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Left Atrial Diameter as a Risk Factor for Atrial Fibrillation Recurrence After Surgical Ablation: A Systematic Review and Meta-analysis

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Atrial Fibrillation Recurrence; Surgical Ablation; Left Atrial Diameter; Meta-Analysis

1. Abstract

1.1. Background: Surgical Ablation (SA) is widely performed to eliminate Atrial Fibrillation (AF) and maintain atrial contraction. A larger Left Atrial Diameter (LAD) has long been associated with the late recurrence of AF post-ablation.

1.2. Objectives: We conducted a meta-analysis to assess the relationship between LAD and AF recurrence after SA and investigated the effect of LAD cut-off values on the probability of AF recurrence via subgroup analysis.

1.3. Methods: The literature search was performed in the MEDLINE and Cochrane Central Register of Controlled Trials databases, from inception to July 2021. A random-effects model was used to estimate the Odds Ratios (ORs) and 95% Confidence Intervals (CIs). From 401 initial articles, 16 studies, comprising a total of 4,291 patients, were included in this review.

1.4. Results: A meta-analysis of 10 studies (2,599 patients) demonstrated that the predicted probability of AF recurrence was 7% greater with each 1 mm increase in LAD (OR: 1.07; 95% CI: 1.04–1.09; P<0.01). Meanwhile, subgroup analysis revealed that the larger the cut-off value, the higher the risk of AF recurrence. The synthesis effect value (OR: 2.45; 95% CI: 1.77–3.39) was close to the OR when the LAD cut-off value was 55 mm (OR: 2.56; 95% CI: 1.22–5.38).

1.5. Conclusions: In conclusion, a larger LAD is a significant risk factor for predicting AF recurrence after SA. More rigorously designed studies with larger sample sizes are needed to identify the best cut-off value of LAD when performing SA.

2. Introduction

Atrial Fibrillation (AF) is the most common form of arrhythmia in clinical practice, accounting for approximately one-third of all patients hospitalized due to arrhythmia [1] and is an important contributor to cardiovascular morbidity and mortality [2]. Statistically, AF affects an estimated 2.8% of the general population [3] and 10% of patients undergoing cardiac surgery [4].

Surgical Ablation (SA) is performed to eliminate AF and maintain atrial contraction by using surgical lesions to block electrical conduction, which inhibits the generation and propagation of macro-reentry circuits in the atria [5-6]. When performed concomitantly with another indicated cardiac surgery, the technique has been shown to reduce the burden of AF on follow-up [7-8]. The lesions created during this procedure are categorized into three groups: Pulmonary Vein Isolation (PVI), Left Atrial (LA) lesion sets, and biatrial lesion sets [9-10]. Although concomitant ablation of AF during cardiac surgery is beneficial for the maintenance of Sinus Rhythm (SR), the late recurrence of AF remains a problem [11].

Left Atrial Diameter (LAD) has long been considered associated with recurrent AF post-ablation [8]. Several studies have confirmed that the larger the LAD, the higher the rate of AF recurrence [12-13]. Specifically, it has been suggested that patients with AF with an LAD > 55 mm have a significantly increased recurrence rate after catheter ablation conducted according to guidelines and expert consensus [8,14]. Therefore, such patients should be counseled as to the increased risk of operation failure. However, there is inconsistency in the reported threshold LAD value at which AF recurrence after SA occurs [15-18].

Our aim was to conduct a meta-analysis examining the association between LAD and AF recurrence after SA and investigate the effect of LAD cut-off values on the probability of AF recurrence via subgroup analysis.

3. Methods

This study follows the MOOSE guidelines for meta-analysis reporting [19]. Two investigators searched the MEDLINE and the Cochrane Central Register of Controlled Trials databases, from inception to July 2021. We searched for a combination of English terms and Medical Subject Headings (MeSH) descriptors, consisting of five keywords, as follows: ("surgical ablation" or "maze" or "surgical treatment") and "atrial fibrillation" and "left atrial." Each title and abstract were independently analyzed by two investigators who each selected articles relevant to the review. Subsequently, the full texts of the remaining articles were reviewed to select which would be included in the qualitative and quantitative analyses. In case of disagreement, a third investigator joined the discussion and made the decision.

Studies were included if they met the following criteria: (1) evaluated AF recurrence after SA in human participants; (2) measured the association between LAD and AF recurrence; (3) included no less than 50 participants; and (4) had a mean/median follow-up duration of more than 6 months.

Studies were ineligible if they did not report the odds ratio (OR)/hazard ratio (HR) and the 95% confidence interval (CI) of LAD as a risk factor for AF recurrence. Furthermore, studies were excluded if LAD was reported in centimeters. When institutions published duplicate reports of a study, with accumulating number of patients or increased follow-up durations, only the most complete reports were included for quantitative assessment. For the subgroup analysis, only articles that fulfilled all the previous criteria and reported OR/HR and 95% CI of LAD at each threshold were included.

Data extraction was performed using a standard form by two investigators and cross-verified by a third. Extracted data included (1) first author's last name, publication year, and country; (2) study characteristics, specifically number of patients, study design, lesion set, energy, definition of AF recurrence, and method of AF detection; and (3) outcome results, specifically OR/HR and 95% CI of LAD in multivariate analysis, and endpoint rates (including overall death, SR, stroke, and pacemaker insertion) at the final follow-up.

The risk of bias in the studies was evaluated using the National Heart, Lung and Blood Institute Quality Assessment Tool for Case Series Studies [20], which rate studies as "good," "fair," or "poor." The evaluation was done independently by two raters, and in case of disagreement, a third rater joined the discussion and made the decision. The quality assessment of the included studies is reported in (Table 1).

The association between AF recurrence after SA and LAD was measured using OR/HR and 95% CIs. The log of each OR/HR was obtained by calculating the natural logarithm. Standard errors were determined from the logarithmic scale and corresponding 95% CIs. The inverse variance method was used to weigh studies according to the combined overall statistics. Statistical significance was defined as $p < 0.05$. Heterogeneity between studies was assessed using the Cochran's Q test and I^2 statistic and then evaluated using I^2 values. The random-effects model was chosen because of the different lesion sets, which could lead to heterogeneity. Sensitivity analysis was performed by excluding studies and checking the consistency of the overall effect estimate. The results are presented in a forest plot with 95% CIs. Publication bias was verified using a funnel plot. Possible asymmetry was investigated using trim-and-fill analysis [21]. All analyses were performed using Review Manager (version 5.3) and R statistical package (version 3.6.1).

Table 1: Characteristics of the included studies

First Author	Year	Sample, n	Design	Lesion set	Energy	Surgery type	Definition of AF recurrence	Monitoring	Follow-up, months	Primary outcome of the last follow-up	Cut-off value of LAD, mm	Quality
Kamata et al[1]	1997	96	Retrospective, single-center	BA	CS+CY	MV, AV, CABG, CHD, and COMB-	Persistent AF and paroxysmal AF	Ambulatory electrocardiographic monitoring and ECG	Not less than 6	Death:4.2% SR:79.1% Stroke:NR PM:6.5%	65	Good
Baek et al[2]	2006	170	Retrospective, single center	BA	CS+CY	MV +/- (AV or TV or CABG)	Documented episodes of AF or atrial flutter	ECG and 24h-Holter monitoring	26.6 (mean)	Death:2.4% SR:82.9% Stroke:2.4% PM:1.8%	65	Good
Grubitzsch et al[3]	2007	212	Retrospective, single center	LA	MW, RF	MV, AV, CABG, and COMB-	Documented episodes of AF or atrial flutter	ECG and 24h-Holter monitoring	13 (mean)	Death:7.1% SR:70.7% Stroke:2.4% PM:3.3%	NR	Good
Melo et al[4]	2008	972	Retrospective, multicenter	BA, LA, PVI	RF, MW, CY	MV +/- (AV or TV or CABG or other)	Documented episodes of AF or atrial flutter	ECG or 24h-Holter monitoring	29 (mean)	Death:6.6% SR:66% Stroke:3% PM:3%	55	Good

Beukema et al[5]	2008	285	Retrospective, single center	BA	RF	MV, AV, CABG, and COMB-	Atrial flutter/atrial tachycardia or AF	ECG or 24h-Holter monitoring	43.6 (mean)	Death:27.4% SR:56% Stroke:2.1% PM:NR	60	Good
Je et al[6]	2009	560	Retrospective, single-center	BA	CY, MW	MV, AV, TV, CABG, and COMB-	Documented episodes of AF or atrial f lutter	ECG or 24h-Holter monitoring	29.7 (median)	Death:3.8% SR:84.1% Stroke:1.3% PM:2.3%	60	Good
Funatsu et al[7]	2009	268	Retrospective, single center	BA	CY	MV +/- (AV or TV or CABG)	Documented episodes of AF or atrial flutter	ECG or Holter ECG	45.6 (mean)	Dearth:1.9% SR:80.2% Stroke:NR PM:8.3%	70	Good
Kim et al[8]	2010	435	Retrospective, single center	BA	CY, MW	MV +/- (AV or TV or CABG or other)	Atrial flutter/atrial tachycardia or AF	ECG or 24h-Holter monitoring	40.6(median)	Death:4.0% SR:82.7% Stroke:1.4% PM:2.3%	60	Good
Kainuma et al[9]	2013	50	Retrospective, single center	BA	CY	MV +/- (AV or TV or CABG)	Rapid irregular rhythm with disorganized atrial activity	ECG or 24h-Holter monitoring, echo	59 (mean)	Death:6% SR:78% Stroke:2% PM:16%	60	Good
Dong et al[10]	2013	191	Retrospective, single center	BA	RF	MV +/- (AV or TV)	Episode of AF, atrial flutter, or atrial tachycardia that lasted more than 30 seconds	ECG or 24h-Holter monitoring	43.7 (mean)	Death:1.6% SR:79.11% Stroke:0% PM:0%	60	Good
Choi et al[11]	2013	89	Retrospective, single center	BA	CS+CY, RF+CY	MV, AV, CABG, CHD, and COMB-	NR	ECG or 24h-Holter monitoring	51.0 (mean)	Death:NR SR:88.8% Stroke:NR PM:2.2%	NR	Good
Tsai et al[12]	2015	287	Retrospective, single-center	BA	RF+CY	MV, AV, CABG, TV, and COMB-	Episode of AF, atrial flutter, or atrial tachycardia that lasted more than 30 seconds	ECG and 24h-Holter monitoring	38.0 (mean)	Death:NR SR:75.8% Stroke:NR PM:NR	NR	Good
Kainuma et al[13]	2015	160	Retrospective, single center	PVI	RF	AV, CABG, and COMB-	Atrial flutter/atrial tachycardia or AF	ECG and 24h-Holter monitoring	47 (mean)	Death:5.3% SR:85% Stroke:2.4% PM:1.4%	45	Good
Wu et al[14]	2017	207	Retrospective, single center	BA, LA	RF	MV +/- (AV or TV or CHD)	NR	ECG or 24h-Holter monitoring	101 (mean)	Death:8.2% SR:74.4% Stroke:1.4% PM:3.9%	59.85	Good
Pyo et al[15]	2019	146	Retrospective, single center	BA, LA	CY, MW	MV and/or AV, +/- (TV or CABG)	Episode of AF, atrial flutter, or atrial tachycardia that lasted more than 30 seconds	ECG and 24h-Holter monitoring	22.5 (mean)	Death:19.4% SR:59.8% Stroke:2.2% PM:6.5%	57.5	Good
Raissouni et al[16]	2019	163	Retrospective, single center	LA, PVI	RF	MV, AV, CABG, , and COMB-	NR	ECG or 24h-Holter monitoring	Not less than 6	Death:5.3% SR:61% Stroke:2.1% PM:2.7%	40	Good

AF, atrial fibrillation; AV, aortic valve surgery; BA, biatrial; CABG, coronary artery bypass grafting; COMB-, combinations; CS, cut and sew; CY, cryoablation; echo, echocardiography; ECG, Electrocardiograph; LA, left atrial; MV, mitral valve surgery; MW, microwave; NR, not reported; PM, pacemaker; PVI, pulmonary vein isolation; RF, radiofrequency; SR, sinus rhythm; TV, tricuspid valve surgery.

4. Results

Initially, a total of 401 articles were identified across the two databases: 331 in MEDLINE and 70 in the Cochrane Central Register of Controlled Trials. We identified 48 duplicate articles, which were subsequently excluded. We screened the resulting 353 studies and excluded 311 that did not fulfill the eligibility criteria based on the review of the title and abstract and reviewed the full texts of the remaining 42 studies and identified 26 that were not eligible for inclusion. Thus, 16 studies were included in the qualitative analysis and 10 in the meta-analysis. The study selection process is illustrated in (Figure 1).

Table 1 summarizes the general characteristics of the 16 studies. Data on 4,291 patients were reported across the 16 studies [15-16,18,22-34], which were all retrospective single-center cohort studies, except that by Melo et al. [26], which was a multicenter study. The mean follow-up duration ranged from 1 to 10 years. Holter monitoring was performed in all studies to diagnose AF. Fifteen studies included biatrial lesions or LA lesions in their protocol, while one study by Kainuma et al. [31], performed only the PVI procedure because the included patients had undergone concomitant aortic valve replacement and/or coronary artery bypass grafting. The results of these studies were satisfactory, with SR rates ranging from 56% to 88.8% and stroke rates ranging from 0% to 3% at the final follow-up.

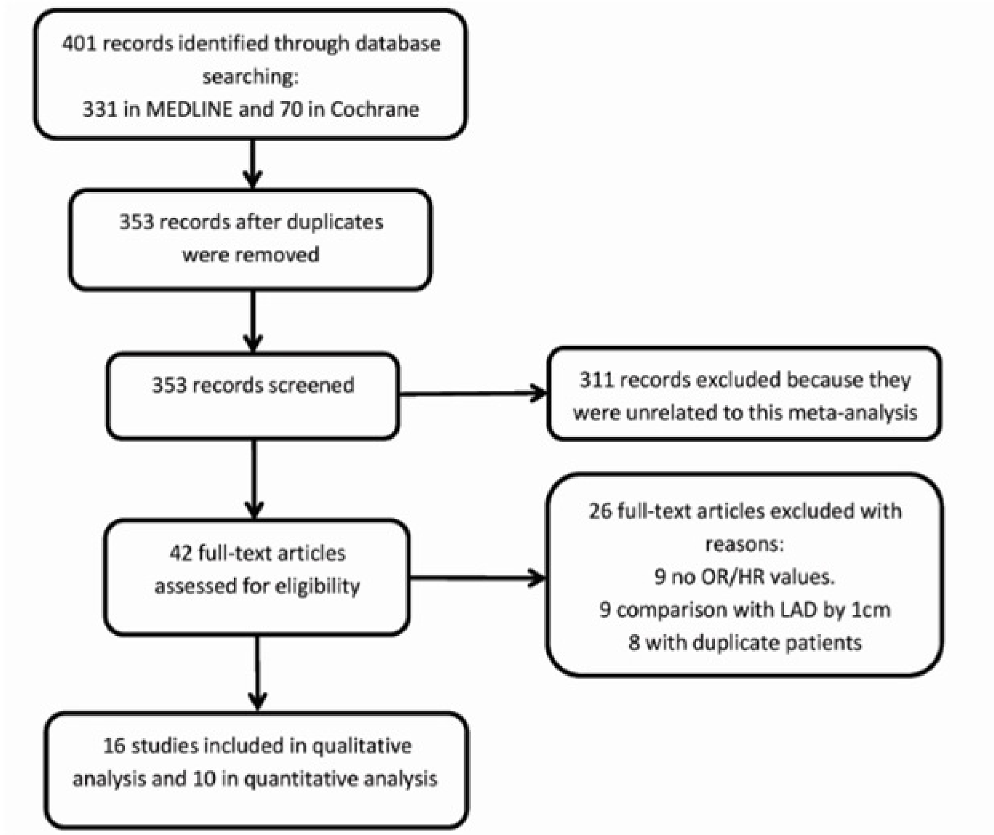

Figure 1: Flow diagram of the study selection. HR: hazard ratio; LAD: left atrial diameter; OR: odds ratio.

Our meta-analysis of 10 studies [24-26,28-34] (2,599 patients) identified larger LAD to be associated with a higher AF recurrence after (OR: 1.07; 95% CI: 1.04–1.09; P<0.01, Figure 2), meaning that the predicted probability of AF recurrence increased by 7% with each 1 mm increase in LAD. The heterogeneity test indicated significant differences between studies (P<0.01, I^2 = 67%). The sensitivity analysis, performed to determine the origin of the heterogeneity, revealed that after removing the Kainuma et al. study [31], which only used the PVI protocol, and the Pyo et al. study [34], which only included patients aged over 60 years who had undergone bioprosthetic valve replacement, no significant heterogeneity across the studies remained (P>0.05, I^2 = 48%). Nevertheless, the overall outcome remained the same (OR: 1.07; 95% CI: 1.05–1.10; P<0.01). Visual inspection of a funnel plot confirmed the presence of publication bias (Figure 3). Using the imputed trim-and-fill method, we found that three studies were estimated to be "missing," with the point estimate adjusted slightly from 1.07 (95% CI: 1.04–1.09) to 1.06 (95% CI: 1.04–1.08).

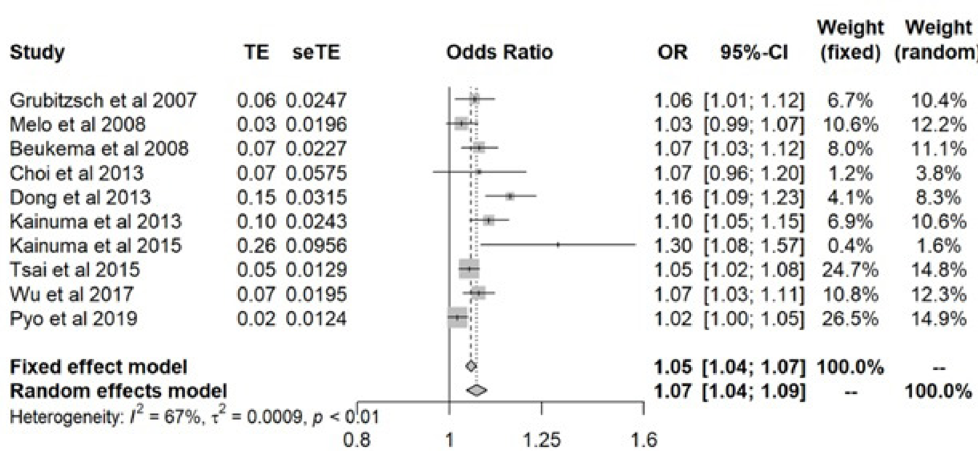

Figure 2: Forest plot showing left atrial diameter as a predictor of atrial fibrillation recurrence after surgical ablation.

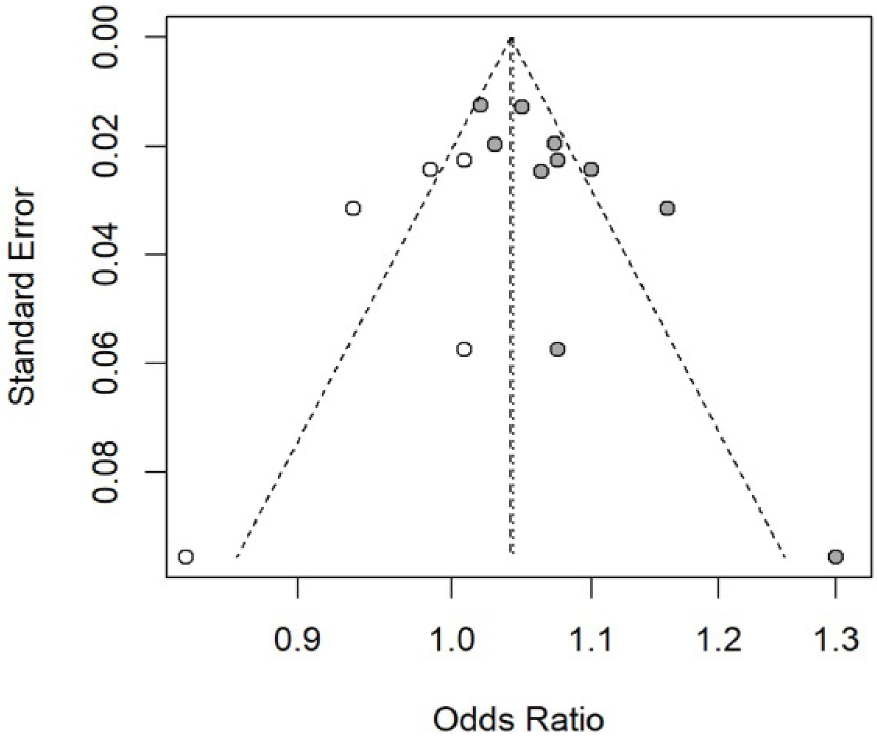

Figure 3: Risk of bias funnel plot.

Across the studies, there was disagreement over the cut-off value of LAD associated with AF recurrence after SA. Because different patients, lesion sets, ablation energies, and especially statistical methods were used, we could not identify the best cut-off value of LAD beyond which the risk of AF recurrence increased significantly. Hence, we conducted a subgroup analysis to assess the association between LAD, measured as a dichotomous variable, and AF recurrence after SA. Eight studies [15-16,18,22-23,26-27,30] were included in the subgroup analysis, which found that the larger the cut-off value, the higher the risk of AF recurrence after SA. In the random-effects model (Figure 4), the synthesis effect value (OR: 2.45; 95% CI: 1.77–3.39) was close to the OR value when the LAD cut-off value was 55 mm (OR: 2.56; 95% CI: 1.22–5.38). The heterogeneity test did not identify any significant difference between the studies (P=0.22, I^2= 26%).

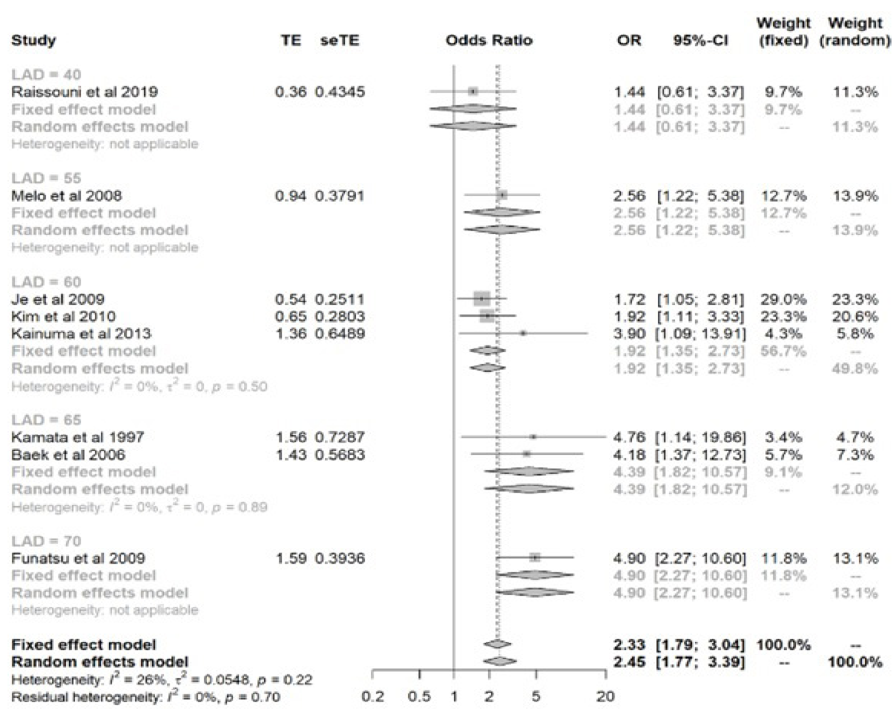

Figure 4: Subgroup analysis shows that the larger the cut-off value, the higher the risk of AF recurrence after SA, and the synthesis effect value is close to the OR value when the LAD cut-off value is 55 mm. AF: atrial fibrillation; LAD: left atrial diameter; OR: odds ratio; SA: surgical ablation.

5. Discussion

Surgical AF ablation is widely performed worldwide to concomitantly treat AF in cardiac surgery, although it does not resolve AF in all patients, some of whom experience late recurrence of AF [35-37]. This meta-analysis first quantitatively demonstrated that, despite some limitations, a larger LAD was a strong risk factor for AF recurrence after SA, with a 7% greater probability of recurrence with each 1 mm increase in LAD. A previous review found that the mean preoperative LAD among patients with AF was consistently over 60 mm and that the relationship between preoperative LAD and failure of the maze procedure appeared continuous; the authors thus concluded that patients should be counseled as to the increased risk of failure as they increase above an LAD of 60 mm [38]. This was similar to the result of our subgroup analysis showing that the risk of AF recurrence increased over a cut-off value greater than 60 mm.

LA enlargement is usually caused by excessive atrial load, which leads to stretching of the atrial wall. Atrial stretch activates the renin-angiotensin-aldosterone system, which generates multiple downstream profibrotic factors, including transforming growth factor-beta 1, and then promotes atrial fibrosis. Extensive cardiomyocyte-fibroblast electric interaction, with the induction of reentry and spontaneous ectopic activity, is an important contributor to the AF substrate [39-41]. Thus, it can be inferred that an enlarged left atrium is closely associated with AF recurrence post-ablation.

Patients with AF with an LAD > 55 mm have significantly higher recurrence rates after catheter ablation [14,42]. However, there is still disagreement over the most appropriate cut-off value of LAD associated with AF recurrence after SA. For example, Feyrer et al. [43] analyzed 103 patients (78 with LAD < 50 mm and 25 with LAD > 50 mm) undergoing SA and found that 67% of those with LAD < 50 mm were successfully converted to SR by 3 months post-ablation, while only 48% of patients with LAD > 50 mm were successfully converted. Meanwhile, Vural et al. [44] found that LAD was associated with AF recurrence and that the sensitivity and specificity associated with an LAD cut-off value of 50.5 mm for the maintenance of SR were 85.7% and 70.7%, respectively. In addition, some studies have described the association between an LAD cut-off value of 60 mm and AF recurrence after SA, and all confirmed that LAD > 60 mm was a reasonable predictor of AF recurrence after SA [25,45-47]. Otherwise, whether LA size reduction improves SA success is controversial. Yalcinkaya et al. [48] used the posterior LA wall plication technique for LA size reduction in patients undergoing mitral valve surgery and achieved satisfactory results in terms of mid-term restoration and preservation of normal SR, while Damiano et al. [49] reported no benefit of atrial reduction plasty in patients with an LAD > 70 mm.

Additionally, other factors such as age, longer preoperative AF duration, and persistent AF are associated with the late recurrence of AF, and the selection of different patients and lesion sets may affect the long-term efficacy of SA [8,50]. Nevertheless, considering that LAD can be measured more accurately and easily, we believe that a more reliable threshold value of LAD is still needed for the evaluation of patients undergoing SA in clinical practice. The results of our subgroup analysis indicated that an LAD cut-off of 55 mm might also be applied for surgical ablation, considering that the risk of SA failure significantly increased at that threshold. Further well-designed cohort studies should be conducted to verify this conclusion. Furthermore, Kim et al. [51] suggested that the addition of the maze procedure in patients with AF undergoing mechanical mitral valve replacement was associated with reduced thromboembolic complications and improved long-term event-free survival. However, whether these patients could benefit from SA when presenting an LAD > 55 mm remains unclear. Especially, two-thirds of the world's population live in developing countries with a high prevalence of rheumatic fever or rheumatic heart disease [52], resulting in a large population with mitral stenosis combined with a larger LAD above 55 mm as a result of poverty and late medical treatment. Since these patients undergoing mechanical valve replacement have significant recurrence after ablation, whether SA is obligatory given the surgical cost remains controversial. Further studies are warranted to identify an effective surgical strategy for patients with AF undergoing mechanical valve replacement with an LAD > 55 mm.

Studies included in this meta-analysis used various definitions of AF recurrence, ranging from paroxysmal or persistent AF to any episode of AF, atrial flutter, or atrial tachycardia lasting more than 30 sec. Ablation strategy and patient selection across the studies also varied. Combined, this caused heterogeneity. In addition, although adjusted OR/HR values from multivariate analyses were used to reduce the effects of confounding variables, their influence could not be excluded completely. Therefore, despite considerable evidence for an increased risk of AF recurrence with LA enlargement, further studies are needed to better understand the relationship between LAD and AF and identify a reliable cut-off value of LAD when performing SA.

6. Conclusions

In conclusion, LAD is a significant risk factor for AF recurrence after SA. The larger the preoperative LAD, the higher the probability of AF recurrence. More rigorously designed studies with larger sample sizes are needed to identify the most reliable cut-off value of LAD when performing SA.

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