Is Epicardial Adipose Tissue Associated with Atrial Fibrillation after Cardiac Surgery? A Systematic Review and Meta-analysis

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Abstract

Background: Although epicardial adipose tissue (EAT) has been proved be associated with atrial fibrillation (AF) and post-ablation AF recurrence, the relationship between EAT and AF after cardiac surgery (AFACS) is not evident, yet. Objective: In the study, we aim to perform a systematic review and meta-analysis to assess the association between EAT and AFACS and whether it is independent of the measurement methods. Methods: Systematic reach was implemented until May, 30, 2020, which "atrial fibrillation" and "epicardial adipose tissue" were as the main items in electronic databases. Analysis was stratified by EAT measurement methods into three pooled meta-analyses on 1) total EAT volume, 2) left atrium (LA)-EAT volume and 3) EAT thickness between two groups with and without AFACS, estimating standardized mean difference (SMD) with a random effect model. Results: Eight articles with ten studies (546 patients) were included. Accordingly, the results of meta-analysis showed that EAT was higher in AFACS subjects, regardless of the methods of EAT measurement.[total EAT volume: SMD = 0.56 ml; 95% confidence interval (CI) = 0.56-1.10ml, I2 = 0.90, P=0.04; EAT thickness: SMD = 0.85mm; 95% CI = 0.04-1.65mm, I2 = 0.90, P=0.04; LA-EAT volume: SMD = 0.57ml, 95% CI = 0.23-0.92ml, I2 = 0.00, P=0.001.] And there was no evidence of publication bias. Conclusion: EAT may be a potential marker and therapeutic target for AFACS. However, larger scale studies are still required, and evaluation is needed to for further estimation.

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ABSTRACT

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Objective : In the study, we aim to perform a systematic review and meta-analysis to assess the association between EAT and AFACS and whether it is independent of the measurement methods.

Methods : Systematic reach was implemented until May, 30, 2020, which "atrial fibrillation" and "epicardial adipose tissue" were as the main items in electronic databases. Analysis was stratified by EAT measurement methods into three pooled meta-analyses on 1) total EAT volume, 2) left atrium (LA)-EAT volume and 3) EAT thickness between two groups with and without AFACS, estimating standardized mean difference (SMD) with a random effect model.

Results: Eight articles with ten studies (546 patients) were included. Accordingly, the results of meta-analysis showed that EAT was higher in AFACS subjects, regardless of the methods of EAT measurement.[total EAT volume: SMD = 0.56 ml; 95% confidence interval (CI) = 0.56-1.10ml, I^2 = 0.90, P=0.04; EAT thickness: SMD = 0.85mm; 95% CI = 0.04-1.65mm, I^2 = 0.90, P=0.04; LA-EAT volume: SMD = 0.57ml, 95% CI = 0.23-0.92ml, I^2 = 0.00, P=0.001.] And there was no evidence of publication bias.

Conclusion : EAT may be a potential marker and therapeutic target for AFACS. However, larger scale studies are still required, and evaluation is needed to for further estimation.

Keywords: Atrial fibrillation; epicardial adipose tissue; cardiac surgery; meta-analysis; echocardiography.

1.Background

Atrial fibrillation (AF) is the most common arrhythmia with an increasing rate of morbidity and mortality [1]. AF after an cardiac surgery (AFACS) is the most frequent postoperative complication of cardiac surgical procedures, and occurs in up to 30% patients [2]. Although cardiac surgery-associated morbidity and mortality reduced, the incidence of AFACS was almost unchanged [3,4]. AFACS may have a negative influence on post-operative results in the long term. It can result in a two-fold increase in all-cause 30-day and 6-month mortality after surgery compared to patients with sinus rhythm[5].

Recently, more attention has been drawn to the relationship between epicardial adipose tissue (EAT) and AF because of its inflammatory and endocrine properties [6]. EAT is an ectopic adipose tissue, which includes fat depots located between the myocardium and the visceral pericardium, such as pericardial fat, perivascular fat and myocardial steatosis. According to the location, it is easy to understand that the physiological functions of epicardial adipose tissue, including the storage of lipids as an energy supply for cardiomyocytes, protection of autonomic ganglia and nerve tissue, as well as regulation in the diameter and flow of coronary vessels[7]. Therefore, we speculate that EAT may play a central role in the pathogenesis of cardiovascular disease. A number of studies have shown an increasing relationship between EAT and coronary artery disease, atherosclerosis and the progression of coronary plaque burden [8-10], major adverse cardiovascular events [11] and AF[12-15].

The relationship between EAT and AFACS was firstly described by Charilaos et al. [16] in 2014, while more than ten studies have been undergone investigation thus far. However, these studies have been conducted in different populations, operations (Coronary Artery Bypass Grafting or valve replacement), with a variety of EAT measurement methods [computed tomography (CT) or echocardiography], and diverse intervals of follow-up[7,16-22]. This study was the first attempt to prove the association between AFACS and EAT, via conducting a systemic review and meta-analysis in patients with and without AF occurrence after cardiac surgery.

2. Materials and Methods

2.1 Search Strategy

The search was performed using the PubMed, Cochrane and Embase databases with the start date prior to May 30, 2020. To identify and retrieve all potentially relevant articles, the search was performed utilizing the following expression: [('epicardial adipose tissue' OR 'epicardial fat' OR 'pericardial adipose tissue' OR'pericardial fat' OR 'paracardial adipose tissue' OR 'paracardial fat') AND ('atrial fibrillation' OR Arrhythmias, Cardiac')]. Additionally, hand searches of the reference list of included studies were performed. We conducted this meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The systematic review registered in PROSPERO (ID: 219400). As per the different measuring methods of EAT, eligible studies fall into three sub-groups, including total EAT volume, EAT thickness and LA-EAT volume.

2.2 **Eligibility criteria**

Case reports and review articles were excluded. Only English publications in peer-reviewed journals were eligible for this meta-analysis if they: (1) reported EAT thickness or volume with at least one of the following main confounders: age, gender, hypertension and Body Mass Index (BMI); (2) reported EAT parameters in two groups of patients with and without AF occurrence after cardiac surgeries, and 3) measured EAT by CT, magnetic resonance imaging or echocardiography. The literature search was independently reviewed by two assessors to ensure full compliance with the study inclusion criteria. If no agreement could be reached, it would be decided by a third senior author.

2.3 **Study quality assessment**

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [23] was used to evaluate the quality of the included studies. STROBE consists of 22 items assessing quality of the information reported in the abstract, including introduction, study design and setting, statistical evaluation, results, discussion and findings. The point of STROBE judgment for all included studies was prepared based on rating scale ranging from 0 to 22 with higher score resulting in high quality. The STROBE score was independently evaluated by two investigators. And a third senior author was consulted when there were discrepancies. In the case of conference abstracts, which are without full-text, we used another 12-item STROBE checklist. All quantity scores were included in Table 1.

2.4 **Statistical methods**

The Cochrane Q test and I squared index were used to evaluate heterogeneity of individual studies. $I^2 >$ 50% suggested high heterogeneity. In the case of high heterogeneity, a random effect model was adopted. Considering the small size of samples, we used sensitivity analysis to explore probable sources of heterogeneity. The possibility of publication bias was evaluated through the Funnel plots and Egger's regression test. Statistical analysis was performed using STATA package vers.16 (StataCorp, College Station, TX, USA). $P<0.05$ was considered statistically significant.

3. **RESULTS**

3.1 Study selection

The literature search resulted in 1054 records, and 3 more records were identified through hand search of reference list of those articles. Excluding 449 duplicated records, there are 604 remaining records, in which 567 were not related to the topic. After reading the full texts of the 37 remaining articles, 29 articles were excluded because of a lack of EAT measurement (n=11), cardiac surgery (n=13), atrial fibrillation occurrence (n=2) or comparison (n=3). Finally, the findings of the 10 studies published in 8 articles with 3 sub-groups were enrolled in the study (Fig. 1).

3.2 Study characteristics

Patients with AF occurrence (n=154) and patients without AF occurrence (n=392) post operation were named as AFACS and non-AFACS respectively. Most [7,16-19] of the studies were in the full text format, while only one [22] study was in the conference abstract. EAT measurement involved EAT volume and LA EAT volume, which were assessed by CT, as well as EAT thickness assessed by echocardiography. EAT thickness was defined as an echo-free region between the right ventricular outer wall and the visceral pericardium. Other patient demographics and basic characteristics are described in Table 1.

3.3 Total epicardial fat volume

3 studies including 309 patients were involved in EAT volume. The comparison of total EAT volume between AFACS vs non-AFACS showed an SMD of 0.56 ml [95% confidence interval (CI) = 0.02, 1.10, P=0.04], indicating that EAT volume was higher in AF occurrence patients. Apparent significant heterogeneity was found among the studies' results ($I^2 = 76\%$, P = 0.01) (Fig. 2-A).

3.4 Epicardial fat thickness

There were 5 studies including 334 patients in measuring EAT thickness with echocardiography. The patients with AFACS occurrence had a significantly higher EAT thickness than those non-AFACS. (SMD=0.85mm, 95% CI=0.04-1.65, p=0.04, $I^2= 90\%$) (Fig.2-B).

3.5 Left atrium epicardial fat volume

2 studies including 178 patients measured LA-EAT. The results showed that there was a significant difference in the SMD between patients with and without AF occurrence (0.57 ml, 95% CI = 0.23–0.92, P=0.001, $I^2=0.0\%$), suggesting a higher LA-EAT volume in patients with AF occurrence. (Fig. 2-C).

3.6 Quality assessment and publication bias

Almost all studies in this meta-analysis were not of the same quality; the lowest STROBE score was 17, and the highest was 20 for the articles with full-text (Table 1). Potential sources of bias were not clear in most of the articles. Moreover, the eligibility criteria of selection of participants were not clear in the most of the articles. Figure 3 illustrates the relative symmetry of funnel plots of publications. At the same time, there was no evidence of publication bias by the calculation of the Egger test for small-study effects (P=0.160).

4. DISCUSSION

4.1 Main results

This study mainly showed an association between increasing EAT and AFACS occurrence. To investigate the relationship between EAT volume, both total and LA specified EAT, as well as EAT thickness and AFACS occurrence, three different meta-analyses were conducted. The findings were similar, which showed a positive association between increased EAT and AFACS occurrence. Surprisingly, the similar findings in EAT thickness and EAT volume put emphasis on the value of echocardiography in evaluation of EAT, which is a safe and non-invasive imaging modality[24].This study, the first attempt to prove the association between EAT and AFACS occurrence, suggested a new possible imaging marker to predict AFACS, which will require further research.

4.2 EAT and AFACS

Although the mechanism of increased EAT leading to AFACS is still unclear, studies that demonstrated association between abundant EAT and AF can be taken into account. EAT locates between the myocardium and visceral pericardium, mainly on the right ventricle surface and anterior wall of the left ventricle. It also surrounds atrioventricular grooves and great coronary vessels, reaching the main thickness at the anterior and lateral walls of right atrium [25]. Due to the position, It exerts local paracrine effect with findings of increased expression of numerous inflammatory markers, and as a metabolically active tissue modulating the adjacent myocardial tissue with abundant ganglionated plexus of autonomic nervous system[15,26,27]. At the same time, abundant EAT has been illustrated to be associated with fatty infiltration into adjacent myocardium by histopathological evidence [28]. Mahajan and Zghaib et al [29,30] proved EAT could cause lower bipolar voltage and electrogram fractionation as electrophysiologic substrates for AF. Besides, there is a speculate that the imbalance between excessive oxidative stress and the protective effect of adiponectin ultimately leads to the occurrence of AF[31].

The similarity is that AFACS associates with a combination of factors: clinical variables, intraoperative surgical variables, electrocardiograph markers and echocardiographic predictors. In detail, advanced age, hypertension, male gender, right coronary artery stenosis, depressed left ventricular function, a remote history of previous AF, combined valve replacement/coronary artery bypass grafting procedures, prolonged aortic cross-clamp and bypass times, PR-interval, QRS duration, abnormal left ventricular systolic and diastolic function, left ventricular hypertrophy and increased left atrial volume may predispose to postoperative AF [32-36]. And AFACS was also proved to be associated with the occurrence of systemic inflammatory response syndrome with inflammatory markers, including IL-6, IL-8, C-reactive protein, tumor necrosis factor-α and indices of neutrophil and platelet activation, increasing significantly in the systemic bloodstream [37,38]. Electrolyte imbalance, especially hypokalaemia, is also considered to be a triggering factor of AFACS [37,39].

It has been proved that obesity or a high BMI was a risk factor for AF[40,41]. Compared with non-obese people, obese individuals have a higher probability (49%) of suffering with AF, which may be related with atrial enlargement, ventricular diastolic dysfunction and increased ectopic fat depot [41]. And, in other reports, EAT was proved to be associated with AF even after adjustment for AF risk factors, including a high BMI[13,42]. However, Echahidi et al. [37]reported that metabolic syndrome and obesity were independent risk factors for AFACS. And EAT is associated with obesity or high BMI[42]. So, whether EAT should be regarded as an independent trigger or a modulator of obesity of AFACS requires further delineation.

In this study, it is known that increased EAT is associated with AFACS, soreducing EAT maybe potential to decrease the AFACS. Antidiabetic drugs were used for diabetes mellitus patients, which might decrease EAT and the accumulation of EAT, including Thiazolidinediones[43], glucagon-like peptide 1 receptor agonists[44], Dipeptidyl peptidase-4 inhibitors[45] and Sodium-dependent glucose transporters 2 inhibitors[46]. Besides, weight loss by diet control or exercise suggested to decrease EAT in interventricular groove, which suggests a correlation with improved insulin resistance and insulin sensitivity indexes[47]. A control study (in vivo and in vitro) performed on aortic stenosis patients who underwent a cardiac surgery suggested that statin therapy was related to EAT thickness reduction, which seemed secondary to the characteristics of statins anti-inflammatory effect[48]. Considering EAT containing large amount of ganglionated plexi, an increasing number of studies aimed at lowered AF inducibility due to injecting botulinum toxin into canine epicardial autonomic ganglia[49]. Although it was hypothetical, still promising to be a potential novel therapeutic option. All of these therapies not only might reduce EAT, but decrease incidence of many other diseases, especially metabolic diseases which is closely associated with AFACS.

Ten studies fell into sub-groups as per measuring methods of EAT, including echocardiography and CT. Comparatively, the results measured by CT were more preferred than echocardiography, because EAT was not uniformly distributed around the heart. Echocardiographic probe angulation on 2-dimensional imaging could decrease reproducibility and accuracy, as well as unable to measure periatrial fat or total EAT volume. And echocardiographic measurement might increase the EAT thickness, because overlapping with perivascular adipose tissue. But when patients had coronary atherosclerosis history, which enlarged thickness of EAT, image analysis probably provided accurate measurement. Accordingly, Nerlekar et.al[50] proved that EAT measured by CT compared with echocardiography revealed poor correlation, and discrepancy was particularly obvious at higher EAT thickness.

4.3 Cause of Heterogeneity

In this study, obvious heterogeneity was reported in two meta-analyses of comparing EAT volumes and EAT thickness in two groups with and without AF occurrence. Given the obtained heterogeneity, the random effect model was used. However, f the classification of studies into three categories of LA-EAT volume, total EAT volume, and EAT thickness reduced heterogeneity. Because of small sample sizes, a subgroup analysis or meta regression could not find the possible sources among various factors, such as female gender, cardiac surgery types, EAT evaluation methods as well as quality of studies based on STROBE Checklist. Moreover, BMI and age, as well as other classical AF risk factors were additional possible sources of heterogeneity. According to the sensitivity analysis (Table 2-a), it is suggested that the study of Ertugrul et al. [21] be one of the sources of heterogeneity. The endpoint of other studies was AF occurrence, which was defined according to the guidelines for the management of atrial fibrillation of European Society of Cardiology. But in this study, AFACS was defined as arrhythmic episodes that deteriorate hemodynamics, lasts more than 20 minutes per episode, or lasts more than 60 minutes during a 24-hour follow up, which underestimates the occurrence of AFACS. The study by Ertugrul et al. omitted, the sensitivity analysis results showed there was no heterogeneity resource (Table 2-b).

4.4 **Study Limitations**

The studies observational nature limits the study that by itself had no high position in the Evidence-Based Medicine Pyramid. And lacking access to patient detailed data, it didn't allow us to adjust for other covariates that may influence EAT including age, gender, and AF risk factors of hypertension, obstructive sleep apnea hypopnea syndrome, BMI and so on. Included studies were single-center trials with a small sample size, which might result in unreliable data. The inclusion of only 2 studies evaluating EAT thickness was limited because of the potential lack of power and the inability to draw firm conclusions. Finally, there was a significant degree of heterogeneity in the study, which might be a limitation that has been demonstrated in other published EAT meta-analyses with I^2 values >90% [51-53].

5. Conclusions

This meta-analysis suggested that total and LA-EAT volumes, as well as EAT thickness, be higher in patients with AF occurrence in comparison to those without AF occurrence after cardiac surgery. The results showed that EAT may be a potential biomarker and therapeutic target for AFACS, which can be measured by both volume and thickness measurements. Further well-designed prospective studies are required to confirm this finding in order to guide the clinical practice.

6. Author contributions:

Rina Sha: Conceptualization, Methodology, Software, Formal analysis, Writing – Original Draft, Writing – Review & Editing;

Wenqiang Han: Methodology, Formal analysis, Investigation, Data Curation; Mingjie Lin: Conceptualization, Writing – Original Draft, Writing – Review & Editing;

Jingquan Zhong: Conceptualization, Writing – Review & Editing, Supervision, Funding acquisition.

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Figure legends:

Fig.1 Flow chart of included studies. EAT- epicardial adipose tissue.

Fig. 2-a random effect meta-analysis comparing total EAT volume of patients with AF occurrence and without AF occurrence; b random effect meta-analysis comparing EAT thickness of patients with AF occurrence and without AF occurrence; c Random effect meta-analysis comparing LA-EAT volume of patients with AF occurrence and without AF occurrence. AF-atrial fibrillation. EAT- epicardial adipose tissue. LA-left atrial.

Fig.3 Illustration of funnel plot asymmetry due to heterogeneity including all studies.

Table 1

Characteristics of the included studies.

Reference	Year	Country	N	AF occurrence	AF occurrence	non-AF occurence	non-AF occurence	Type of EAT	Imaging
				n	Mean±SD	n	Mean±SD		
Charilaos	2014	Greece	83	28	195 ± 80	55	126 ± 47	EAT volume (ml)	CT
Kerem	2018	Turkey	149	35	135.71±46.78	114	118.71±42.85	EAT volume (ml)	CT
Marta	2019	Poland	46	14	7.1 ± 1.2	32	7.4 ± 1.2	EAT thickness(mm)	Echo
Qing(VHD)	2018	China	49	20	7.62±0.69	57	7.14±1.14	EAT thickness(mm)	ECho
Qing (NVHD)	2018	China	40	12	7.61±1.01		6.11±0.91	EAT thickness(mm)	ECho
Liu	2019	China	74	37	5.6±1.1	37	5±1.3	EAT thickness(mm)	Echo
Ertugrul	2020	Turkey	125	45	7.28±0.57	80	6.42±0.35	EAT thickness(mm)	Echo
Adam	2015	Poland	102	24	5.6±3.0	78	4.0±2.5	LA EAT volume(ml)	CT
Hiroko	2018	Japan	77	21	177.7±69.8	56	165.9±65.9	EAT volume (ml)	CT
		Japan	77	21	55.65±23.15	56	43.8±21.6	LA EAT volume(ml)	CT

LA: left atrium; EAT: epicardial adipose tissue, CT: computed tomography; OA: original article; CA: conference abstract; VHD: valvular heart disease; NVHD: non-valvular heart disease;

Notice: Unit of the volume and thickness variables are milliliter (ml) and millimeter (mm), respectively

Table 2-a

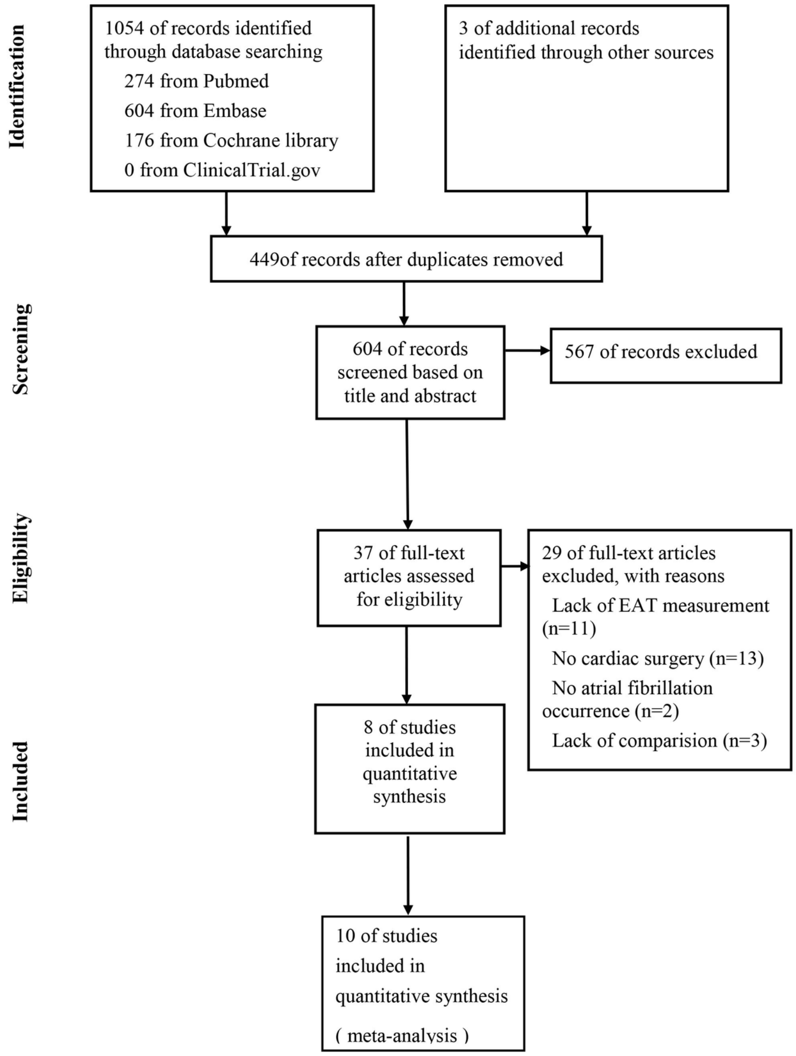
Results of sensitivity analysis

Study omitted	Estimate	95% Conf. Interval	95% Conf. Interval
Charilaos (2014)	0.66642737	0.50066859	0.8321861
Kerem (2018)	0.78323132	0.61100805	0.95545459

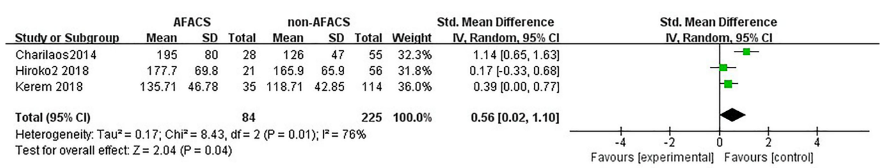
Study omitted	Estimate	95% Conf. Interval	95% Conf. Interval
Hiroko(2018)	0.77475089	0.60951865	0.93998313
Marta(2019)	0.78021538	0.61814988	0.94228089
Qing (VHD(2018)	0.73446065	0.57137752	0.89754385
Qing (NVHD)(2018)	0.67772061	0.51735497	0.83808631
Liu(2019)	0.74463749	0.57779455	0.91148037
Ertugrul(2020)	0.53569818	0.36762503	0.70377135
Adam(2015)	0.72998023	0.56324661	0.89671385
Hiroko(2018)	0.73505941	0.57005066	0.9000591
Combined	0.7163113	0.5593527	0.8732699

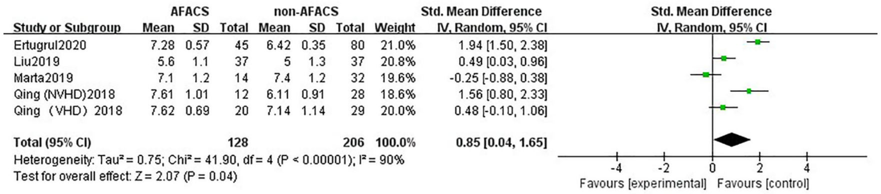
b. Results of sensitivity analysis leaving out the study by Ertugrul et al

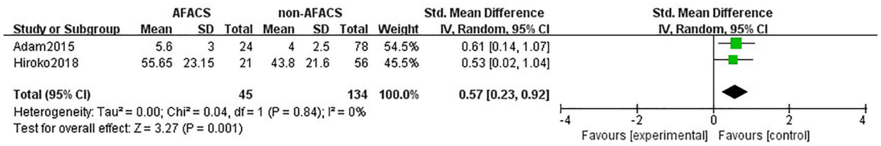
Study omitted	Estimate	95% Conf. Interval	95% Conf. Interval
Charilaos (2014)	0. 45323172	0.27421573	0..63224769
Kerem (2018)	0.57125425	0.38401416	0.75849438
Hiroko(2018)	0.58101773	0.40266448	0.75937104
Marta(2019)	0.59586072	0.42147139	0.77025008
Qing (VHD(2018)	0.54008275	0.71574193	0.71574193
Qing (NVHD)(2018)	0.48201472	0.30973798	0.65429145
Liu(2019)	0.54138154	0.36099765	0.72176534
Adam(2015)	0.52456343	0.36762503	0.70377137
Hiroko(2018)	0.53541028	0.35734367	0.7134769
Combined	0.5356982	0.5593527	0.8732699

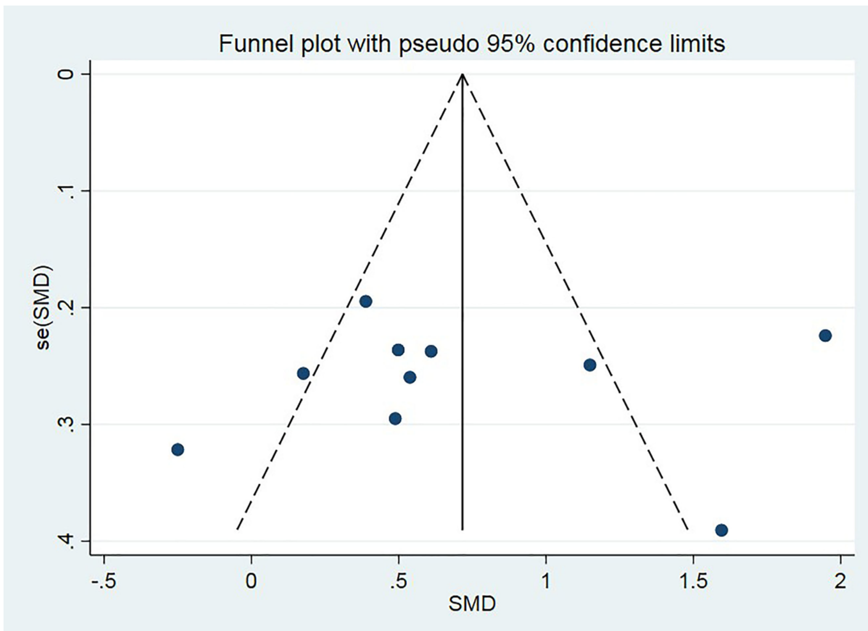

Identification
Screening
Eligibility
Included
1054 of records identified through database searching
274 from Pubmed
604 from Embase
176 from Cochrane library
0 from ClinicalTrial.gov
3 of additional records identified through other sources
449of records after duplicates removed
604 of records screened based on title and abstract
567 of records excluded
37 of full-text articles assessed for eligibility
29 of full-text articles excluded, with reasons
Lack of EAT measurement (n=11)
No cardiac surgery (n=13)
No atrial fibrillation occurrence (n=2)
Lack of comparision (n=3)
8 of studies included in quantitative synthesis
10 of studies included in quantitative synthesis
(meta-analysis)

1


AFACS
non-AFACS
Std. Mean Difference
Study or Subgroup
Mean
SD
Total
Weight
IV, Random, 95% CI
Charilaos2014 195 80 28 126 47 55 32.3% 1.14 [0.65, 1.63]
Hiroko2 2018 177.7 69.8 21 165.9 65.9 56 31.8% 0.17 [-0.33, 0.68]
Kerem 2018 135.71 46.78 35 118.71 42.85 114 36.0% 0.39 [0.00, 0.77]
Total (95% CI) 84 225 100.0% 0.56 [0.02, 1.10]
Heterogeneity: Tau² = 0.17; Chi² = 8.43, df = 2 (P = 0.01); I² = 76%
Test for overall effect: Z = 2.04 (P = 0.04)
Std. Mean Difference
IV, Random, 95% CI
-4
-2
0
2
4
Favours [experimental]
Favours [control]


AFACS
non-AFACS
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Ertugrul2020 7.28 0.57 45 6.42 0.35 80 21.0% 1.94 [1.50, 2.38]
Liu2019 5.6 1.1 37 5 1.3 37 20.8% 0.49 [0.03, 0.96]
Marta2019 7.1 1.2 14 7.4 1.2 32 19.6% -0.25 [-0.88, 0.38]
Qing (NVHD)2018 7.61 1.01 12 6.11 0.91 28 18.6% 1.56 [0.80, 2.33]
Qing （VHD）2018 7.62 0.69 20 7.14 1.14 29 20.0% 0.48 [-0.10, 1.06]
Total (95% CI) 128 206 100.0% 0.85 [0.04, 1.65]
Heterogeneity: Tau² = 0.75; Chi² = 41.90, df = 4 (P < 0.00001); I² = 90%
Test for overall effect: Z = 2.07 (P = 0.04)
-4 -2 0 2 4
Favours [experimental] Favours [control]


AFACS
non-AFACS
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Adam2015 5.6 3 24 4 2.5 78 54.5% 0.61 [0.14, 1.07]
Hiroko2018 55.65 23.15 21 43.8 21.6 56 45.5% 0.53 [0.02, 1.04]
Total (95% CI) 45 134 100.0% 0.57 [0.23, 0.92]
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 3.27 (P = 0.001)
-4 -2 0 2 4
Favours [experimental] Favours [control]


Funnel plot with pseudo 95% confidence limits
se(SMD)
0
.1
.2
.3
.4
-.5
0
.5
1
1.5
2
SMD