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Quantification of epicardial adipose tissue by computed tomographic scanning as a prognostic criterion of atrial fibrillation recurrence after catheter ablation

Aim	This study focused on a systematic review and meta-analysis on the predictive role of quantifying the epicardial adipose tissue (EAT) volume using data of computed tomography (CT) in patients after catheter ablation for atrial fibrillation (AF).
Material and methods	We performed a search in PubMed and Google Scholar for studies that examined the predictive value of EAT volume measured by CT for AF recurrence in patients after undergoing pulmonary venous isolation. Risk ratio (RR) values from studies, where similar scoring criteria were available, were pooled for the meta-analysis.
Results	Eighteen studies were selected from 901 publications for these systematic review and meta-analysis. In total, 4087 patients were included in this analysis (mean age, 59.0 years; mean follow-up duration, 14.9 mos). Patients with recurrent AF after ablation had higher left atrial EAT volume compared to patients without relapse (weighted mean difference, 5.99 ml; 95% CI: –10.04 to –1.94; p=0.004). An increase in left atrial EAT volume per ml was significantly associated with the development of AF recurrence after ablation (RR 1.08; 95% CI: 1.01 to 1.16; p=0.03). Patients with recurrent AF after ablation also had higher total EAT values than patients without relapse (difference in weighted values, 11.67 ml; 95% CI: – 19.81 to –3.54; p = 0.005). However, no significant association was found between the total EAT volume and the risk of AF relapse (RR 1.00; 95% CI: 1.00 to 1.01; p=0.06).
Conclusions	The volume of left atrial EAT measured by CT has a significant predictive value in AF patients after catheter ablation and can be used for stratification of the risk for recurrent AF.

Keywords	Atrial fibrillation; epicardial adipose tissue; catheter ablation; atrial fibrillation recurrence; predictive value; prognosis
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Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia diagnosed in clinical practice. Better understood mechanisms of atrial fibrillation and novel interventional and surgical treatments have changed the management of patients with this form of arrhythmia. Pulmonary vein isolation (PVI) performed by an appropriately trained surgeon is a safe and effective alternative to antiarrhythmic drug therapy. The 12-month success of the intervention is about 60–65% after the first procedure and 80% after several procedures [1, 2]. Identification of patient groups at higher risk of recurrent AF after catheter PVI can be useful in the development of preventive strategies and adaptation of rhythm control therapy after catheter ablation. During the search of AF mechanisms, several hypotheses were made regarding the predictors of AF, which currently include patient's baseline clinical characteristics and life record, structural and functional changes in the atrial myocardium, pro-inflammatory biomarkers, etc. [3]. Obesity is a known risk factor for AF and has a major impact on cardiovascular morbidity and mortality [4]. The Framingham Heart Study showed that increased pericardial fat was strongly associated with the risk of AF, even after being adjusted for body mass index (BMI) [5]. The quantitative and qualitative evaluation of epicardial adipose tissue (EAT) generates a growing interest due to the development of imaging techniques. EAT can be measured using magnetic resonance imaging (MRI), two-dimensional echocardiography and computed tomography (CT) of the heart [6]. The latter is the most common imaging technique used in clinical practice to assess the anatomy of PV and left atrial (LA) volume before PV catheter ablation. However, the studies investigating the prognostic role of measuring EAT by CT to predict the risk of recurrent AF produce limited data and show inconsistent results. Moreover, most of these studies were single-center and with small samples.

In this regard, we conducted a systematic review and a meta-analysis to investigate the prognostic role of quantitative assessment of EAT volume by CT in patients after catheter ablation for AF.

Material and Methods

Search for papers and selection of studies

The information search algorithm was developed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement in the PubMed (MEDLINE) and Google Scholar databases. The latest search of data to be included in this analysis was performed on April 10, 2022. The search for information in the PubMed (MEDLINE) database was carried out using the following query: ((atrial fibrillation)) AND ((adipose tissue) OR (epicardial adipose) OR (epicardial fat) OR (epicardial adipose tissue)) AND ((CT)) OR (computed tomography)) AND (catheter ablation) AND ((predictive value) OR (prognostic value) OR (atrial fibrillation recurrence)). The search was performed in Google Scholar using the following query: atrial fibrillation, epicardial adipose, epicardial fat, catheter ablation, computed tomography, atrial fibrillation recurrence, predictive value, hazard ratio cox regression. Two authors examined independently whether abstracts and full-text reports meet inclusion and exclusion criteria to select eligible studies for this systematic review and meta-analysis.

Inclusion/exclusion criteria

The criteria for including primary studies in the systematic review with subsequent meta-analysis were the availability of full texts; subjects of 18 years and older; studies with adequately presented baseline data, mainly the results of the quantitative assessment of EAT based on CT findings. Another prerequisite for including publications in the meta-analysis was the presentation of data on clinical outcomes, such as recurrent AF in the long term, and the presentation of the univariate Cox regression analysis results with hazard ratios (HR). The lower threshold for the follow-up duration was 6 months (mean follow-up period). The meta-analysis did not include articles written in languages other than English, case reports, nonclinical studies, reviews, and expert opinions.

Methods for the assessment of epicardial adipose tissue volume

Several protocols were used in different post-processing software to assess EAT volume in the studies included in our analysis. In most studies, EAT was identified using threshold values ranging from –50 to –200 Hounsfield units (HU). Total volume of EAT was calculated by semi-automatic reconstruction in various software based on adjacent 0.5 mm axial slices from the bifurcation of pulmonary trunk to the diaphragm. The volume of LA EAT was manually segmented from total EAT by removing the volume of left ventricular EAT in front of the mitral annulus and right atrial EAT in front of the right superior PV, and then under the coronary sinus [7, 8]. The main characteristics of the CT system and software are presented in Table 1.

Assessment of methodological quality

The quality of the studies was determined using the Newcastle-Ottawa Quality Assessment Scale for cohort studies [25]. The studies were assessed based on the following main criteria: selection of study groups, comparability of groups, and determination of the outcome of interest. All inconsistencies were eliminated by the discussion between the authors.

Statistical analysis

Data was processed in Review Manager (RevMan), version 5.4.1 (The Cochrane Collaboration, 2020) and Comprehensive Meta-Analysis 3.0 (Biostat, NJ). The meta-analysis was conducted using a random effects model and the inverse-variance approach. The main results are presented as a forest plot. Statistical heterogeneity was assessed using the Pearson's chi-square test and the heterogeneity index I^2. Statistical heterogeneity was interpreted based on the I^2 index according to the Cochrane Handbook: $I^2 = 0–40\%$ corresponds to insignificant heterogeneity; 30–60% – moderate heterogeneity; 50–90% – significant heterogeneity; 75–100% – high heterogeneity. The values of unadjusted hazard ratio (HR) obtained for the univariate model and determined for a change in EAT volume were used for the meta-analysis as the baseline values of the survival indicators. The difference was considered statistically significant with the p-value less than 0.05. Publication bias was evaluated using the Egger test.

Results

Results of literature search

A total of 901 papers were found using keyword searches in PubMed (MEDLINE) and Google Scholar databases. When duplicates were excluded, the number of papers decreased to 874. After analyzing the headlines and abstracts,

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Table 1. Specification of CT systems for EAT measurement

Study	CT system	HU	Post-processing software
Tsao, 2011 [9]	Aquilion 64 CFX, Toshiba Medical System, Tokyo, Japan	From −50 to −200	NR
Nagashima, 2011 [7]	Toshiba Medical Systems, Tokyo, Japan	From −50 to −200	Zio M900 Quadra; Amin, Tokyo, Japan
Kim, 2014 [10]	Philips, Brilliance 63, Netherlands	From −30 to −190	ITK-SNAP, Penn Image Computing and Science Laboratory (PICSL), University of Pennsylvania, USA
Nakahara, 2014 [8]	Somatom-Definition; Siemens-Medical Solutions, Forchheim, Germany	From −50 to −200	NavX system image integration software (EnSite-Verismo; St. Jude Medical)
Kocyigit, 2015 [11]	Somatom Definition; Siemens, Erlangen, Germany	From −30 to −250	Leonardo workstation, Siemens, Erlangen, Germany
Kocyigit, 2015 [12]	Aquilion ONE; Toshiba Medical Systems, Tochigi, Japan	From −50 to −200	Zio M900 Quadra; Amin, Tokyo, Japan
Maeda, 2018 [13]	NR	From −30 to −190	NR
Sanghai, 2018 [14]	Somatom Definition; Siemens, Erlangen, Germany	NR	NR
Kawasaki, 2019 [15]	Aquilion One ViSION Edition; Toshiba Medical, Otawara, Japan	From −195 to −45	Ziostation2 version 2.9; Ziosoft Inc., Tokyo, Japan
Tanisawa, 2020 [16]	SOMATOM Definition AS + Siemens Medical Solutions, Forchheim, Germany	From −50 to −200	Synapse Vincent; Fujifilm, Tokyo, Japan
Romanov, 2021 [17]	NR	From 0 to −190	Advantage workstation 4.7 v (GE)
Hammache 2021 [18]	Revolution CT, GE	From −50 to −250	Advantage workstation 4.7 v (GE)
El Mahdiui, 2021 [19]	Brilliance iCT 256, Phillips Healthcare, Best, the Netherlands	From −45 to −195	MASS software (Leiden University Medical Centre, Leiden, the Netherlands)
Beyer, 2021 [20]	NR	From −5 to −195	AW Server 3.2, General Electric
Yang, 2022 [21]	Somatom Force, Siemens Heathineers, Forchheim, Germany	From −50 to −200	SyngoVia, VB20, Siemens Healthineers, Forchheim, Germany
Matos, 2022 [22]	Somatom Definition®, Siemens Healthineers®, Erlangen, Germany	From −30 to −250	TeraRecon Aquarius® Workstation (version 4.4.12, TeraRecon®, San Mateo, CA, USA)
Ilyushenkova, 2022 [23]	GE Discovery NM/CT 570c, GE Healthcare, Milwaukee, WI, USA	From −30 to −190	Advantage Workstation 4.6, GE Healthcare
Jian, 2022 [24]	CT (Toshiba and Germany)	From −50 to −200	NR

CT, computed tomography; EAT, epicardial adipose tissue.

61 eligible publications were left. After abstract screening, 29 articles were subjected to further full-text analysis, of which 18 studies were definitively included in our review. The process of selecting relevant studies is shown in Figure 1.

General characteristics of the studies

A total of 4,087 patients who had been subjected to the quantitative assessment of EAT volume based on CT data were included in this analysis. The mean age was 59.0 years. The mean follow-up period was 14.9 months. The baseline patient characteristics are summarized in Table 2. Recurrent AF following PV catheter ablation was the primary endpoint of the studies included in this analysis.

Volume of left atrial epicardial adipose tissue

Six studies provided mean values of LA EAT volume depending on the development of recurrent AF. We performed a meta-analysis of the difference in the mean LA EAT volumes in patients with and without recurrent AF (Figure 2A). As shown in Figure 2A, patients without recurrent AF after catheter ablation had lower LA EAT volumes than patients with recurrent AF. Thus, standardized mean difference in LA EAT values was 5.99 ml (95% CI: −10.04 – −1.94 ml); the differences were statistically significant (p=0.004). It should be noted that the evaluation of the homogeneity of the studies produced a statistically significant result (p=0.0006; I^2 = 77%). We also analyzed HR values based on the Cox univariate regression analysis for EAT volume or thickness values as a predictor of recurrent AF in the long-term follow-up period after PV catheter isolation. The estimated change in EAT volume or thickness and respective HR were presented in 9 studies (Table 3).

Only 2 studies provided data of the univariate analysis of changes in the risks of recurrent AF using continuous estimates of LA EAT volume as a predictor (Table 3). The study data were comparable as the same predictor assessment criterion (changes per 1 ml) was used, which allowed performing a meta-analysis of those papers. In these studies, the number of patients with recurrent AF was 62 (48.4% of 128 patients); the mean follow-up period was 20.0 months. The pooled analysis showed that higher rates of LA EAT were associated with a statistically significant increase in a weighted mean risk of recurrent AF (HR: 1.08 for a 1-mL increase in LA EAT; 95% CI: 1.01–1.16; p=0.03) (Figure 3A).

Volume of total epicardial adipose tissue

Seven studies provided mean volumes of total EAT depending on the development of recurrent AF. We performed a meta-analysis of the difference in the mean total EAT volumes in patients with and without recurrent AF (Figure 2B). As shown in Figure 2B, patients without recurrent AF after catheter ablation had lower total EAT volumes than patients with recurrent AF. Thus, standardized mean difference in LA EAT values was 11.67 ml (95% CI: −19.81 – −3.54 ml); the differences were statistically significant (p=0.005). It should be noted that the evaluation the study homogeneity produced a statistically significant result ($p<0.0001$; $I^2=83\%$), which implies higher general inconsistency for all studies and points to the need for careful interpretation of the pooled evaluation of the difference in mean values.

Four studies provided data of the univariate analysis of changes in the risks of recurrent AF using continuous estimates of total EAT volume as a predictor (Table 3). In these studies, the number of patients with recurrent AF was 356 (35.8% of 995 patients); the mean follow-up period was 14.9 months. A pooled analysis showed no statistically significant association of higher total EAT with the risk of recurrent AF (HR 1.00; 95% CI: 1.00–1.01; p=0.06) (Fig. 3B).

Evaluation of publication bias

Publication bias was evaluated using the Egger test, which showed a statistically significant publication bias for LA EAT data in the groups with and without recurrent AF (t = 2.47; df = 4.00; p (1 tailed) = 0.03). According to the Egger test results, there was no statistically significant publication bias for total EAT volume (t = 0.45; df = 6.00; p (1 tailed) = 0.33).

Discussion

AF is the most common cardiac arrhythmia closely associated with the risk of stroke, heart failure, and poor

Table 2. General characteristics of studies included in the systematic review

Title (first author), year	Patients, n	Follow-up period, months	Age, years	Male, n (%)	BMI, kg/m²	AH, n (%)	DM, n (%)	Paroxysmal AF, n (%)	Recurrent AF, n (%)
Tsao, 2011[9]	68	7.5	54.7 ± 8.5	52 (76 %)	25.6 ± 3.3	10 (15)	7 (10)	43 (63.2)	24 (35.2)
Nagashima, 2011[7]	40	10.2	58.0 ± 10.2	31 (77.5)	23.0 ± 2.6	15 (37.5 %)	NR	24 (57.1)	15 (37.5)
Kim, 2014 [10]	665	19.3 ± 8.5	57.2 ± 11.1	510 (76.7)	24.7 ± 3.0	309 (46.5)	87 (13.1)	450 (67.7)	176 (26.4)
Nakahara, 2014[8]	60	16.0 [12–16]	63.1 ± 10.4	50 (83 %)	NR	NR	NR	0	47 (78.3)
Kocyigit, 2015[11]	249	29 [8–48]	55.6 ± 10.7	120 (48.2)	24.3 ± 1.6	107 (43.0)	34 (13.7)	203 (81.5)	60 (24.1)
Kocyigit, 2015 [12]	53	16 ± 4	61 ± 11	36 (68)	24.2 ± 3.2	26 (49)	10 (19)	22 (42)	24 (45)
Maeda, 2018 [13]	221	17.36	64.0 ± 10.1	163 (74.8)	25.7 ± 3.8	146 (67.0)	58 (26.6)	143 (64.7)	157 (71)
Sanghai, 2018 [14]	274	12	61 ± 10	138 (51)	32 ± 9	195 (71)	56 (20)	189 (69)	109 (39.8)
Kawasaki, 2019 [15]	64	11 ± 4	71 ± 9	32 (50)	23.9 ± 3.5	36 (56.2)	2 (0.03)	64 (100)	14 (21.8)
Tanisawa, 2020 [16]	68	24	65 ± 11	39 (57.3)	24.45	39 (57.3)	8 (11.7)	42 (61.7)	15 (22)
Romanov, 2021 [17]	45	12	55.2 ± 10.2	25 (55.5)	31.3 ± 4.6	32 (71.1)	5 (11.1)	15 (33.3)	9 (20)
Hammache 2021 [18]	389	12	58.1 ± 11.1	256 (65.8)	27.1 ± 4.7	156 (40.1)	28 (7.2)	–	128 (32.9)
El Mahdiui, 2021 [19]	460	18 [6–32]	61 ± 10	302 (66)	29 ± 5	330 (72)	70 (15)	354 (77)	168 (36.5)
Beyer, 2021 [20]	732	7	57.5	536	26.9	338	30	NR	270 (36.8)
Yang, 2022 [21]	251	12	62 [55–67]	148 (59.0)	25.01 ± 3.00	136 (54.2 %)	35 (13.9 %)	173 (68.9)	68 (27.1)
Matos, 2022 [22]	68	22 [12–31]	61 ± 12	46 (67.6)	28 ± 4	41 (60.3)	6 (8.8)	48 (70.6)	31 (45.6)
Ilyushenkova, 2022 [23]	43	12 [5.2–12.2]	42 [35–47]	35 (81.3)	28.3 [24.8–30.8]	NR	NR	20 (46.5)	19 (44.2)
Jian, 2022 [24]	337	12	55	210	25	NR	53	NR	235 (69.7)

AH, arterial hypertension; BMI, body mass index; DM, diabetes mellitus; AF, atrial fibrillation.

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quality of life. Obesity is an independent risk factor for the onset and progression of AF [26]. Given the extreme heterogeneity of BMI determinants and the distribution of adipose tissue appearing to be a key factor in determining the risk of cardiovascular disease, it is not surprising that the role of individual fat tissue depots is of great interest [27].

Modern imaging techniques such as CT and MRI have been increasingly used in recent years for cardiac imaging, including EAT, which can be measured using these imaging techniques. Increasingly more clinical studies demonstrate an association between EAT volume and the development, severity, and recurrence of AF, including after PV catheter ablation [28].

A meta-analysis by Gaeta et al. (2017) showed that patients with AF have significantly higher volumes of EAT compared to healthy subjects. Standardized mean difference in EAT volume between patients with AF and healthy subjects was 32.0 ml (95% CI: 21.5–42.5) [29].

The study by Sepehri Shamloo et al. (2019) was the first meta-analysis that investigated the association between EAT and recurrent AF following catheter ablation. It included 12 studies, among them were works assessing the volume of LA and total EAT according to CT (4 studies, respectively), and 4 studies assessed EAT thickness using echocardiography. The meta-analysis showed that LA EAT volume and total EAT volume were higher in patients with recurrent AF after catheter ablation (LA EAT volume: SMD = 0.862 ml, $I^2 = 0$; 95% CI: 0.57–1.16; total EAT volume: SMD=1.02 ml, $I^2 = 0$; 95% CI: 0.75–

Figure 1. Reviewed study selection flowchart

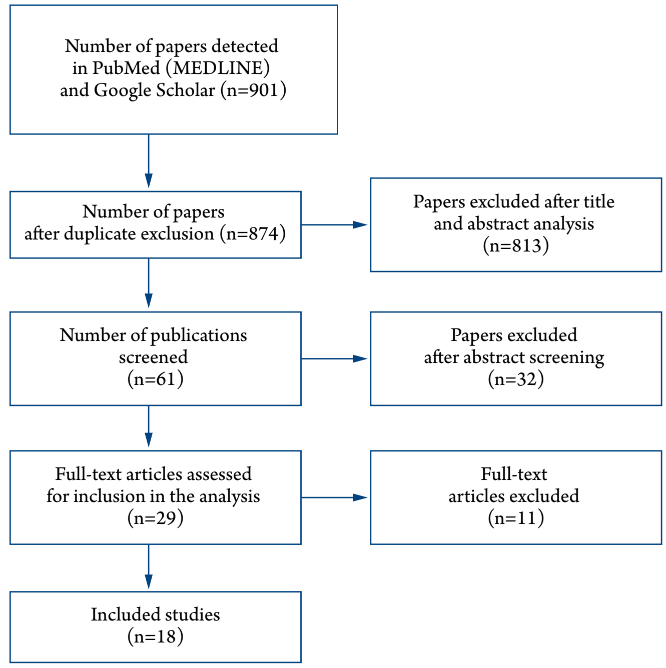
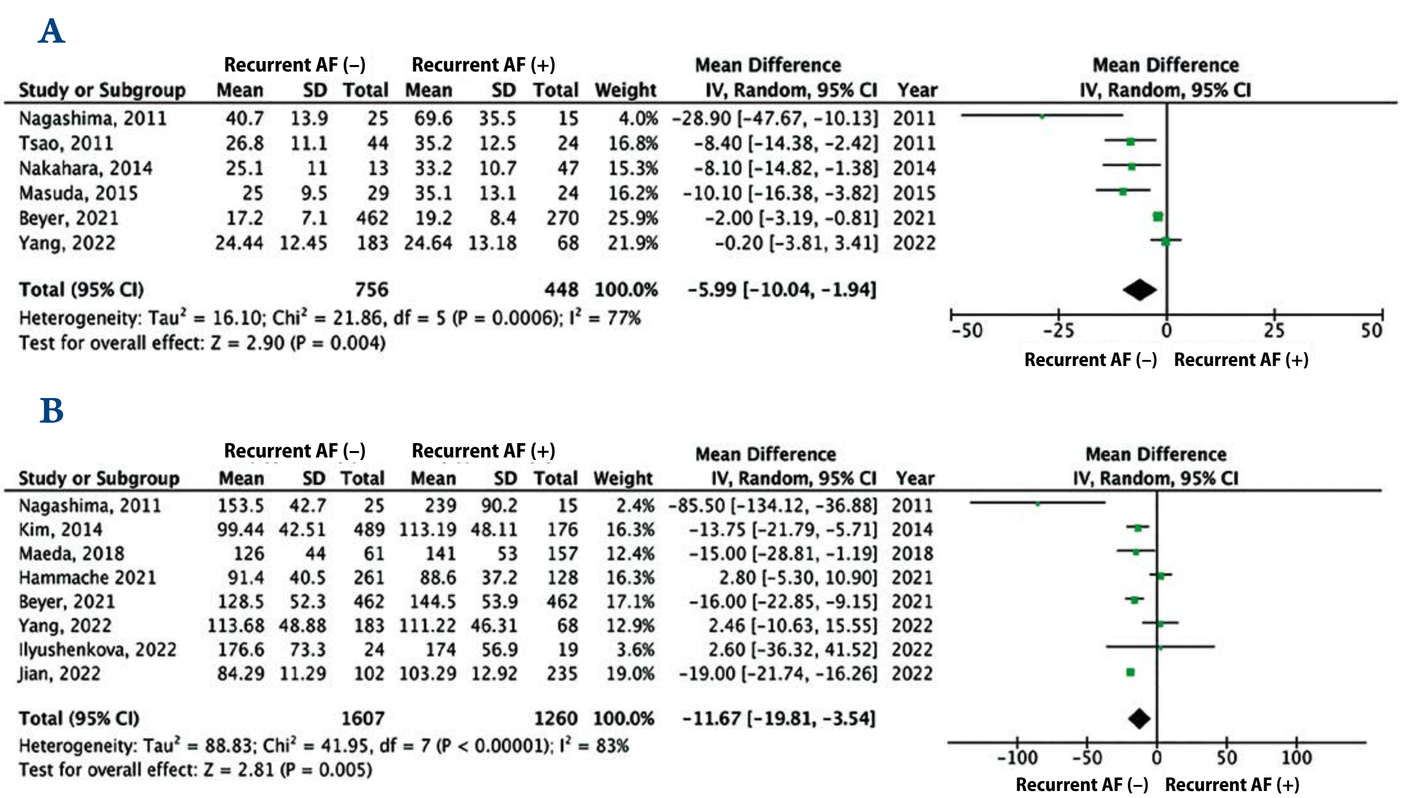
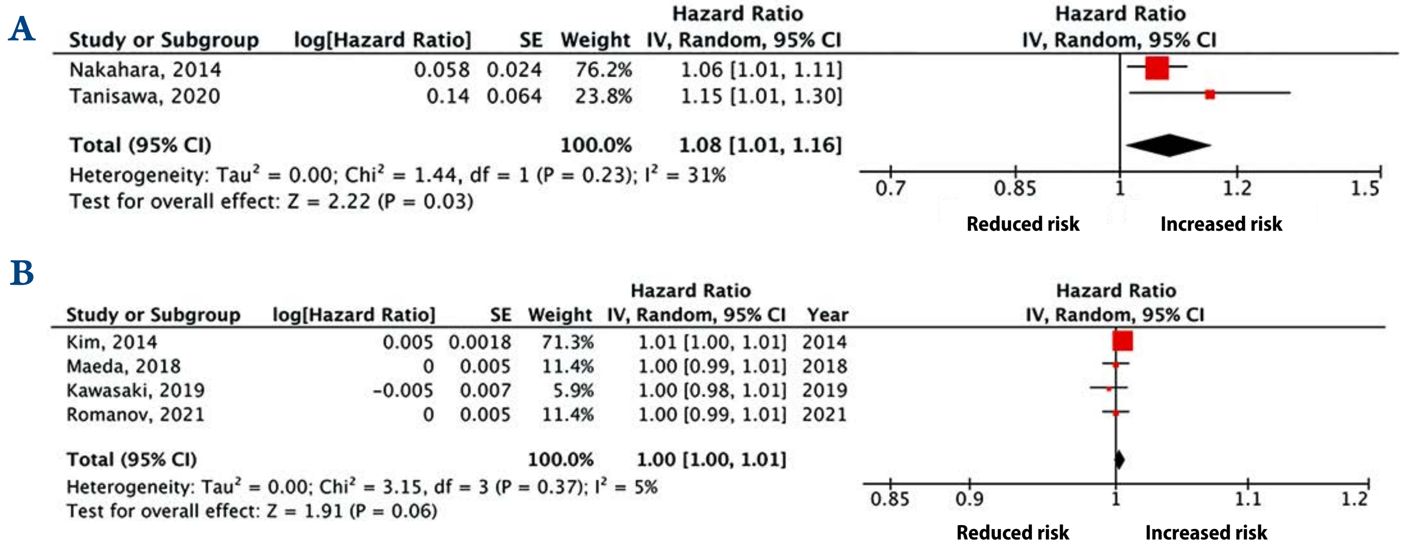


Figure 2. Results of the meta-analysis of the difference between mean LA EAT volume (**A**) and mean total EAT (**B**) in the groups with recurrent AF and without recurrent AF



The green squares show the weighted effect size for each specific study (the sizes of green squares correspond to the study weight), the black segments are 95 % CI, the black diamond corresponds to the weighted difference of the mean LA EAT volumes. CI, confidence interval; LA EAT, left atrial epicardial adipose tissue; AF, atrial fibrillation.

Figure 3. Results of the meta-analysis of HRs of recurrent AF with a 1-ml increase in LA EAT volume (**A**) and total EAT (**B**) per 1 ml



The red squares show the weighted effect size for each specific study (the size of red square corresponds to the study weight), the black segments are 95 % CI, and the black diamond corresponds to the weighted mean HR.
CI, confidence interval; HR, hazard ratio; LA EAT, left atrial epicardial adipose tissue; AF, atrial fibrillation.

1.29). Moreover, patients with recurrent AF had statistically significantly greater thickness of EAT compared to patients without recurrent AF (SMD = 0.81 mm, $I^2 = 91.2$; 95% CI: 0.21–1.40) [30]. However, this meta-analysis included a limited number of studies, and there was no pooled analysis of HR results according to the Cox regression analysis, where EAT measures were included as predictors.

According to the results of our meta-analysis, patients with recurrent AF after catheter ablation had statistically significantly greater volumes of LA EAT, and total EAT. Thus,

Table 3. Estimated change in EAT volume or thickness and respective HR according to univariate Cox regression analysis

Study	Parameter	HR	95% CI	Log HR	SE
Kim, 2014	Total EAT volume, 10 cm³	1.05	1.02–1.09	0.049	0.015
	Total EAT volume, 1 cm³	1.005	1.002–1.009	0.00499	0.00177
Nakahara, 2014	LA EAT volume, mL	1.06	1.01–1.11	0.058	0.024
Kocyigit, 2015	Periatrial EAT, mm	1.099	1.058–1.142	–	–
	Total EAT, mm	1.010	0.999–1.022	–	–
Maeda, 2018	Total EAT volume, 1 ml	1.00	1.00–1.01	0.000	0.005
	Total EAT volume index, mL/m²	1.02	1.00–1.03	–	–
Kawasaki, 2019	Total EAT volume, 1 ml	0.995	0.980–1.009	–0.005	0.007
	Periatrial EAT volume, mL	1.018	0.957–1.064	–	–
	Periatrial-to-total EAT ratio, %	1.131	1.008–1.270	–	–
	Periatrial-to-total EAT ratio ≥ 17.1 %	7.772	2.118–49.951	–	–
Tanisawa, 2020	LA EAT volume, mL	1.15	1.02-–1.31	0.140	0.064
	RA EAT volume, mL	1.14	1.06–1.24	–	–
	LA EAT volume ≥ 6.8 ml	3.3	1.0–10.3	–	–
	RA EAT volume ≥ 6.2 ml	5.4	1.2–24.0	–	–
Romanov, 2021	Total EAT volume, 1 ml	1.00	0.99–1.01	0.000	0.005
	Periatrial EAT volume, mL	1.02	0.99–1.05	–	–
	Periatrial EAT volume/total EAT volume	1.07	0.96–1.19	–	–
	Total EAT volume/BMI	0.95	0.65–1.40	–	–
	Periatrial EAT volume/BMI	1.55	0.47–5.07	–	–
El Mahdiui, 2021	LA (posterior) adipose tissue mass, g	1.00	0.97–1.03	–	–
Matos, 2022	Total EAT volume index LM	2.19	1.65–2.91	–	–

CI, confidence interval; HR, hazard ratio; BMI, body mass index; LA EAT, left atrial epicardial adipose tissue; RA EAT right atrial epicardial adipose tissue; AF, atrial fibrillation; EAT, epicardial adipose tissue; SE, standard error.

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the difference in standardized mean values was 5.99 ml (95% CI: −10.04; −1.94 mL) and −11.67 mL (95% CI: −19.81; −3.54 ml) respectively. We were first to conduct a pooled analysis of EAT measures as predictors of recurrent AF after catheter ablation based on the Cox regression analysis data. According to our findings, a 1-ml increase in LA EAT volume was statistically significantly associated with the risk of recurrent AF after catheter ablation by 8%, and there was only a trend to statistically significant association between total EAT volume and the development of recurrent AF (p=0.06).

Limitations

Firstly, our systematic review and meta-analysis included only few studies concerning HR estimation. Secondly, the analysis included only the HR data obtained for EAT volume according to the univariate Cox regression analysis, and we did not study the multivariate HR (adjusted) because various variables (age, sex, left ventricular ejection fraction (LVEF), etc.) were included in the multivariate analysis as well as the EAT volume in different studies. Moreover, most studies do not provide data on antiarrhythmic therapy administered after catheter isolation of pulmonary veins. Finally, different protocols were used to assess EAT volume using various data post-processing software.

Conclusion

We believe that LA EAT volume assessment based on CT data may be an acceptable strategy for stratifying the risk of recurrent AF following catheter ablation. These data require further verification in larger specific populations during a longer follow-up period. There is a need for common protocols for the EAT volume assessment in order to standardize measurement techniques and ensure their reproducibility.

No conflict of interest is reported.

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