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Epicardial fat modifies the relationship between coronary calcium score and all-cause mortality: The St. Francis Heart Study

Lu Q. Chen [a], Jonathan Scheiner [a], Niloofar Fouladi Nashta [b], Jonathan Weber [a], Qingtao Zhou [a], Kathleen Rapelje [a], Damini Dey [c], J. Jane Cao [a,*]

[a] St Francis Hospital & Heart Center, The Heart Center 101 Northern Boulevard, Roslyn, NY 11548, United States
[b] Sol Price School of Health Policy, University of Southern California, Los Angeles, CA, United States
[c] Cedars Sinai Medical Center, Los Angeles, CA, United States

HIGHLIGHTS

- The risk of epicardial fat is not clear in the presence of coronary artery calcium (CAC) as it too is a powerful predictor of adverse outcomes.
- We investigated the relationship between epicardial fat features and coronary artery calcium (CAC) scores as predictors of long-term mortality.
- Using epicardial fat features measured by a semi-automated CT software on non-contrast images, we found that increased epicardial fat volume was associated with increased hazards of all-cause mortality after a mean follow-up period of 17 years.
- Those with increased epicardial fat and increased CAC had the highest risk of death, demonstrating the effect-modifying relationship of epicardial fat on CAC predicting mortality.
- Nested model comparisons demonstrated increased model fit predicting all-cause mortality when including epicardial fat parameters over traditional risk factors and calcium score alone.

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Epicardial fat density
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ABSTRACT

Objective: Epicardial fat is associated with cardiovascular risk factors and adverse outcomes. However, it is not clear if epicardial fat remains to be a mortality risk when coronary calcium score (CAC) is taken into account.
Methods: We studied the 1005 participants from the St. Francis Heart Study who were apparently healthy with CAC scores at 80th percentile or higher for age and gender, randomly assigned to placebo or statin therapy. At baseline, lipid profiles and non-contrast CT images were obtained where the epicardial fat volume was analyzed. Likelihood ratio testing was used to assess the additional prognostic value of epicardial fat to CAC for the risk of all-cause mortality.
Results: Increased epicardial fat volume was associated with higher CAC. For each unit increase in lnCAC, the average epicardial fat volume increased by 3.34 mL/m^2. After a mean follow-up period of 17 years, 179 (18%) participants died. Increased epicardial fat volume was associated with an adjusted hazard ratio of 1.11 (95% CI: 1.02 to 1.20) predicting all-cause mortality. In the stratified analysis testing strata of epicardial fat and CAC, those with increased epicardial fat and increased CAC had the highest risk of death. Compared with a model containing lnCAC and traditional risk factors, a model additionally containing epicardial fat volume yielded a better model fit (likelihood ratio test $p < 0.001$).
Conclusion: Increased epicardial fat volume is associated with increased all-cause mortality risk. In addition, it portends incremental prognostic value to CAC score in mortality prediction.

* Corresponding author.
E-mail address: Jane.Cao@chsli.org (J.J. Cao).

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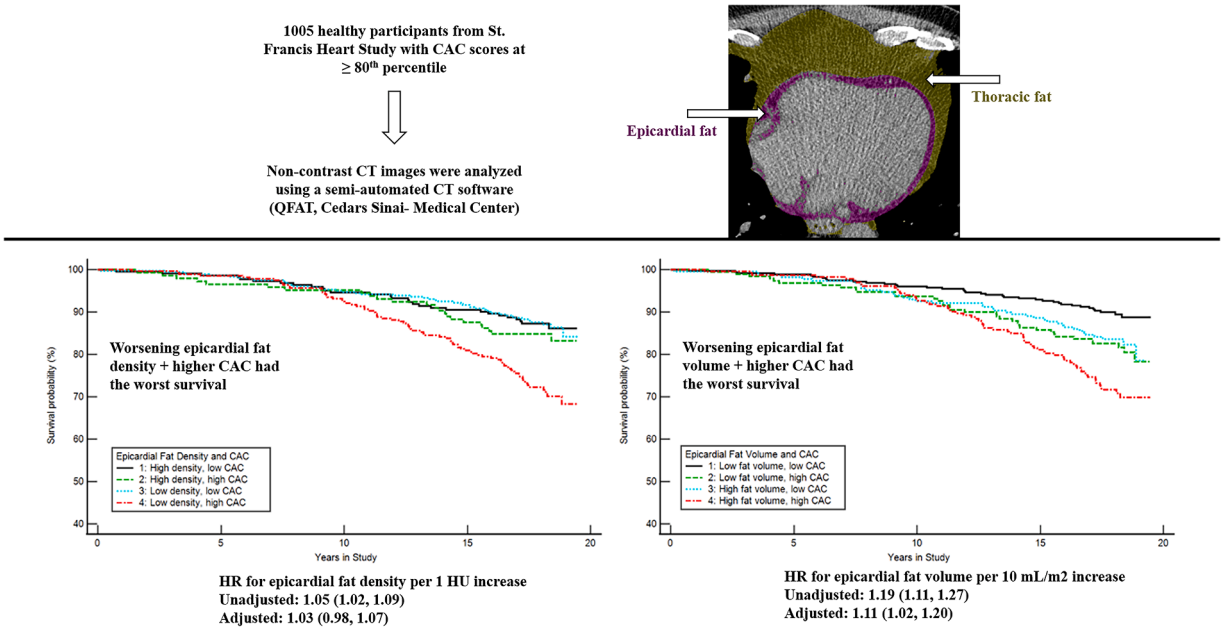

Central illustration: In a sample of 1005 participants from the St. Francis Heart Study who were apparently healthy with CAC scores at 80th percentile or higher for age and gender, epicardial fat measured on CT was found to provide additional prognostic value to CAC score for predicting long-term mortality.

1. Introduction

Epicardial fat tissue, the adipose tissue surrounding the coronary artery tree within the pericardium, has raised research interests in its role in atherosclerosis. There are immunohistological and epidemiological studies suggesting an association between presence of coronary artery atherosclerosis and inflammation seen in the epicardial fat tissue [1–4]. In addition, there is evidence suggesting that low epicardial fat density and high epicardial fat volume are associated with traditional risk factors and adverse lipid profiles [5–8]. Lastly, epicardial fat is also associated with adverse clinical outcomes [3,9–14]. However, the risk of epicardial fat is not clear in the presence of coronary artery calcium (CAC) as it too is a powerful predictor of adverse outcomes [15,16]. In this study, we investigated the relationship between epicardial fat features and coronary artery calcium (CAC) scores as predictors of long-term mortality and their prognostic value when combined with traditional risk factors.

2. Materials and methods

2.1. Patient selection and data collection

We conducted a retrospective cohort-study analysis of subjects who were originally participants in the St. Francis Heart Study. Briefly, the sample consisted of participants who were asymptomatic and apparently healthy with CAC scores at 80th percentile or higher for age and gender who were randomly assigned to placebo or statin therapy (atorvastatin 20 mg/day) and had undergone electron-beam CT [17,18]. Written informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and the study protocol has been approved by the St. Francis Institutional Review Board. Traditional risk factors such as hypertension, diabetes, hyperlipidemia, smoking history and family history of premature cardiovascular diseases (CAD) were directly determined by physical exam, laboratory evaluation and self-reported medical history at baseline. Fasting lipid profiles such as low density lipoprotein - cholesterol (LDL-C), triglyceride (TG), high density lipoprotein - cholesterol (HDL -C), and total cholesterol (TC) were collected at baseline and subsequent follow-up visits. Non-contrast CT images were analyzed using a semi-automated CT software (QFAT, Cedars Sinai- Medical Center) to quantify epicardial fat density in Hounsfield units (HU) and volume in cm^3 (reported in mL and indexed by body surface area in m^2) [3]. The fat voxels between HU limits of −190 to −30 enclosed by the visceral pericardium, between the levels of pulmonary artery bifurcation and posterior descending artery, were analyzed by the software. An example is given by Fig. 1 with a sample axial slice through the heart excluding (A) and including (B) epicardial and thoracic fat outlines. Reproducibility was excellent with inter-rater correlation coefficients of 0.96 and 0.92 for epicardial fat volume and density, respectively. All-cause mortality data was ascertained from the National Death Index from the start of the original trial until December 31, 2018.

2.2. Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median ± interquartile range (IQR) and compared using two-sample or paired *t*-tests or Wilcoxon-Mann-Whitney as appropriate. Categorical variables are presented as frequency (%) and compared using χ^2 tests. Epicardial fat density is presented on the Hounsfield scale, and epicardial fat volume is presented as volume indexed by body surface area (mL/m^2). We selected cut-points of epicardial fat parameters by finding the optimal value which maximizes Youden's J Statistic (where J = sensitivity + specificity −1). High-risk CAC was defined as CAC >400 AU [19]. Stratified analyses combining fat volume and density with CAC were performed to assess their associations with long term all-cause mortality using Kaplan-Meier curves. Effect-measure modification by lnCAC was assessed with interaction terms (multiplicative) and through calculation of the relative excess risk due to interaction (additive). We then conducted *post-hoc* analyses to evaluate the added prognostic value of epicardial fat parameters to traditional risk factors and CAC predicting all-cause mortality. Hazard ratios with 95% confidence intervals were calculated using multivariable Cox proportional hazards models examining the effect of worsening epicardial fat features on all-cause mortality. Nested models were compared by adding

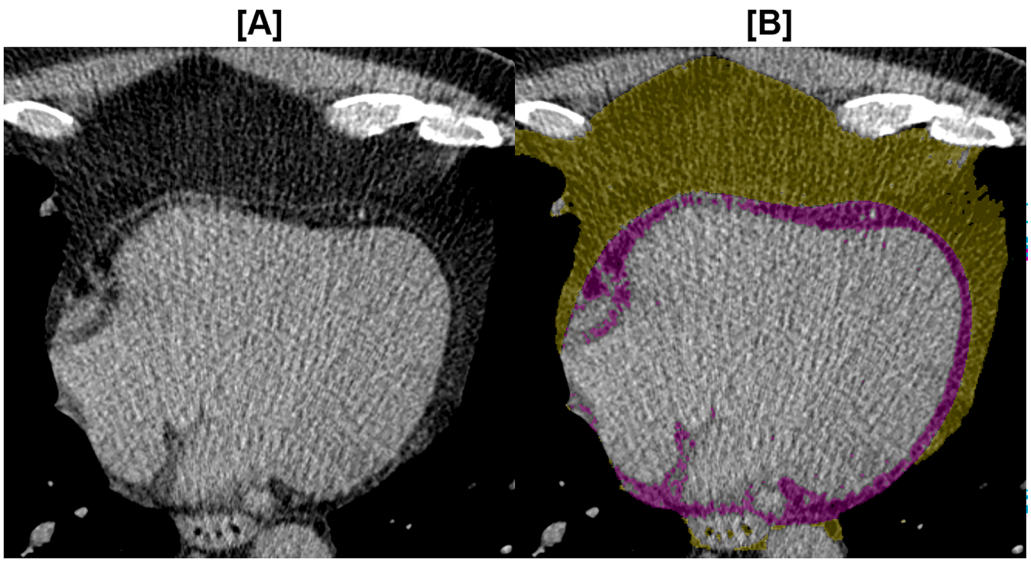

Fig. 1. Non-contrast CT images to quantify epicardial fat density and volume.
Non-contrast CT images were analyzed using a semi-automated CT software (QFAT, Cedars Sinai- Medical Center) to quantify epicardial fat density and volume, demonstrated by a sample axial slice through the heart (Fig. 1A) with overlays (Fig. 1B) illustrating epicardial fat (colored purple) and thoracic fat (colored yellow) outlines from the software.

Table 1
Baseline demographics ($N = 1005$).

	Mean ± SD / N (%)
Age (years)	59 ± 6
Gender-male	741 (73)
Body mass index (Kg/m^2)	29 ± 5
Total cholesterol (mg/dL)	226 ± 35
Low-density lipoprotein (mg/dL)	147 ± 30
High-density lipoprotein (mg/dL)	50 ± 14
Triglycerides (mg/dL)	143 ± 91
Calcium score, baseline	528 ± 614
Epicardial fat density (HU) mean ± SD, median (IQR)	76 ± 4, −76 (−79 to −73)
Epicardial fat volume (mL) mean ± SD, median (IQR)	97 ± 44, 91 (66 to 121)
Epicardial fat volume index (mL/m^2) mean ± SD, median (IQR)	48 ± 19, 46 (34 to 59)
Hypertension (%)	315 (31)
Diabetes (%)	73 (7)
Smoking history, any (%)	669 (67)
Family history of early ischemic disease (%)	539 (54)
Calcium score	
0–100	102 (11)
100–400	414 (44)
> 400	423 (45)

HU: Hounsfield units; IQR: interquartile range; SD: standard deviation.

epicardial fat parameters to models containing either calcium score or traditional risk factors with differences assessed using the likelihood ratio test. Finally, multivariable Cox models were stratified by presence of metabolic syndrome [20]. Two-sided p values <0.05 were considered statistically significant. All analyses were performed using SAS v. 9.4 (SAS Institute, Inc., Cary, NC).

3. Results

There were 1005 subjects enrolled. The mean age was 59 ± 6 years and 74% were male (Table 1). Male subjects were found to have a higher body surface area adjusted epicardial fat volume and a lower epicardial fat density compared to female subjects (data not shown). Increased epicardial fat volume and reduced epicardial fat density were significantly associated with presence of traditional risk factors such as hypertension, diabetes, higher BMI, higher TG and lower HDL-C (all $p \leq 0.01$, Table 2). In contrast, higher LDL-C and TC values were not associated with epicardial fat volume or density (data not shown). Worsening epicardial fat features were also associated with higher CAC. For each unit increase in lnCAC, the average epicardial fat volume increased by 3.34 mL/m^2 and epicardial fat density decreased by 0.54 HU.

After a mean follow-up period of 17 years, 179 (18%) participants died. The optimal cut-points for epicardial fat volume and density were 46 mL/m^2 and −75 HU, respectively. When compared to subjects with lower epicardial fat volumes and CAC scores, subjects with higher epicardial fat volume and CAC scores had lower probability of long-term survival (Fig. 2A) and those with lower epicardial fat and CAC had the highest probability of survival. However, those either having higher epicardial fat/lower CAC or having lower epicardial fat/higher CAC shared similar survival probability. As for epicardial density, subjects with lower epicardial fat density and higher CAC had the lowest survival probabilities than all the other subgroups (Fig. 2B). In contrast, the survival probabilities were not well differentiated among the other 3 subgroups.

When assessing the role of epicardial fat parameters using Cox proportional hazards models, worsening epicardial fat volume was associated with a hazard ratio of 1.11 (95% CI: 1.02 to 1.20) after adjustment for logarithm-transformed calcium score (lnCAC), age, gender, body mass index, baseline HDL-C and triglyceride values, hypertension, diabetes, and statin assignment. Worsening epicardial fat density was associated with a hazard ratio of 1.03 (95% CI: 0.98 to 1.07) when adjusted for the above variables (Table 3). No multiplicative or additive interactions were found between either of the epicardial fat parameters and lnCAC.

In order to evaluate the added prognostic value of epicardial fat parameters to traditional risk factors predicting all-cause mortality, we performed likelihood ratio testing of nested models. Compared with a model containing lnCAC alone, a model with lnCAC + epicardial fat volume or epicardial fat density yielded a significant likelihood ratio test $p < 0.001$ (Table 3) for both models. Using a model containing traditional risk factors and lnCAC, a similar nested model analysis yielded a significant likelihood ratio test with $p < 0.001$ for epicardial fat volume and $p = 0.002$ for epicardial fat density (Table 3). Upon stratification by metabolic syndrome, epicardial fat volume was associated with a hazard ratio of 1.07 (95% CI: 0.94–1.22) and 1.14 (95% CI: 1.04–1.26), and epicardial fat density was associated with a hazard ratio of 1.00 (95% CI:

Table 2
Bivariable analysis between epicardial fat density and volume with lipid profile at baseline, ($N = 1005$).

	Epicardial fat density (HU)			Epicardial fat volume (mL/m2)		
	B coefficient (LL, UL)		*p-value*	*B coefficient (LL, UL)*		*p-value*
Age	−0.02	(−0.11, 0.07)	0.6392	0.04	(0.02, 0.06)	<0.0001
Body mass index (kg/m2)	−0.37	(−0.42, −0.32)	<0.0001	3.63	(3.13, 4.14)	<0.0001
High-density lipoprotein	0.1	(0.09, 0.12)	<0.0001	−0.33	(−0.41, −0.24)	<0.0001
Triglycerides	−0.01	(−0.02, −0.01)	<0.0001	0.05	(0.04, 0.06)	<0.0001
	Mean	*SD*	*p-value*	*Mean*	*SD*	*p-value*
Male	−76.78	4.33	<0.001	49.92	19.79	<0.001
Female	−74.76	4.15		42.24	17.24	
Hypertension	−76.98	4.36	0.0005	51.68	19.9	<0.001
No Hypertension	−75.92	4.34		46.2	19	
Diabetes	−77.66	4.43	0.0065	55.44	20.8	0.0013

HU: Hounsfield units; LL: 95% lower limit; SD: standard deviation; UL: 95% upper limit.

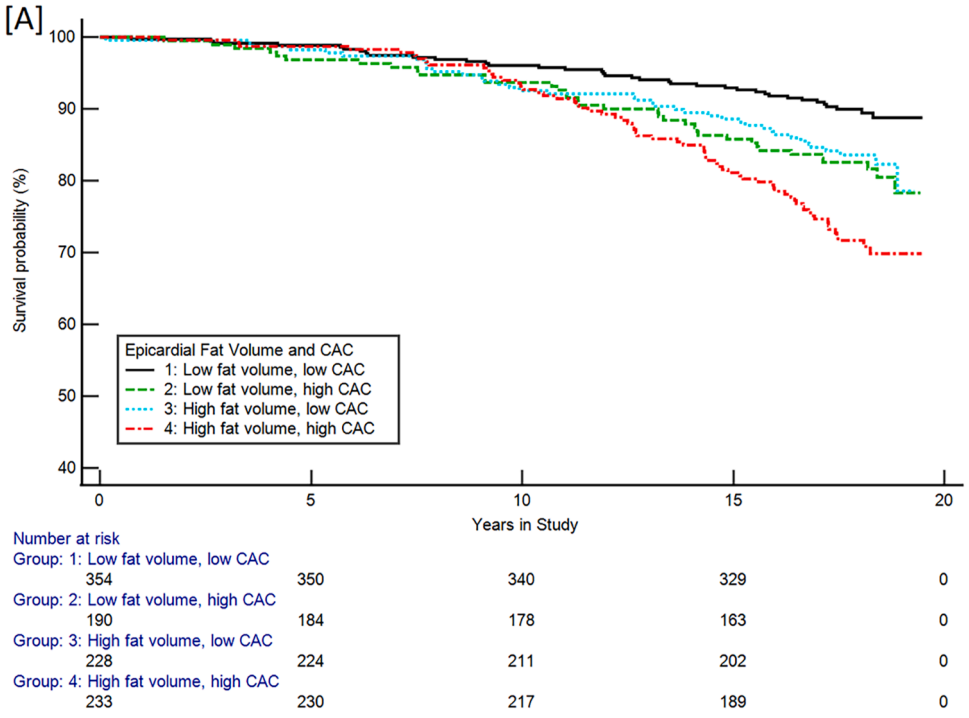

Fig. 2A. Kaplan Meier Curves, stratified by epicardial fat volume and CAC
Those with lowest epicardial fat volume and coronary calcium score had the best probability of survival and those with higher volume and calcium score had the worst survival.
CAC: coronary calcium score.

0.94–1.06) and 1.05 (95% CI: 1.01–1.11) for those without and with metabolic syndrome, respectively.

4. Discussion

There has been an increased interest in studying the role of adipose tissue given the increased prevalence of obesity and metabolic diseases [21]. There are different types of adipocytes, including white, brown and beige adipocytes, on a cellular level. Based on functionality, we typically classify adipose tissue into white and brown adipose tissue. While white adipose tissue is being studies in obesity, there is a growing interest that brown adipose tissue as a target in promoting cardiometablic health [22]. Nature also published an article on brown adipose tissue prevents glucose intolerance and cardiac remodeling in a mice model [23]. This led us to investigate the role in adipose tissue in the epicardial space.

In this study, we confirmed prior publications evaluating the relationship between increased epicardial fat volume or decreased fat density and increasing CAC [3,6,8,24,25]. We also demonstrated that higher epicardial fat volume is an additional mortality risk over increased CAC. Furthermore, we showed that when CAC is significantly increased, increased fat volume or decreased fat density portends the highest mortality risk [26,27].

It is consistent in the literature that increased epicardial fat volume is significantly associated with conventional cardiovascular risk factors and with increased CAC [4,6–8]. Epicardial fat is significantly larger among those with higher BMI and in male subjects. While few studies normalize epicardial fat volume with BSA, we believe it is essential to do so to mitigate the significant confounding from body size. In addition, increased epicardial fat volume and CAC are both risks of all-cause

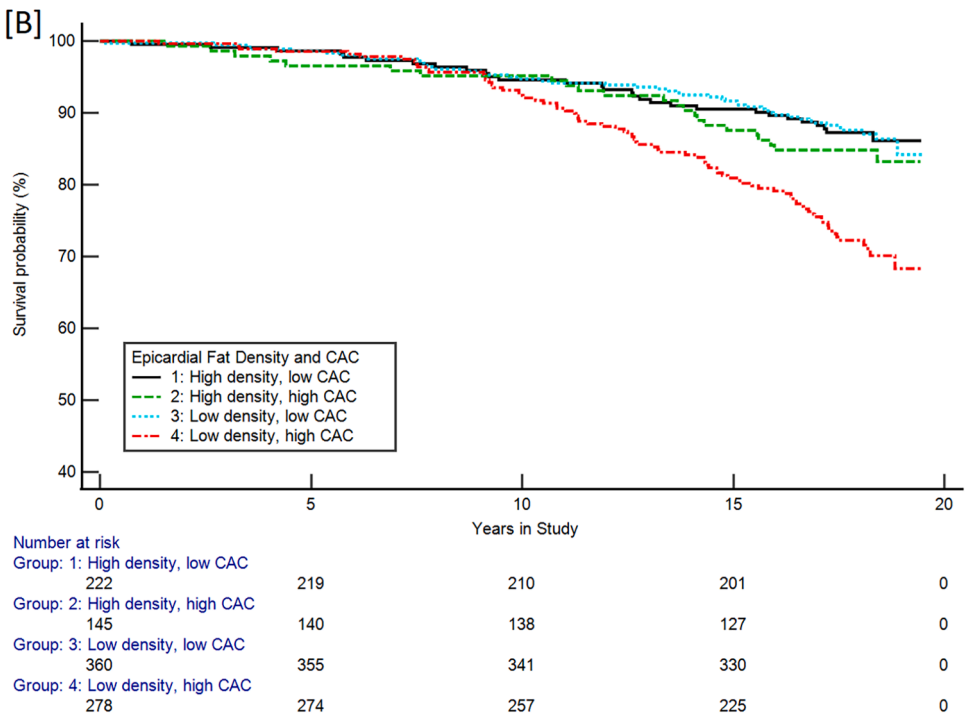

Fig. 2B. Kaplan Meier Curves, stratified by epicardial fat density and CAC
Those with worsening epicardial fat density and higher calcium score had the worst survival.
CAC: coronary calcium score.

Table 3
Cox proportional hazards models depicting relationship between epicardial fat parameters and all-cause mortality.

Model[1]	Variable	Epicardial fat parameter, per continuous unit					
		Epicardial fat volume (Per 10 mL/m2 increase)			Epicardial fat density (Per HU increase)		
		HR	*LL*	*UL*	*HR*	*LL*	*UL*
1	Epicardial fat parameter	1.19	1.11	1.27	1.05	1.02	1.09
2	Epicardial fat parameter	1.16	1.08	1.24	1.04	1.01	1.08
3	Epicardial fat parameter	1.11	1.02	1.20	1.03	0.98	1.07

HR: hazard ratio; HU: Hounsfield units; LL: 95% lower limit; UL: 95% upper limit.
[1] Model 1: Unadjusted
Model 2: adjusted for log-transformed calcium score
Model 3: Model 2 + age, gender, BMI, HDL-C, triglycerides, hypertension, diabetes, statin assignment.

mortality [11,28,29]. The mechanisms of association between epicardial fat and CAC are likely complex. On the one hand, they share similar associations with conventional cardiovascular risk factors. On the other hand, they may be intertwined in same pathway of atherosclerosis development. For example, the lower attenuation of the pericardial fat is probably atherogenic, directly contributing to the inflammation of coronary artery, not only promoting the atherosclerosis development but also causing instability of coronary endothelium subsequently leading to acute coronary syndrome [24]. A recent study by Goeller et al. [3]. reported that epicardial fat volume and density are associated with circulating pro-inflammatory biomarkers such as PAI-1, MCP-1 and adiponectin supporting a mechanistic link between epicardial fat and inflammation. Therefore, it is plausible that the association of the 2 biomarkers are not simply the result of their shared relationships with cardiovascular risk factors, which may have explained why there is synergistic effect in the mortality risk where combined higher epicardial volume and higher CAC have the worst probability of survival when compared to those with lower fat volume or lower CAC. This was true upon stratification by metabolic syndrome, where the effect was attenuated among those without metabolic syndrome. Interestingly, higher fat volume alone or higher CAC alone shares similar survival probability, which is worse than having neither. In light of well-established high risk in association with high CAC it is intriguing to find comparable reduced survival from those with higher fat volume in the absence of high CAC.

Our results expanded on a recent analysis of the EISNER study [25], which demonstrated similar associations between epicardial fat parameters and major adverse cardiovascular events even though our sample reflected a worse cardiovascular risk-profile (older baseline age, more prevalent hypercholesterolemia, family history of coronary artery disease, smoking history). The EISNER study considered the confounding relationship of CAC on epicardial fat and adverse events and epicardial fat-CAC strata, which we validated. We additionally evaluated presence of effect modification/interaction on the multiplicative and additive scales. Finally, we performed nested model evaluations with likelihood-ratio testing to demonstrate the additive benefit of using epicardial fat as a prognostic indicator in addition to already established biomarkers.

To compare the mortality risk of pericardial fat with that of CAC not only provides a reference point to understand the relative risk of pericardial fat as the risk of CAC is high which is well established but also to establish the clinical relevance of epicardial fat as a biomarker. Based on the nested models using likelihood ratio testing, we illustrated that increased epicardial fat volume provides additional prognostic values to CAC in predicting long-term mortality. This observation is clinically important as it demonstrates that epicardial fat is not simply a surrogate of collective cardiovascular risk factors. Rather, it is a highly relevant biomarker in its own right.

Similar to epicardial fat volume, epicardial fat density is also associated with conventional cardiovascular risk factors and CAC. Epicardial density is not an independent mortality risk factor in the fully adjusted model. When combined with CAC the combination of the lower density and higher CAC is associated with reduced survival probability. Those without reduced density regardless of high or low CAC did not seem to have the survival advantage. It appears that epicardial density is not as sensitive of a biomarker as epicardial fat volume in risk stratification. In recent years, there is growing interest in the features of pericoronary fat which appears to have close association with acute coronary syndrome [30–32] perhaps due to the direct proinflammatory effect of fat to the coronary vessel. When pericoronary fat is analyzed it is only within 5 mm of the coronary vessel. While the pericoronary fat is part of the pericardial fat tissue, it only represents perivascular space, not the entire epicardial space. Therefore, we cannot extrapolate the mean epicardial fat density to represent that of the pericoronary fat.

We acknowledge the limitations of our study. First, 73% of the patient population were male and majority was self-reported as Caucasian. In addition, all subjects in this study are at high cardiovascular risk, given the inclusion criteria of baseline CAC at 80th or higher percentile for age and gender. To that end, we still observed a mortality difference among patients with unfavorable epicardial fat parameters. Secondly, like many published reports, we assessed only the global epicardial fat. It is foreseeable that the regional analyses of epicardial fat surrounding the coronary artery may yield different observations. Using global assessment, we have observed that worsening epicardial fat features provided additional prognostic values in combination with traditional cardiovascular risk factors, including elevated CAC. Lastly, given the long interval from the initial patients' enrollment to mortality events, other confounders such as lifestyle and pharmacologic interventions during that interval would attenuate our results. With that said, we did try to adjust for traditional risk factors including CAC, in our Cox proportional hazards models. Despite all the confounders that might attenuate the results, we still found an additional prognostic value of epicardial fat features in all-cause mortality.

5. Conclusions

Increased epicardial fat volume is associated with increased long-term mortality. It provides additional prognostic values to CAC in mortality prediction.

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Data statement

The data used for this research is unavailable to access due to confidentiality.

CRediT authorship contribution statement

Lu Q. Chen: Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **Jonathan Scheiner:** Writing – review & editing, Formal analysis, Data curation. **Niloofar Fouladi Nashta:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Jonathan Weber:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Qingtao Zhou:** Writing – review & editing, Visualization, Formal analysis, Data curation. **Kathleen Rapelje:** Writing – review & editing, Supervision, Resources, Data curation. **Damini Dey:** Writing – review & editing, Software, Conceptualization. **J. Jane Cao:** Writing – review & editing, Visualization, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Damini Dey has patent with royalties paid to QFAT Software. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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