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Prognostic value of epicardial fat volume measurements by computed tomography: a systematic review of the literature

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Abstract

Objectives To perform a systematic review of the growing body of literature evaluating the prognostic value of epicardial fat volume (EFV) quantified by cross-sectional imaging.

Methods Two independent reviewers performed systematic searches on both PubMed and Scopus using search terms developed with a medical librarian. Peer-reviewed articles were selected based on the inclusion of outcome data, utilization of epicardial fat volume and sufficient reporting for analysis.

Results A total of 411 studies were evaluated with nine studies meeting the inclusion criteria. In all, the studies evaluated 10,252 patients. All nine studies were based on CT measurements. Seven studies evaluated the prognostic value of EFV unadjusted for calcium score, and six of these studies found a significant association between EFV and clinical outcomes. Seven studies evaluated the incremental value of EFV beyond calcium scoring, and six of these studies found a significant association.

Conclusions The majority of studies suggest that EFV quantification is significantly associated with clinical outcomes and provides incremental prognostic value over coronary artery calcium scoring. Future research should use a binary cut-off of 125 mL for evaluation of EFV to provide consistency with other research.

Key Points

- *Epicardial fat volume (EFV) has prognostic value for adverse cardiac events*
- *Establishment of standardized quantitative categories for EFV is needed*
- *Quantification of EFV could improve risk assessment with calcium scoring*

Keywords Epicardial fat · Coronary artery calcium · Cardiac computed tomography · Major adverse cardiac events · Prognostic value

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Abbreviations

CAC	Coronary artery calcium scoring
CT	Computed tomography
EFV	Epicardial fat volume
HR	Hazard ratio
MACE	Major adverse cardiac event
OR	Odds ratio

Introduction

Epicardial fat volume (EFV) has been correlated with numerous disease processes including coronary artery disease, atrial fibrillation and diabetes [1–5]. It has been demonstrated that

epicardial fat is metabolically different from other visceral fat both biochemically and in terms of its correlation to cardiac risk factors [6–9]. Emerging techniques for the measurement of EFV are reducing the complexity of its measurement and opening the potential for its inclusion into clinical workflows [10, 11].

EFV measurements by computed tomography (CT) have been shown to be predictive of myocardial ischaemia by single-photon emission CT (SPECT) [12] and positron emission tomography (PET) [13]. Several studies have investigated the prognostic value of EFV using non-contrast CT and cardiac CT angiography [7, 14–19]. These studies postulate a prognostic role of EFV for clinical outcomes although there is variation in classification and methodology of fat measurement [7, 14–18, 20]. In particular, it is currently not clear whether EFV quantification provides incremental diagnostic value over coronary artery calcium (CAC) scoring on CT. This is of particular clinical interest, since it would provide the rationale for adding routine quantification of EFV to the evaluation of CAC scoring studies.

The present review, therefore, sought to summarize the available evidence on the prognostic value of EFV measurements on cross-sectional imaging for clinical outcomes through a systematic review of the literature.

Methods

Search strategy

The present study sought to investigate the prognostic value of EFV for major adverse cardiac events (MACE) or all-cause mortality. In coordination with a medical librarian (T.L.H.) experienced in systemic literature reviews, these elements were used to develop a comprehensive search strategy for PubMed and Scopus. The PubMed search included the medical subject heading (MeSH) terms ‘diagnostic imaging’, ‘adipose tissue’ and ‘pericardium’, as well as the keywords (‘epicardial’ OR ‘pericardial’) and (‘fat’ OR ‘adipose’). The results were also filtered for human subjects and English language which yielded 218 relevant publications. The Scopus search included the terms and filters mentioned above and excluded the Medline results and review publications yielding 193 relevant studies. Searches were carried out in June 2014. We additionally hand-searched the references list of all eligible studies and relevant review articles and consulted a cardiac imaging expert in order to ensure that no relevant studies had been missed.

Search strategy

Two investigators independently reviewed the search results and determined study eligibility. Studies were evaluated for inclusion into the systematic review if they (a) were performed with cross-sectional imaging−CT (both contrast-enhanced and non-contrast examinations) or magnetic resonance imaging (MRI)−and (b) included prognostic analysis using MACE or all-cause mortality as the endpoint. Because thickness of cardiac fat has been shown to be widely anatomically variable by region of measurement [21], sonographic studies of fat thickness were not included. Since we were specifically interested in the prognostic value of EFV, we only included longitudinal studies reporting the association between EFV and adverse events occurring after the imaging examination. We did not consider cross-sectional studies on the association between EFV and the prevalence of cardiovacular disease at the time of the imaging examination. The Framingham Heart Study Offspring cohort has previously demonstrated a significant cross-sectional association between EFV and prevalent cardiovascular disease [22].

Data extraction

Two independent investigators (J.V.S. and M.R.) extracted information on the following variables: Number of patients included into the study; inclusion and exclusion criteria; endpoint definition; gender; age; presence or absence of diabetes or hypertension; measurements of body mass index, Framingham Risk Score, CAC score; EFV; years of follow up; number of events; statistical model used; multivariate adjustments; and methods of EFV aggregation. Discrepancies between the two investigators were resolved by discussion and re-examination of the corresponding studies together with a senior investigator (F.G.M.). The number of events was derived from the original studies for each type of endpoint. If the absolute number of events was not directly provided in the manuscript, they were derived from the provided information whenever possible. We extracted the hazard ratios (HRs) or odds ratios (ORs) and the corresponding 95 % confidence intervals (CIs) of the individual studies as well as the corresponding increments of EFV. In order to minimize confounding, we used the most extensively adjusted HR/OR derived from multivariate regression analysis, if available.

Study quality assessment

Study quality assessment was performed to allow readers to judge the overall quality of the studies included in this systematic review. We did not exclude any studies on the grounds of insufficient study quality. Study quality indicators were chosen as described in a previous meta-analysis [23] and included a clear description of the target population, clear description of and justification for exclusion of patients after enrolment, presence of an endpoint

committee, quantification of EFV blinded to outcome, outcome assessment blinded to EFV, adjustment for age, gender and cardiovascular risk factors, clear description of EFV quantification method, and clear description of endpoints. Each item was rated by two independent reviewers (J.V.S. and A.W.K.) as either 1 for completely fulfilled, 0.5 for partially fulfilled or 0 for not described/not fulfilled. Thus the quality score of a study could theoretically range from 0 to 8.

Results

Study selection and characteristics

After exclusion of duplicates, a total of 411 studies were identified using our search criteria in Scopus and PubMed and hand-searching reference lists (Fig. 1). Of these, 376 were discarded based on the abstract. The 35 remaining studies were analysed in full text. Nine of them met the criteria for inclusion in this systematic review. The characteristics of the included studies are summarized in Table 1. The majority of included studies had a single-centre design (five of nine) and were conducted in Asia, Europe or the USA (two, one and six, respectively). Of the nine studies there were one prospective study [15], three case control studies (two of which matched from the same cohort) [16, 18, 24] and five retrospective reanalyses of previously published prospective studies on CAC scoring [7, 14, 17, 19, 20].

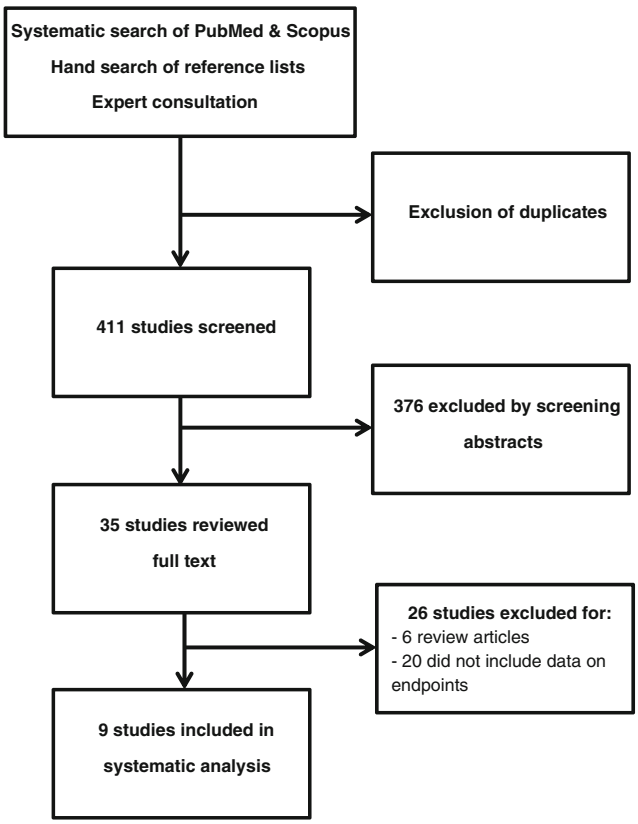

Fig. 1 Diagrammatic representation of study selection process as recommended for systematic reviews and meta-analyses in the QUOROM statement [31]

In all, the studies evaluated 10,252 patients. The patient population was dominated by two large population-based cohort studies with 4093 and 3086 patients [7, 20], respectively, with a total of 3073 patients in the remaining seven studies (Table 2). One study specifically included patients with acute chest pain suggestive of ischaemia [15]. Two of the studies used the same population from a registry of 232 asymptomatic patients with no known cardiac disease [16, 18]. One study was a random selection from the MESA cohort study [24]. One study was a subset of patients with CAC scores in a low to intermediate risk category [14]. One study included only patients on haemodialysis [17]. One study included patients undergoing calcium scoring without proven CAD [19]. A summary of the inclusion and exclusion criteria of all studies is shown in Table 1. Table 3 summarizes the length of follow-up and number of events for each study.

All nine studies were based on CT measurements; no eligible studies on MRI were identified. Seven of the nine studies measured only the adipose tissue contained within the pericardium (regardless of whether this was referred to as 'epicardial' or 'pericardial' fat). Two studies measured fat around the heart both within ('epicardial') and adjacent to the pericardium ('paracardial') and referred to the sum of both as 'pericardial' fat [15, 24]. Endpoints were MACE in eight studies, and all-cause mortality in two studies (one study used both endpoints). Mortality from cardiac causes was also reported in seven studies but not used for the prognostic analysis.

There was great variability in the statistical methods used for evaluation, primarily due to differences in study design. The six cohort studies performed Cox regression analysis and calculated HRs. The three case-control studies calculated ORs based on multivariate logistic regression. The increments of EFV used varied widely. Some studies evaluated it using incremental gradations [17]. Some studies used tertiles [20] or doublings [7]; and yet others used a binary threshold from the literature of 125 mL [14]. One study, re-evaluating the same population as Cheng et al. [16], used the binary threshold normalized to the surface area of the patient [18], which they referred to as indexed EFV. Greif and colleagues [15] evaluated the HR at 200 mL increments. Kunita et al. [19] based EFV HRs on individual values being above or below the median (107.2 mL) of the included patients [19]. Ding et al. [24] measured EFV only in a limited stack of images at the level of the left main coronary artery (this method was validated against total EFV in a small subset of patients) and used a binary cutoff for their analysis of prognostic value.

Table 1 Summary of included studies

First author (reference no.)	Year	Inclusion criteria	Exclusion criteria	Primary endpoints
Britton [20]	2013	Third generation of Framingham heart study who underwent multi-detector CT	None	MACE as myocardial infarction, angina pectoris, coronary insufficiency, cerebrovascular accident, transient ischaemic attack, intermittent claudication, congestive heart failure, cardiovascular death, cancer (excluding non-melanoma skin cancer) or all-cause mortality
Cheng [16]	2010	Men≥55 y or women≥65 y of age; men≥45 y of age with at least one traditional CAD risk factor	History of myocardial infarction, coronary revascularization, cardiomyopathy, peripheral artery disease, angina or stroke; prior CAC score; invasive angiogram; active pregnancy; significant comorbidity	MACE as cardiac death, myocardial infarction, stroke, late percutaneous or surgical revascularization
Ding [24]	2009	Randomly selected from Multi-Ethnic Study of Atherosclerosis (MESA) participants and MESA participants who developed incident coronary heart disease	Individuals with physician-diagnosed cardiovascular disease or any related procedures at baseline were not eligible	Coronary heart disease events such as myocardial infarction, resuscitated cardiac arrest, angina or fatal coronary heart disease
D'Marco [17]	2013	Renagel in New Dialysis – CKD stage 5 with no history of dialysis at outset, transplant, coronary bypass graft or intra coronary stenting, atrial fibrillation or atrial flutter	Error in the image file, or inadvertent exclusion of parts of the pericardium at the time of image acquisition	All-cause mortality
Forouzandeh [14]	2013	Age>18 y; chest pain within 24 hours suggestive of ischaemia, admission under observational status	Prior CAD, ischaemic electrocardiogram findings diagnostic of an acute coronary syndrome, troponin >0.1 ng/mL, haemodynamic instability	MACE as cardiac death, nonfatal myocardial infarction, and unstable angina pectoris
Greif [15]	2012	Coronary artery stenosis (one >50 % blockage in coronary angiography) or prior myocardial infarction	Acute coronary syndrome, advanced ischaemic cardiomyopathy, or coronary artery by-pass grafting	Severe cardiac events such as cardiac death, myocardial infarction or coronary revascularization
Kunita[19]	2014	No proven CAD, no history of myocardial infarction, prior coronary revascularization, status of acute coronary syndrome or typical effort angina	Proven cardiomyopathy, severe valvular heart disease, renal impairments (creatinine>1.5 mg/dl), serious life-threatening illness or early coronary revascularizations	Cardiac death, non-fatal myocardial infarction, or unstable angina requiring hospitalization, and late coronary revascularizations
Mahabadi [7]	2013	Heinz Nixdorf Recall−population-based cohort study with subjects randomly selected from mandatory lists of residence	Known coronary artery disease, history of myocardial infarction, or open heart surgery (including bypass and valve surgery)	Nonfatal myocardial infarction or cardiac death
Shmilovich [18]	2011	Asymptomatic status with no known cardiovascular disease, diabetes mellitus or smoking; CAC=0, LDL <160, triglyceride <500, FRS <6 %	Pericardial effusion or thickening, lower-than-excellent image quality on non-contrast-enhanced cardiac CT	MACE as cardiovascular death, myocardial infarction, stroke, percutaneous or surgical coronary artery revascularization

CAC coronary artery calcium score, *CAD* coronary artery disease, *CKD* chronic kidney disease, *FRS* Framingham Risk Score, *LDL* low density lipoprotein, *MACE* major adverse cardiac event

Table 2 Summary of patient characteristics of included studies

First author (reference no.)	Total no.	Male	Age* (y)	BMI* (kg/m^2)	Diabetes	Hypertension	FRS*	CAC*	EFV* (mL)
Britton [20]	3086	51 %	50.2±10	27.7±5.2	5.4 %	27 %	NR	NR	111±43
Cheng [16]	232	79 %	61±9	28.5±4.9	18 %	65 %	13±7	50.4±7.8	89±41
Ding [24]	1119	47 %	60±10	27.9	10.7 %	37 %	NR	NR	82
D'Marco [17]	95	61 %	58±15	25.4±15.3	59 %	97 %	NR	95.7	113
Forouzandeh [14]	760	41 %	54±14	30.6±7.3	15 %	57 %	8±8	125±429	127±61
Greif [15]	145	65 %	60±10	NR	17 %	74 %	NR	847±1,555	240±110
Kunita[19]	722	61 %	65±11	23.7±3.5	33 %	58 %	NR	24	107
Mahabadi [7]	4093	47 %	59±8	NR	12 %	32 %	NR	NR	86
Shmilovich [18]	226	51 %	52±9	26.8±4.9	0 %	34 %	2	NR	65

* Values are represented as averages±standard deviation, otherwise values are medians

BMI body mass index, *CAC* coronary artery calcium score, *EFV* epicardial fat volume, *FRS* Framingham Risk Score

Study quality

The quality assessment results are shown in Fig. 2. The overall mean of the quality scores was high (mean 6.4, range 4.5–7.5) with two studies scoring below 6 on our 0- to 8-point scale. Only four studies used endpoint committees and only four clearly described blinding assessment of outcomes. Similarly, blinding of patient information for EFV measurement was only sufficiently described in four studies. Descriptions were very clear, however, for study populations, exclusion criteria, EFV measurement techniques and endpoints. All studies included adjustments for risk factors, though risk factor selection varied (Table 4).

Prognostic value of EFV

Seven studies with a total of 10,149 patients evaluated the prognostic value of EFV unadjusted for CAC score (Table 4). Six of these studies evaluating a total of 7063 patients found a significant prognostic value of EFV for future adverse events. Of these studies, five were adjusted for age, gender and cardiovascular risk factors and one reported an unadjusted OR. The seventh study analysing 3086 patients found a significant association of EFV with outcome when adjusting only for age and gender, but the prognostic value was no longer significant when cardiovascular risk factors were added as covariates.

Incremental prognostic value of EFV beyond CAC scoring

Seven studies with a total of 6271 patients evaluated the prognostic value of EFV adjusted for CAC score to determine if there is an incremental prognostic value of EFV beyond CAC scoring (Table 5). In all of these studies, a multivariate analysis was performed with CAC score, age, gender and cardiovascular risk factors as covariates. Six of these studies with a total of 5511 patients reported that EFV is an independent predictor of adverse events after adjusting for CAC score. One of these analysed a population of 760 patients and found a trend towards a prognostic value (HR=1.59 (0.81−3.09) for EFV>125 mL), which did not reach statistical significance. One study found that indexing EFV to body surface area

Table 3 Adverse events by study

First author (reference no.)	Follow-up, y	Total, n	Deaths from any cause, n	Deaths from cardiac cause, n	MACEs, n
Britton [20]	5	3086	71	NR	90
Cheng [16]	4	232	NR	4	58
Ding [24]	2	1119	NR	NR	147
D'Marco [17]	4.1	95	27	NR	NR
Forouzandeh [14]	3.3	760	NR	6	45
Greif [15]	5.4	145	6	4	32
Kunita [19]	3.7	722	NR	5	37
Mahabadi [7]	8	4093	NR	39	130
Shmilovich [18]	4	290	NR	4	58

MACE major adverse cardiac event, *NR* not reported

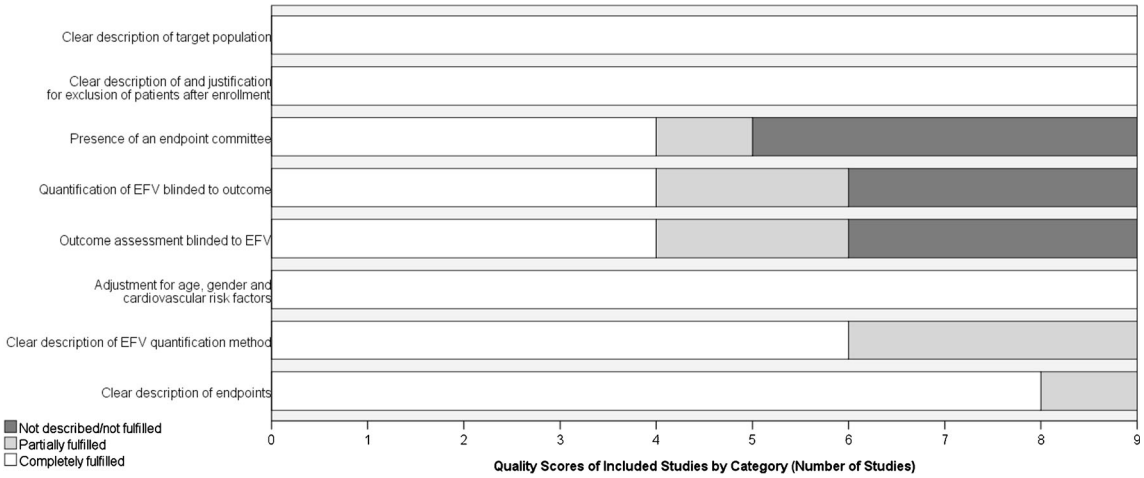

Fig. 2 Summary of study quality of articles included in the systematic review. **EFV** epicardial fat volume

improved its incremental prognostic value over CAC scoring and cardiovascular risk factors [18].

Discussion

Our study performed a systematic review of the available literature on the prognostic value of EFV quantification on cross-sectional imaging for clinical outcomes. Although the findings are not consistent across all of the nine studies, there is a clear trend that EFV has value as a prognostic metric for future adverse events and improves risk prediction beyond CAC scoring.

A number of studies have established a unique pathophysiological role of epicardial fat that distinguishes it from thoracic fat [16], aortic fat [20] and other adipose tissue in the body [9, 25]. While the findings are somewhat mixed depending on the study design, it is clear that fat tissue surrounding the heart plays a unique role in cardiac disease. It is thought that the fat directly surrounding the coronary arteries fosters development of atherosclerosis [21], arterial stiffness [26] and calcification, although the exact process is not fully understood. It has been shown that this fat tissue has metabolic activity and produces cytokines implicated in the pathophysiology of coronary atherosclerosis [27]. One challenge to determining the specific pathology is an unclear relationship between epicardial fat and pericardial fat [28]. There is even some disagreement as to the meaning of each of these terms. Choi et al. [28] provided a clear delineation by measuring both values and defining epicardial fat as all fat within the border of the pericardium and pericardial fat as being exterior and adjacent to the pericardium. Based on the inconsistency of terminology found in the literature, we recommend that these definitions be consistently applied in future research to avoid misinterpretation.

Our systematic review demonstrated that the majority of studies reported an incremental prognostic value of EFV quantification beyond CAC scoring. Thus, the potential clinical role of EFV could be projected as an 'add-on' analysis of CAC-scoring CT studies. As such, EFV quantification does not require additional radiation exposure or acquisition time. Recent studies on coronary CT angiography datasets suggested that EFV quantification can be performed semi-automatically with good accuracy thus reducing the time required for the analysis to less than 2 min [10]. It is reasonable to assume that a similar time would be necessary for semi-automated EFV quantification on non-contrast CAC-scoring CT data. Similar to CAC scoring, EFV quantification can be easily performed by a non-radiologist (such as a technologist) after a moderate amount of training [10].

We had initially intended to also synthesize the available evidence on the prognostic value of EFV in the form of a meta-analysis. Unfortunately, due to the wide variability in the study designs and in the statistical methods associated with EFV evaluation – in particular the various EFV increments used−calculation of pooled ORs or HRs was not possible. The results of our analysis indicate a need to standardize the quantitative evaluation of EFV. In CAC scoring, standardized quantitative categories (0, 1−100, 101−400, 401−1000 and >1000) have been established and are used in all pertinent studies with minor variations. Similarly, it would be beneficial to establish standardized quantitative categories for EFV, which would allow direct comparison of prognostic metrics between studies, synthesis of their results and provide guidance in the interpretation of quantitative EFV measurements in clinical routine. The study by Greif and colleagues [15] measured fat both inside and outside the pericardium (epicardial plus pericardial fat according to the definitions by Choi [28]) and demonstrated that increasing the binary cutoff for EFV beyond 200 mL did not significantly improve prognostic value. Thus, based on the available evidence, cutoffs of

Table 4 Prognostic value of epicardial fat volume (EFV)

First author (reference no.)	Total, n	Outcome	Events	EFV aggregation	OR	HR	Multivariate adjustments
Britton [20]	3086	All-cause mortality MACE	71 90	One standard deviation increments		1.31 (1.10−1.55) 1.24 (1.05−1.46)	Age, gender
		All-cause mortality MACE	71 90			1.17 (0.95−1.44) 1.11 (0.91−1.35)	Age, gender, systolic blood pressure, diabetes, total cholesterol, HDL cholesterol, smoking, hypertension treatment and BMI
Ding [24]	1119	MACE	147	One standard deviation		1.26 (1.01−1.59)	Age, sex, ethnicity, BMI, smoking, alcohol, physical activity, education, systolic blood pressure, antihypertensive medication, cholesterol, fasting glucose, diabetes medication and C-reactive protein
Forouzandeh [14]	760	MACE	45	>125 mL		2.31 (1.21−4.42)	FRS and BMI
Greif [15]	143 (2 excluded)	MACE	32	200-mL increments		>200 mL: 2.1 (1.4−3.2) >400 mL: 2.2 (1.5−3.4) >600 mL: 2.5 (1.6−3.9)	Age, gender and coronary risk factors
Kunita [19]	722	MACE	37	>107.2 mL		2.65 (1.23−5.70)	Adjusted for age, sex, BMI, hypertension, diabetes mellitus and smoking
Mahabadi [7]	4,093	MACE	130	Doubling of Volume		1.54 (1.09−2.19)	Age, gender and traditional risk factors
Shmilovich [18]	226	MACE	58	>68 mL/m^2	3.1 (1.4−6.9)		Unadjusted (EFV indexed to BSA – roughly equivalent to 125 mL)

BMI body mass index, BSA body surface area, FRS Framingham Risk Score, HDL high density lipoprotein, HR hazard ratio; MACE – major adverse cardiac event, OR odds ratio

Table 5 Incremental prognostic value of epicardial fat volume (EFV) beyond coronary artery calcium scoring

First author (Reference no.)	Total, n	Outcome	Events	EFV aggregation	OR	HR	Multivariate adjustments
Cheng [16]	232	MACE	58	Log of volume in continuous increments	1.74 (1.03−2.95)		Age, traditional risk factors, CAC and FRS
D'Marco [17]	95	All-cause mortality	27	10-mL increments		1.06 (1.01−1.05)	Age, gender, race, BMI, HDL cholesterol, total CAC
Forouzandeh [14]	760	MACE	45	>125 mL		1.59 (0.81−3.09)	FRS, BMI and CAC
Greif [15]	143 (2 excluded)	MACE	32	200-mL increments		CAC>400, EFV>200: 2.9 (1.9−4.5) CAC>400, EFV>400: 3.0 (1.9−4.5) CAC>400, EFV>600: 3.0 (1.9−4.9) CAC>800, EFV>200: 4.0 (2.1−5.0) CAC>1600, EFV>200: 7.1 (4.1−10.2)	Age, gender, coronary risk factors and CAC
Kunita [19]	722	MACE	37	>107.2 mL		2.48 (1.16−5.31)	Age, sex, BMI, hypertension, hypercholesterolemia, diabetes mellitus, current smoking and CAC>100
Mahabadi [7]	4093	MACE	130	Doubling of Volume		1.50 (1.07−2.11)	Age, gender, traditional risk factors and CAC
Shmilovich [18]	226	MACE	58	>68 mL/m^2 *	2.8 (1.3−6.4)		CAC and FRS (EFV indexed to BSA – roughly equivalent to 125 mL)

* This is roughly equivalent to 125 mL/1.7 m^2 (close to the average adult BSA)

BMI body mass index, *BSA* body surface area, *CAC* coronary artery calcium score, *FRS* Framingham Risk Score, *HDL* – high density lipoproteins, *HR* hazard ratio, *MACE* major adverse cardiac event, *OR* odds ratio

125 mL for epicardial fat and 200 mL for epicardial plus pericardial fat appear most appropriate for prognostic risk stratification, if binary cutoffs are used. Thus far, only one relatively small study [18] has demonstrated that indexing EFV to body surface area (68 mL/m^2) improves its prognostic value; this should be confirmed in larger cohorts.

In most studies included in our analysis, there was a substantial overlap in EFV values between patients who did and did not develop events during follow-up. Accordingly, EFV alone should never be used to determine the appropriate management of an individual patient. However, in combination with established clinical risk factors and CAC score, EFV quantification can provide patients and their health-care providers with a more accurate risk estimate than would otherwise be possible. A substantial number of studies did not describe who determined outcomes (presence of an endpoint committee) or whether outcome assessment was performed blinded to EFV measurements and vice versa. This is remarkable considering that the derivation of endpoint is a crucial step in the data evaluation.

The results of our study should be viewed in light of the study design and its limitations. One limitation is that we did not assess whether EFV quantification provides incremental value over findings on contrast-enhanced coronary CT angiography. Considering the high prognostic value of CT angiography incremental to CAC scoring [29], the quantification of EFV may not offer any additional benefit if CT angiography is performed. CT angiography is an appropriate diagnostic test in selected stable but symptomatic patients [30]. EFV quantification as an 'add-on' to CAC scoring may be of particular benefit in the asymptomatic patients for whom coronary CT angiography is not recommended. As a general limitation of systematic reviews, the validity of our findings depends on the quality of the included studies. As discussed above, the available data did not lend itself to a meta-analysis due to variability in the study designs and statistical methods used. Individual patient outcome data could not be derived from the published data, which could have provided more insights and allowed for subgroup analyses for specific subgroups of patients.

Despite these limitations, the available evidence suggests that EFV quantification is a significant predictor of clinical outcomes and provides incremental prognostic value over traditional cardiovascular risk factors and CAC scoring.

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