	
Current smoker (Yes)	5 (16.13)	1 (12.50)	0 (0.00)	4 (26.67)	0.333 [d]
BMI (kg/m²)	25.58 ± 4.65	23.18 ± 3.81	26.23 ± 5.38	26.50 ± 4.48	0.244 [b]
BSA (m²)	1.74 ± 0.21	1.68 ± 0.27	1.76 ± 0.20	1.75 ± 0.19	0.689 [b]
GFR (mL/min)	23.62 ± 13.96	26.87 ± 12.91	25.51 ± 13.71	20.89 ± 14.97	0.599 [a]
CKD stage					
Stage 3b	13 (41.94)	4 (50.00)	4 (50.00)	5 (33.33)	
Stage 4	7 (22.58)	2 (25.00)	2 (25.00)	3 (20.00)	0.836 [d]
Stage 5	11 (35.48)	2 (25.00)	2 (25.00)	7 (46.67)	
CKD duration					
< 1 year	6 (19.35)	2 (25.00)	2 (25.00)	2 (13.33)	
1 – 5 years	10 (32.26)	3 (37.50)	3 (37.50)	4 (26.67)	0.782 [d]
More than 5 years	15 (48.39)	3 (37.50)	3 (37.50)	9 (60.00)	
Dialysis					
No	22 (70.79)	6 (75.00)	6 (75.00)	10 (66.67)	
≤ 1 year	2 (6.45)	1 (12.50)	0 (0.00)	1 (6.67)	0.733 [d]
1-5 years	1 (3.23)	0 (0.00)	1 (12.50)	0 (0.00)	
> 5 years	6 (19.35)	1 (12.50)	1 (12.50)	4 (26.67)	
Diabetes	13 (41.94)	1 (12.50)	3 (37.50)	9 (60.00)	0.096 [d]
Hypertension	20 (64.52)	4 (50.00)	6 (75.00)	10 (66.67)	0.703 [d]
Dyslipidemia	8 (25.81)	0 (0.00)	3 (37.50)	5 (33.33)	0.159 [d]
CVA	3 (9.68)	0 (0.00)	0 (0.00)	3 (20.00)	0.413 [d]
Coronary artery disease					
No CAD	27 (87.10)	7 (87.50)	7 (87.50)	13 (86.67)	
Mild CAD	2 (6.45)	0 (0.00)	1 (12.50)	1 (6.67)	
SVD	1 (3.23)	1 (12.50)	0 (0.00)	0 (0.00)	0.841 [d]
2VD	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
3VD	1 (3.23)	0 (0.00)	0 (0.00)	1 (6.67)	
Myocardial Infarction	2 (6.45)	1 (12.50)	0 (0.00)	1 (6.67)	1.000 [d]
Heart failure	2 (13.33)	4 (12.90)	1 (12.50)	1 (12.50)	1.000 [d]
Drug history					
Beta-blocker	12 (38.71)	1 (12.50)	4 (50.00)	7 (46.67)	0.229 [d]
Statins	17 (54.84)	3 (37.50)	5 (62.50)	9 (60.00)	0.641 [d]
ACEI/ARBs	19 (61.29)	5 (62.50)	6 (75.00)	8 (53.33)	0.722 [d]
Anti-diabetes oral agents	8 (25.81)	1 (12.50)	3 (37.50)	4 (26.67)	0.513 [d]
Insulin	7 (22.58)	1 (12.50)	2 (25.00)	4 (26.67)	0.864 [d]

Data describes as n (%) or mean ± standard deviation (SD). P-value < 0.05 was considered statistically significant.
[a] estimated based on Kruskal-Wallis test.,
[b] estimated based on one-way analysis of variance (ANOVA).
[c] statistically significant based on post hoc analysis using Dunn's test
[d] estimated based on Fisher's exact test
SVD: single vessel coronary artery disease, 2VD: two vessel coronary artery disease, 3VD: three vessel coronary artery disease, BSA: body surface area, GFR: glomerular filtration rate, CKD: chronic kidney disease, CVA: cerebrovascular accident, CAD: coronary artery disease, ACEI/ARBs: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

and CAD at 12.9% (n = 4). Among high-risk individuals, diabetes prevalence reached 60% (Table 1).

According to the results in Table 1, apart from mean age, there were no statistically significant differences in the mean parameters or other variables among the CAC score groups (P > 0.05). However, a statistically significant difference was

observed in the mean age of patients between CAC score categories (P = 0.003). Additionally, post-hoc analysis showed that the mean age of patients with moderate to severe CAC scores (P < 0.001) and those with minimal/mild CAC scores (P = 0.005) was significantly higher compared to patients with normal CAC scores.

Correlation of CAC score with laboratory's factors and comorbidity index:

Statistical analysis revealed a significant positive correlation between HbA1c levels (correlation coefficient: 0.47, P = 0.006) and Charlson's comorbidity index (correlation coefficient: 0.47, P = 0.006) with the CAC score. Additionally, an inverse (negative) correlation was observed between triglycerides (correlation coefficient: -0.37, P = 0.037) and HDL (correlation coefficient: -0.41, P = 0.019) with the CAC score. However, no other laboratory findings showed a significant correlation with the CAC score (Table 2).

Correlation of CAC score with echocardiography factors

Based on the results in Table 3, after examining the correlation between echocardiography factors and the CAC score, a significant weak negative correlation was observed between LA strain (correlation coefficient: -0.35, P = 0.049). Additionally, a significant moderate inverse correlation was found between E septal (correlation coefficient: -0.51, P = 0.003) and E

Table 2. Correlation of coronary artery calcium score with laboratory's factors and Charlson's comorbidity index

Factors	Mean ± SD	min, max	Spearman's correlation coefficient (r)	P-value
WBC (10^3/ µL)	6.94 ± 2.01	3.80, 12.60	- 0.06	0.714
PMN (10^9/L)	60.51 ± 8.26	42, 70	- 0.05	0.780
Lymphocyte (%)	34.29 ± 8.28	17, 53	0.005	0.977
Platelet (10^9/L)	182.67 ± 49.52	69, 292	0.02	0.876
Hemoglobin (g/dL)	12.42 ± 2.38	8.80, 16.80	- 0.10	0.557
GFR (ml/min)	23.62 ± 13.96	3.4, 43.50	-0.19	0.290
Urea (g/L)	95.77 ± 40.45	34, 220	0.22	0.222
Creatinine (mg/dL)	4.20 ± 3.27	1.60, 11.50	0.16	0.376
Albumin (g/dL)	4.05 ± 0.34	3.40, 4.90	- 0.13	0.463
FBS (mg/dL)	112.16 ± 36.86	75, 240	0.34	0.058
HbA1c (%)	6.31 ± 1.05	4.50, 8.40	0.47	0.006
Triglyceride (mg/dL)	156.03 ± 120.86	45, 760	- 0.37	0.037
Cholesterol (mg/dL)	146.03 ± 41.87	85, 271	- 0.16	0.378
LDL (mg/dL)	81.74 ± 35.35	32, 191	- 0.10	0.574
HDL (mg/dL)	42.77 ± 8.35	27, 63	- 0.41	0.019
TSH (mU/L)	4.20 ± 7.84	0.60, 45	0.21	0.248
T4 (mU/L)	7.11 ± 1.86	1, 10	- 0.16	0.373
T3 (mU/L)	1.51 ± 0.36	0.80, 2.10	- 0.02	0.881
iPTH, pg/mL	93.66 ± 102.86	17, 341	0.23	0.197
Serum calcium (mg/dL)	9.02 ± 0.98	7.30, 12.50	0.02	0.912
Phosphorus (mg/dL)	4.02 ± 1.03	2.50, 7.30	0.22	0.231
Serum 25(OH)D (ng/mL)	39.29 ± 16.22	20, 89	- 0.13	0.462
CRP (mg/L)	10.64 ± 10.13	2, 45	0.15	0.409
Charlson's comorbidity index	1.80 ± 1.95	0, 8	0.47	0.006

Data are presented as mean +SD. P-value < 0.05 was considered statistically significant.
WBC: white blood cell, PMN: polymorph nuclear neutrophils, GFR: glomerular filtration rate, FBS: fasting blood sugar, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TSH: thyroid stimulating hormone, iPTH: intact parathyroid hormone, CRP: c-reactive protein

Table 3. Correlation of coronary artery calcium score with echocardiography factors

Factors	Mean ± SD	min, max	Spearman's correlation coefficient (r)	P-value
LVEF (%)	52.41 ± 7.28	20, 60	- 0.19	0.299
LVEDVI	57.44 ± 13.42	37, 80	0.25	0.165
E velocity	0.79 ± 0.25	0.40, 1.30	- 0.17	0.345
E/A ratio	0.83 ± 0.21	0.50, 1.33	- 0.28	0.122
LA strain reservoir	31.62 ± 10.44	10, 53	- 0.35	0.049
LA strain atrial kick	-15.69 ± 6.85	-33, 1.5	0.18	0.317
E septal	6.90 ± 2.39	4, 14	-0.51	0.003
E lateral	8.00 ± 2.36	5, 15	-0.48	0.006
RVDD	2.96 ± 0.35	2, 4	0.22	0.233
TAPSE	21.01 ± 4.66	1.5, 28	- 0.21	0.235
RVSM	11.45 ± 2.44	7, 21	- 0.33	0.064
LAVI	25.89 ± 8.93	10, 44	0.33	0.066
TRG	22.45 ± 6.52	10, 40	0.16	0.378
PAP (mmHg)	27.96 ± 7.39	15, 45	0.16	0.378
Epicardial fat thickness (mm)	4.62 ± 1.83	2, 8	0.58	<0.001
Pericardial fat thickness (mm)	9.70 ± 3.70	5, 18	0.56	0.001
Calcium score value	391.13 ± 642.67	0, 2209.66	-	-

Data are presented as mean +SD. P-value < 0.05 was considered statistically significant.
LVEF: left ventricular ejection fraction, LVEDVI: left ventricular end-diastolic volume index, LA Strain: left atrial strain, RVDD: right ventricular diastolic diameter, TAPSE: tricuspid annular plane systolic excursion, RVSM: right ventricular peak systolic myocardial velocity, LAVI: left atrial volume index,
TRG: tricuspid regurgitation gradient, PAP: pulmonary artery pressure

Table 4. The results of univariate and multivariable ordinal regression models about association of epicardial fat pad or pericardial fat pad with coronary artery calcium score groups

Factors	Crude OR (95% CI)	P-value	Model 1 OR (95% CI)	P-value	Model 2 (OR 95% CI)	P-value
Epicardial fat thickness (mm)	2.43 (1.40 – 4.20)	0.001	2.64 (1.23 – 5.65)	0.012	2.88 (1.04 – 7.96)	0.041
Pericardial fat thickness (mm)	1.42 (1.11 – 1.82)	0.005	1.51 (1.07 – 2.14)	0.019	1.51 (0.93 – 2.46)	0.093

Data are presented as OR (95% Confidence Interval) and obtained from univariate and multivariable ordinal regression models. P-value < 0.05 was considered statistically significant
Crude: Unadjusted (epicardial fat thickness or pericardial fat thickness)
Model 1: Adjusted for gender, age, body mass index, epicardial fat thickness or pericardial fat thickness
Model 2: Model 1 + GFR, CKD duration, dialysis duration, Charlson's comorbidity index

lateral (correlation coefficient: -0.48, P = 0.006) with the CAC score (Table 3).

Conversely, a positive correlation was observed between EFT and the CAC score, which was statistically significant (correlation coefficient: 0.58, P < 0.001). Similarly, a positive and significant correlation was found between PFT and the CAC score, indicating that as pericardial fat thickness increases, the CAC score also increases (correlation coefficient: 0.56, P = 0.001) (Table 3).

Association between epicardial and pericardial fat thickness with CAC score groups:

In a univariate ordinal regression analysis, a one-unit increase in epicardial fat thickness was associated with 2.43-fold greater odds of having a moderate/severe calcium score compared to a normal CAC score (OR = 2.43, 95% CI = 1.04–4.20, P = 0.001). Similarly, disregarding the influence of other variables, a one-unit increase in pericardial fat thickness was linked to 1.42 times higher odds

of having a moderate/severe CAC score versus normal (OR = 1.42, 95% CI = 1.11–1.82, P = 0.005).

Accounting for additional confounding factors (Model 2), each one-unit increase in epicardial fat thickness was associated with a 2.88-fold greater likelihood of a moderate to severe CAC score compared to a normal CAC score (OR = 2.88, 95% CI = 1.04–7.96, P = 0.041).

Similarly, after adjusting for other variables (Model 2), each one-unit increase in pericardial fat thickness was associated with 1.51 times higher odds of presenting with a moderate to severe CAC score compared to a normal CAC score; however, this result was not statistically significant (OR = 1.51, 95% CI = 0.93–2.46, P = 0.093) (Table 4).

Discussion

The current study revealed that individuals with CKD suffering from severe coronary calcification tend to be older. Furthermore, a negative correlation was noted between HDL and triglycerides and the extent of coronary calcification in patients with CKD. Conversely, a positive correlation was observed between HbA1c levels, comorbidity index, and the severity of coronary calcification.

Additionally, after examining echocardiographic factors, it was observed that reduced heart function (LA strain reservoir, E septal, and E lateral) was correlated with an increase in CAC score, as well as an increase in the thickness of epicardial and pericardial fat with the rising CAC score. After reviewing the results while controlling for confounding variables, the validity of this evidence was confirmed.

This observation aligns with previous research, which has consistently shown that aging is a critical risk factor for cardiovascular disease, including coronary artery calcification[27,28].

Moreover, our study identified a negative correlation between HDL levels and triglycerides with the extent of coronary calcification. This finding supports the hypothesis that lipid metabolism plays a significant role in cardiovascular health among CKD patients. Previous studies have suggested that lower HDL cholesterol levels are associated with increased cardiovascular risk, and impaired lipid profiles are common in CKD populations[29]. The correlation between triglycerides and coronary calcification further emphasizes the importance of managing dyslipidemia in CKD patients to mitigate cardiovascular risks.

Elevated HbA1c levels, indicative of poor glycemic control, have been linked to increased cardiovascular risk in various populations, including those with CKD. This relationship may be attributed to the pro-inflammatory and pro-atherogenic effects of hyperglycemia, which can exacerbate vascular damage and promote calcification processes[30]. Additionally, the correlation of comorbidity scores with coronary calcification highlights the cumulative burden of chronic diseases in this population, suggesting that comprehensive management of comorbid conditions is essential for reducing cardiovascular risk[31].

However, it is important to note that while this correlation exists, it does not establish a causal association. Further observational studies, such as cohort and case-control studies, are needed to explore the underlying mechanisms.

We found that reductions in left atrial (LA) strain reservoir function and changes in early diastolic velocities (E septal and E lateral) correlated with increased CAC scores. These findings underscore the potential of echocardiographic measures as valuable indicators of cardiovascular health in the context of CAC[32].

Moreover, the direct correlation between epicardial and pericardial fat thickness and rising CAC scores adds another layer of complexity to these findings. Epicardial fat is recognized as a metabolically active tissue that may contribute to inflammation and atherosclerosis, thereby influencing coronary artery disease progression[33].

The interrelationship between adiposity and coronary calcification emphasizes the importance of addressing obesity and metabolic health in patients with existing cardiovascular risk factors, including those with CKD. Our findings align with previous research, indicating that epicardial fat is an independent predictor of an elevated CAC score[9,34-36].

Epicardial fat, an active visceral adipose tissue located between the visceral pericardium and the myocardium, plays several physiological roles. In

addition to its metabolic functions, it can secrete multiple pro-inflammatory cytokines and is associated with the pathogenesis of CKD[37].

Furthermore, our study uncovered a link between pericardial fat thickness and CAC score, finding that the former can independently predict the latter. In 2014, Hardana et al. studied 117 patients with CKD to examine this connection, utilizing CT imaging for all participants. Their research revealed that those on peritoneal dialysis had significantly greater pericardial fat volumes. A direct correlation was also established between pericardial fat levels and CAC score[38]. These findings echo the current study's results, demonstrating that patients with CKD possess thicker pericardial fat and confirming the independent association between EFT and CAC score.

Conclusion

Patients with CKD, often linked to the thickening of epicardial or pericardial fat due to visceral obesity, are categorized as a high-risk group. Findings from this study indicate that increased EFT or PFT is an independent risk factor for elevating CAC scores. Since measuring coronary fat is straightforward, non-invasive, and widely available, it can serve as a practical screening tool for assessing the severity of coronary disease in patients with CKD.

Limitations

This study faced several limitations, including a small sample size and restricted access to more CKD patients due to the COVID-19 pandemic. There was also a probable selection bias when enrolling patients, along with information bias during clinical visits. It is hoped that future research will conduct more comprehensive studies with larger sample sizes to enhance the predictive value of epicardial and pericardial fat thickness regarding coronary artery calcification severity and to assess the cost-effectiveness of these non-invasive clinical tools in diagnosing coronary artery calcification in patients at risk for coronary artery disease, especially those with CKD.

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Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: RS; MJF
Data Acquisition: PS
Data Analysis or Interpretation: NT
Manuscript Drafting: PS; NT
Critical Manuscript Revision: RS; TFL; SS; MHA; MPM; MJF
All authors have approved the final manuscript and are responsible for all aspects of the work.

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