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Original Article

Factors associated with sinus rhythm maintenance after surgical ablation in concomitant atrial fibrillation patients: a systematic review and meta-analysis

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Abstracts: Background: The efficacy of surgical ablation in patients with atrial fibrillation (AF) remains controversial. It is currently rather difficult to identify those AF patients who may benefit the most from this surgical strategy. The aim of this study was to perform a systematic review of risk factors for sinus rhythm maintenance after surgical ablation in concomitant AF patients. Methods: Trials of multiple risk factor interventions for the sinus rhythm maintenance of patients with AF after surgical ablation were searched in MEDLINE, PubMed, Cochrane Library, and EMBASE databases, from their inception to Dec 2012. According to the heterogeneity of the studies, two different models, namely, Fixed Effect Model and Random Effect Model were applied to analyze the results. Results: Screened according to inclusion and exclusion standards, eleven trials with a total of 1099 subjects were eventually included in the meta-analysis. Five parameters were associated with recurrence of AF: (1) Duration of AF (Mean Difference: 2.05; 95% confidence interval: 0.29 to 3.80; P=0.0005); (2) Left atrial diameter (Mean Difference: 6.24; 95% confidence interval: 4.85 to 7.62; P<0.0001); (3) Tricuspid valve disease (odds ratio: 2.95; 95% confidence interval: 1.66 to 5.23; P=0.0002); No significant changes were noticed in other parameters. Conclusions: AF patients with long duration of AF, large left atrial diameter, along with tricuspid valve diseases, are more likely to take recurrence of AF after surgical ablation in concomitant AF patients.

Keywords: Atrial fibrillation, surgical ablation, cardiac function, statistics, meta-analysis, postoperative care

Introduction

Atrial fibrillation (AF) is the most common type of tachyarrhythmia encountered in clinical practice. It is estimated over 2.3 million people suffer from AF in the United States alone, and this number is expected to increase to 5.6 million people by 2050 [1]. The FAST investigators have reported that surgical ablation (SA) is more effective than catheter ablation (CA) for the prevention of recurrent arrhythmias in patients with atrial fibrillation (AF) for whom medical therapy has been unsuccessful [1]. Surgery for treatment of AF has evolved from a cut-and-saw technique to ablation using alternative energy sources such as cryotherapy and radiofrequency [3, 4]. As the operative techniques continue to advance, a minimally invasive approach for surgical AF ablation has also been developed [2], which was first described in 2006 as an alternative to the open-heart Cox maze procedure. AF sometimes occurs in people who suffer from coronary artery disease or valvular heart disease and have an indication for cardiac surgery. For these patients it may make sense to consider concomitant surgical ablation of AF during the same operation [3].

Currently, worldwide trials are studying the effectiveness of different interventions, and several small prospective cohort studies have compared the efficiency of surgical ablation with different risk factors, but the conclusions were inconsistent, and there is no consensus as how to select those patients who may benefit the most from this surgical strategy. The objective of the present meta-analysis was to perform a systematic review of risk factors for sinus rhythm maintenance after surgical ablation in concomitant AF patients, which is crucial

Table 1. Assessment quality of included studies

Study	Randomization	allocation concealment	Blinding	Lost follow up	ITT	Grade
Chen [7]	Unclear	Unclear	Unclear	Yes	Yes	B
Funatsu [8]	Adequate	Adequate	Adequate	Yes	Yes	A
Houltz [9]	Adequate	Adequate	Adequate	Yes	Yes	A
Katritsis [10]	Adequate	Unclear	Unclear	Yes	Yes	B
Kim [3]	Unclear	Unclear	Unclear	Yes	Yes	B
Klinkenberg [11]	Unclear	Unclear	Unclear	Yes	Yes	B
Letsas [12]	Adequate	Adequate	Unclear	Yes	Yes	B
Liu [13]	Unclear	Unclear	Unclear	Yes	Yes	B
MacDonald [14]	Adequate	Adequate	Adequate	Yes	Yes	A
Ngaage [15]	Adequate	Unclear	Unclear	Yes	Yes	B
Wang [16]	Unclear	Unclear	Unclear	Yes	Yes	B

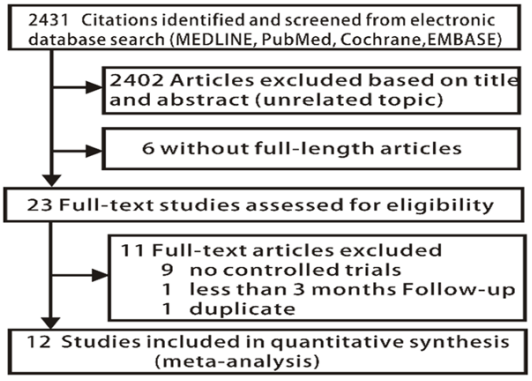

Figure 1. Process of study selection. The excluded 11 articles include nine articles without controlled trials, one article's patients follow-up less than one year and two articles from a single author appeared to include duplication of patients, only the study with the largest patient group was included and the other one was excluded.

for determining the indications for surgical ablation and defining the postoperative management of patients.

Material and methods

Search strategy

Literature search: We reviewed all studies reporting the results of randomized, controlled trials on the efficacy of surgical ablation in patients with atrial fibrillation (AF). Computerized literature searches of MEDLINE, PubMed, Cochrane Library, and EMBASE databases, from their inception to Dec 2012, were undertaken. Search terms used were "surgical ablation", "atrial fibrillation" and "treatment". These terms were used in different combinations with each other. In addition, we reviewed the reference lists of the original articles and reviews on the topic to identify other possible eligible trials.

Study selection: The inclusion criteria for this meta-analysis were as follows: (1) peer-reviewed, full-length articles (English not required); (2) postoperative follow-up more than one year; (3) references provide numeric measures of clinical outcomes on each possible impact factors influencing the success of operations.

Abstracts, surgical ablation trials without follow-up, questionnaires, surveys, case reports and catheter ablation studies were excluded. When multiple publications from a single institution/author appeared to include duplication of patients, only the study with the largest patient group was included.

Data extraction: All literature searches were independently reviewed by 2 authors (C.Y. Duan and M.Y. Liu) to identify relevant trials that met the inclusion criteria and checked by an independent reviewer. We also used Kappa test to evaluate the consistency of our selections. When it was difficult to reach an agreement on an article because of lack of information, we moved it into wait-for-assessment team and connected with one of the authors of that article to get more information, and then decided whether it should be selected into our study or not.

Data on trial size, patient characteristics (age, sex, AF duration, left ventricular size, left ventricular ejection fraction, etc), procedure duration, and patient number of sinus rhythm main-

Table 2. Characteristics of the studies included in the meta-analysis

Study	Year	No.of Patients		Demographics						Cardiac Conditions												Morbidity	Comorbidities	
				Age (Yrs)		Gender		AF type		Duration of Af (Yrs)		LAD (mm)		LVEF (cm^2)		LVEDD (mm)		LVSD (mm)		NYHA class		TVD	Hypertension	Dm
				Mean	SD	Male	Female	Persistent	Paroxysmal	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	n	n	N
Chen [7]	2005	16	Group 1	48.2	8.2	6	10	---	---	8	4.25	61.9	10.2	60.9	10.8	54.4	9.2	36.1	7.9	3.06	0.44	14	3	2
		83	Group 2	51.8	11.7	38	45	---	---	3	3.75	51.7	8.5	62.1	12.3	54.6	9.8	35.5	8.5	2.89	0.58	2	11	11
	Total:	99																						
Funatsu [8]	2009	43	Group 1	---	---	19	24	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
		204	Group 2	---	---	111	93	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	Total:	247																						
Houltz [9]	2010	11	Group 1	---	---	---	---	---	---	---	---	---	---	49	15	50	5	---	---	---	---	---	---	---
		24	Group 2	---	---	---	---	---	---	---	---	---	---	56	9	48	7	---	---	---	---	---	---	---
	Total:	35																						
Katritsis [10]	2005	16	Group 1	45.31	10.26	15	1	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
		16	Group 2	40.5	7.66	13	3	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	Total:	32																						
Kim [3]	2011	20	Group 1	62.2	7.1	6	14	---	---	10.6	6.6	63.9	14.6	---	---	---	---	---	---	---	---	12	---	---
		72	Group 2	54	10.4	27	72	---	---	6.5	6	60.7	10.8	---	---	---	---	---	---	---	---	8	---	---
	Total:	92																						
Klinkenberg [11]	2009	3	Group 1	46	10.54	---	---	1	2	----	----	----	----	---	---	50	1.73	35.67	1.53	---	---	---	---	---
		12	Group 2	46.83	10.22	---	---	3	9	----	----	----	----	---	---	51.58	5.57	34	5.33	---	---	---	---	---
	Total:	15																						
Letsas [12]	2009	28	Group 1	53.3	7.8	24	4	12	16	5.7	3.1	42.9	6.1	54.9	10.2	53.5	4.9	33.6	6.4	---	---	---	9	5
		44	Group 2	55.8	9.4	34	10	14	30	5.3	2.9	39.2	4.9	59.6	7.4	50.3	5.4	31.4	4.9	---	---	---	5	11
	Total:	72																						
Liu [13]	2009	3	Group 1	68	9.9	2	1	2	1	15.5	20.5	46.5	4.9	64.67	6.51	52	6	---	---	---	---	---	1	---
		5	Group 2	55.8	17.5	3	2	1	4	3	6.3	41.7	4.2	57	12.75	49.4	5.59	---	---	---	---	---	2	---
	Total:	8																						
MacDonald [14]	2011	28	Group 1	63.9	8	22	6	---	---	4.83	3.83	---	---	39.2	10.4	---	---	---	---	2.89	0.31	---	18	6
		10	Group 2	60.7	6.7	7	3	---	---	2.87	2.19	---	---	38.2	14.7	---	---	---	---	2.9	0.32	---	6	4
	Total:	38																						
Ngaage [15]	2006	129	Group 1	74	10	87	42	---	---	---	---	---	---	56	16	---	---	---	---	2.57	0.83	16	---	22
		252	Group 2	73	9	166	86	---	---	---	---	---	---	56	16	---	---	---	---	2.72	0.7	113	---	35
	Total:	381																						
Wang [16]	2012	24	Group 1	52.17	12.31	8	24	---	---	2.54	1.96	57.08	3.53	60.58	5.63	49.75	5.17	---	---	2.5	0.52	---	---	---
		56	Group 2	53.96	9.27	22	34	---	---	2.46	1.54	49.82	4.36	59.07	8.99	52.61	6.73	---	---	2.29	0.46	---	---	---
	Total:	80																						

Group 1: Recurrence of AF group; Group 2: No recurrence of AF group; Annotation: LAD: Left atrial diameter; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; NYHA class: New York Heart Association classification; TVD: Tricuspid valve disease; DM: Diabetes Mellitus.

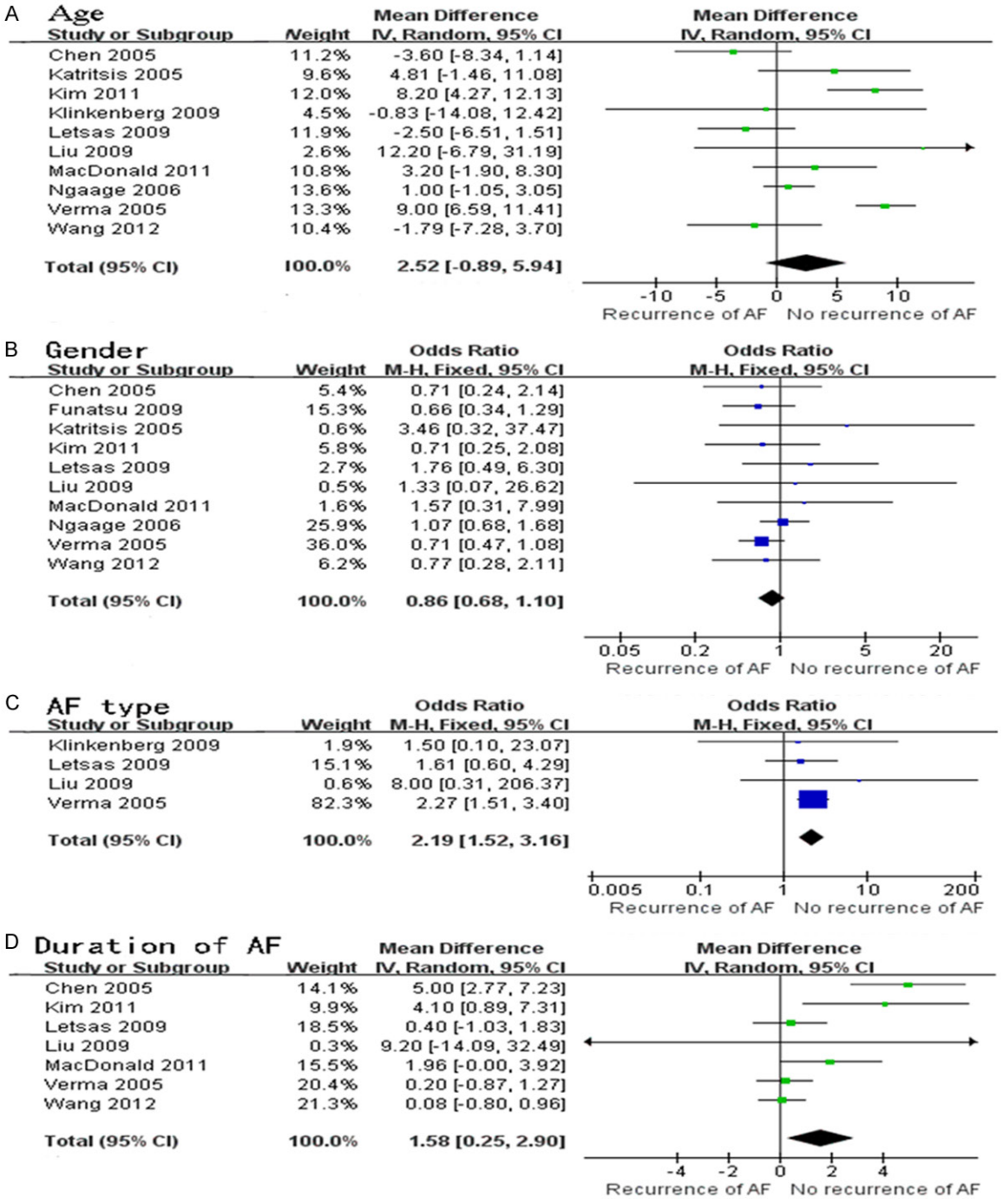

Figure 2. Effects estimates and 95% CIs of AF recurrence odds ratio (OR) associated with demographics. Summary ORs are shown as diamonds, with the middle corresponding to the point estimate and the width representing the 95% CI.

tenance without antiarrhythmic drugs were extracted. Included studies were reviewed based on randomization, allocation concealment, blinding, lost follow-ups and ITT. The truths of the studies were divided into 3 grades according to Cochrane system evaluation handbook: Grade A-cases met all evaluated standards and had correct methodology, which had low risk of bias; Grade B-cases did not describe one or several standards, which had moderate risk of bias; Grade C-cases had one or several standards incorrect, which had high risk of bias. The assessment quality of included studies was listed in **Table 1**.

Table 3. Summary of risk factor associations with demographics

Risk factor	Number of cases	OR/MD [95% CI]	p_Q for Heterogeneity	I^2 for Heterogeneity, %	P for Overall effect
Age	817	1.45 [-1.44, 4.33]	P=0.002	66	0.33
Gender	1049	0.95 [0.71, 1.27]	P=0.80	0	0.72
AF type	95	1.82 [0.76, 4.36]	P=0.64	0	0.18
Duration of AF	389	2.05 [0.29, 3.80]	P=0.0005	77	0.02

Data analysis

Statistical analyses were performed using Review Manager Software (RevMan 5.2; Cochrane Collaboration. Oxford, United Kingdom). Continuous descriptive data of recurrence of AF groups and no recurrence of AF groups are reported as the mean ± standard deviation (*Mean* ± *SD*) and dichotomous data are recorded as the case number (*n*).

The Mantel-Haenszel Q-statistic was used to assess heterogeneity among the studies and the I^2 statistic was computed to examine the proportion of total variation in the study estimate due to heterogeneity. We considered $P>0.10$ or $P\leq0.10$, $I^2\leq50\%$ to indicate no significant heterogeneity between the trials and select fixed effect models to analysis. Besides, we considered $P\leq0.10$, $I^2>50\%$ to indicate significant heterogeneity and use random effect models. The integration results regarded $P\leq0.05$ as the standard of its statistical significance.

Extensive effort was made to remove all duplicated data and to include all studies published to date. Publication bias in outcomes was assessed and treated using standard methodology. Funnel plots were used to visually inspect the relationship between sample size and treatment effects for each of the studied risk factors. Means, standard deviation, and corresponding 95% (CIs) were computed for continuous demographic factors. Event rates corresponding standard errors and confidence intervals were computed for the remaining demographic factors describing proportions of the sample with varying comorbidities.

Results

Search results

A total of 2431 relevant articles were identified in a combined search of MEDLINE, PubMed, Cochrane Library and EMBASE databases, from their inception to Dec 2012, and by a manual approach (search of studies cited in previous reviews and of reference lists from the identified articles); 2403 articles were excluded because they were not relevant to the purpose of this meta-analysis through scanning Title/Abstract. 6 references can't get full-length articles through various ways. Full text assessment of the 22 potentially relevant articles resulted in 11 eligible controlled studies. The reasons for exclusion of the 11 articles were listed in **Figure 1**. Eventually, 11 trials [3, 7-16] with a total of 1099 subjects were included in the meta-analysis.

Study characteristics

Amongst the 19 possible risk factors selected from the 11 trials included in quantitative synthesis, ORs/Mean Differences were summarized for risk factors that were reported in at least three studies, including demographics (age; gender; AF type; duration of AF), Cardiac conditions (LAD; LVEF; LVEDD; LVESD; NYHA class), Cardiac morbidity (Tricuspid valve disease); Comorbidities (Hypertension; Diabetes mellitus).

Characteristics of the studies included in the meta-analysis are listed in **Table 2**.

Other risk factors reported in fewer than three studies only presented the study results, not summarized in meta-analysis. These factors included demographics (BMI), Cardiac conditions (LAA; RAA), Cardiac morbidity (Structural heart disease; CHD; RHD); Comorbidities (Renal dysfunction).

Associations with demographics

Age: Nine studies including 817 cases of sample [3, 7, 10-16] indicated there was no association between age and sinus rhythm maintenance after surgical ablation (Random effect

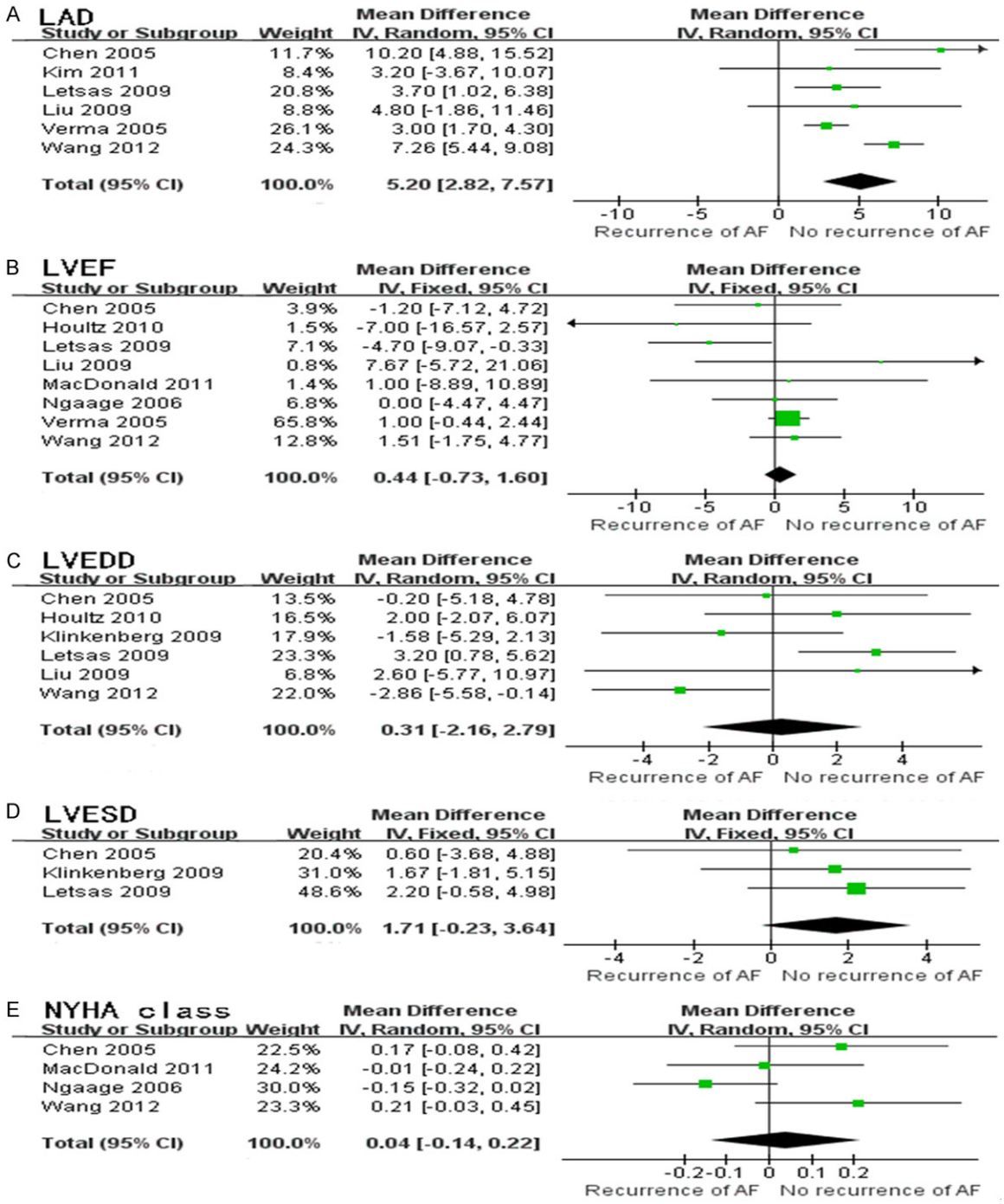

Figure 3. Effects estimates and 95% CIs of AF recurrence odds ratio (OR) associated with cardiac conditions.

model; MD: 1.45, 95% CI: -1.44-4.33) (**Figure 2A**).

Gender: Nine studies including 1049 cases of sample [3, 7, 8, 10, 12-16] indicated there was no association between gender and sinus rhythm maintenance after surgical ablation (Fixed effect model; OR: 0.95, 95% CI: 0.71-1.27) (**Figure 2B**).

AF type: Three studies including 95 cases of sample [11-13] indicated there was no association between AF type and sinus rhythm maintenance after surgical ablation (Fixed effect

Table 4. Summary of risk factor associations with cardiac conditions

Risk factor	Number of cases	OR/MD [95% CI]	p_Q for Heterogeneity	I^2 for Heterogeneity, %	P for Overall effect
LAD	351	6.24 [4.85, 7.62]	P=0.10	48	0.00001
LVEF	713	-0.64 [-2.64, 1.35]	P=0.21	29	0.53
LVEDD	309	0.31 [-2.16, 279]	P=0.03	61	0.80
LVSSD	186	1.71 [-0.23, 3.64]	P=0.83	0	0.08
NYHA class	598	0.04 [-0.14, 0.22]	P=0.05	61	0.66

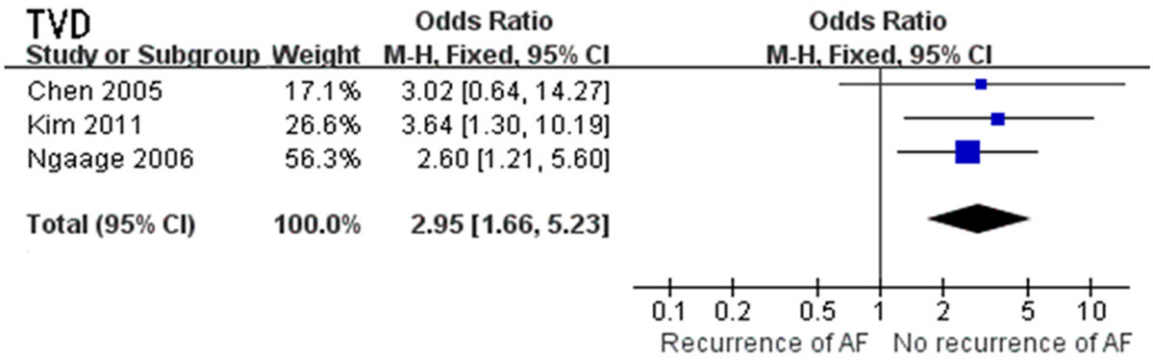

Figure 4. Effects estimates and 95% CIs of AF recurrence odds ratio (OR) associated with cardiac morbidity.

Table 5. Summary of risk factor association with cardiac morbidity

Risk factor	Number of cases	OR/MD [95% CI]	p_Q for Heterogeneity	I^2 for Heterogeneity,%	P for Overall effect
Tricuspid valve disease	572	2.95 [1.66, 5.23]	P=0.88	0	0.0002

model; OR: 1.82, 95% CI: 0.76-4.36) (**Figure 2C**).

Duration of AF: Six studies including 389 cases of sample [3, 7, 12-14] indicated long duration of AF may be a risk factor for sinus rhythm maintenance after surgical ablation (Random effect model; MD: 2.05; 95% CI: 0.29-3.80) (**Figure 2D**).

Summary of risk factor associations with demographics are listed in **Table 3**.

Associations with cardiac conditions

Left atrial diameter (LAD): Five studies including 351 cases of sample [3, 7, 12, 13, 16] indicated large left atrial diameter may be a cause of increased AF prevalence in postoperative patients. (Fixed effect model, OR: 6.24, 95% CI: 4.85-7.62) (**Figure 3A**).

Left ventricular ejection fraction (LVEF): Seven studies including 713 cases of sample [7, 9, 12-16] indicated there was no association between LVEF and sinus rhythm maintenance after surgical ablation (Fixed effect model, OR: -0.64, 95% CI: -2.64-1.35) (**Figure 3B**).

Left ventricular end-diastolic diameter (LVEDD): Six studies including 309 cases of sample [7, 9, 11-13, 16] indicated there was no association between LVEDD and sinus rhythm maintenance after surgical ablation (Random effect model, MD: 0.31, 95% CI: -2.16-2.79) (**Figure 3C**).

Left ventricular end-systolic diameter (LVESD): Three studies including 186 cases of sample [7, 11, 12] indicated there was no association between LVEF and sinus rhythm maintenance after surgical ablation (fixed effect model, MD: 1.71, 95% CI: -0.23-3.64) (**Figure 3D**).

New York Heart Association classification (NYHA class): Four studies including 598 cases of sample [7, 14-16] indicated there was no association between NYHA class and sinus rhythm maintenance after surgical ablation (random effect model, MD: 0.04, 95% CI: -0.14-0.22) (**Figure 3E**).

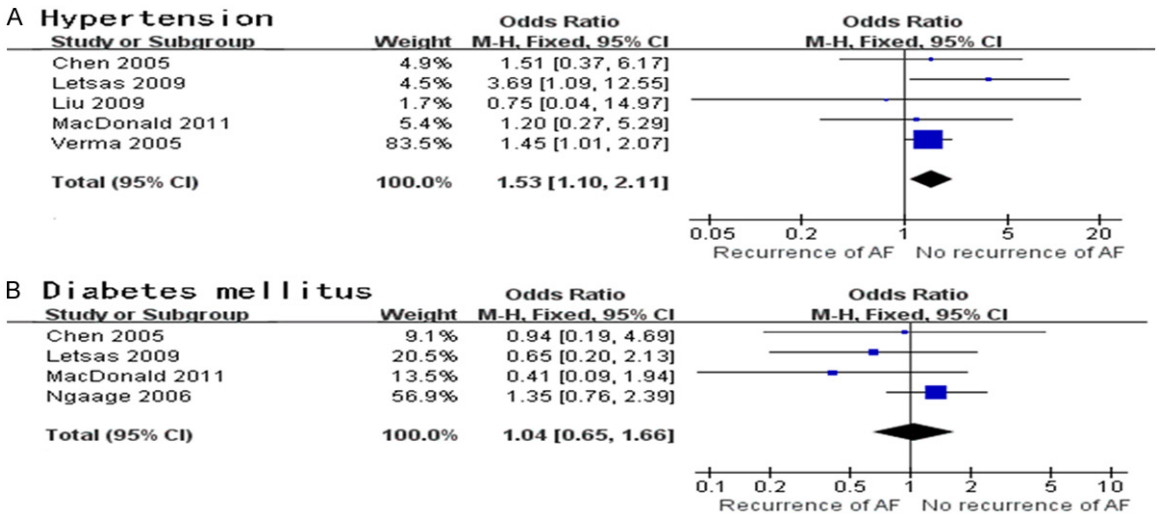

Figure 5. Effects estimates and 95% CIs of AF recurrence odds ratio (OR) associated with comorbidities.

Table 6. Summary of risk factor associations with comorbidities

Risk factor	Number of cases	OR/MD [95% CI]	p_Q for Heterogeneity	I^2 for Heterogeneity,%	P for Overall effect
Hypertension	217	1.93 [0.92, 4.02]	P=0.58	0	0.08
Diabetes mellitus	590	1.04 [0.65, 1.66]	P=0.43	0	0.87

Summary of risk factor associations with cardiac conditions are listed in **Table 4**.

Associations with cardiac morbidity

Tricuspid valve disease (TVD): Three studies including 572 cases of sample [3, 7, 15] indicated persistent patients with tricuspid valve disease are more likely to cause AF recurrence after surgical ablation (Fixed effect model, OR: 2.95, 95% CI: 1.66-5.23) (**Figure 4**). Summary of risk factor associations with cardiac morbidity is listed in **Table 5**.

Associations with comorbidities

Hypertension: Four studies including 217 cases of sample [7, 12-14] indicated there was no association between patients with hypertension and sinus rhythm maintenance after surgical ablation (Fixed effect model, OR: 1.93, 95% CI: 0.92-4.02) (**Figure 5A**).

Diabetes mellitus: Four studies including 590 cases of sample [7, 12, 14, 15] indicated there was no association between patients with diabetes mellitus and sinus rhythm maintenance after surgical ablation (Fixed effect model, OR: 1.04, 95% CI: 0.65 to 1.66) (**Figure 5B**).

Summary of risk factor associations with comorbidities are listed in **Table 6**.

Sensitivity analysis and publication bias

We used fixed/random effect models to test each factors and the results were correlated with the other ones. We did funnel plot for each comparisons (**Figure 6**). The characters of these eight plots were basically inverted funnel-shaped, bilateral symmetry, which indicated that there were no publication bias and the conclusions were reliable.

Discussion

The results of our meta-analysis suggest that major risk factors for sinus rhythm maintenance after surgical ablation in concomitant AF are significantly associated with duration of AF, left atrial diameter and tricuspid valve disease. Until now, only longer duration of AF has been consistently shown to be a risk factor for relapse of AF [4, 17, 18], whereas conflicting results have been reported for other factors. After pooling the results of all available studies, we not only were able to confirm the association between duration of AF and AF recurrence (P=0.02), but also could demonstrate for the

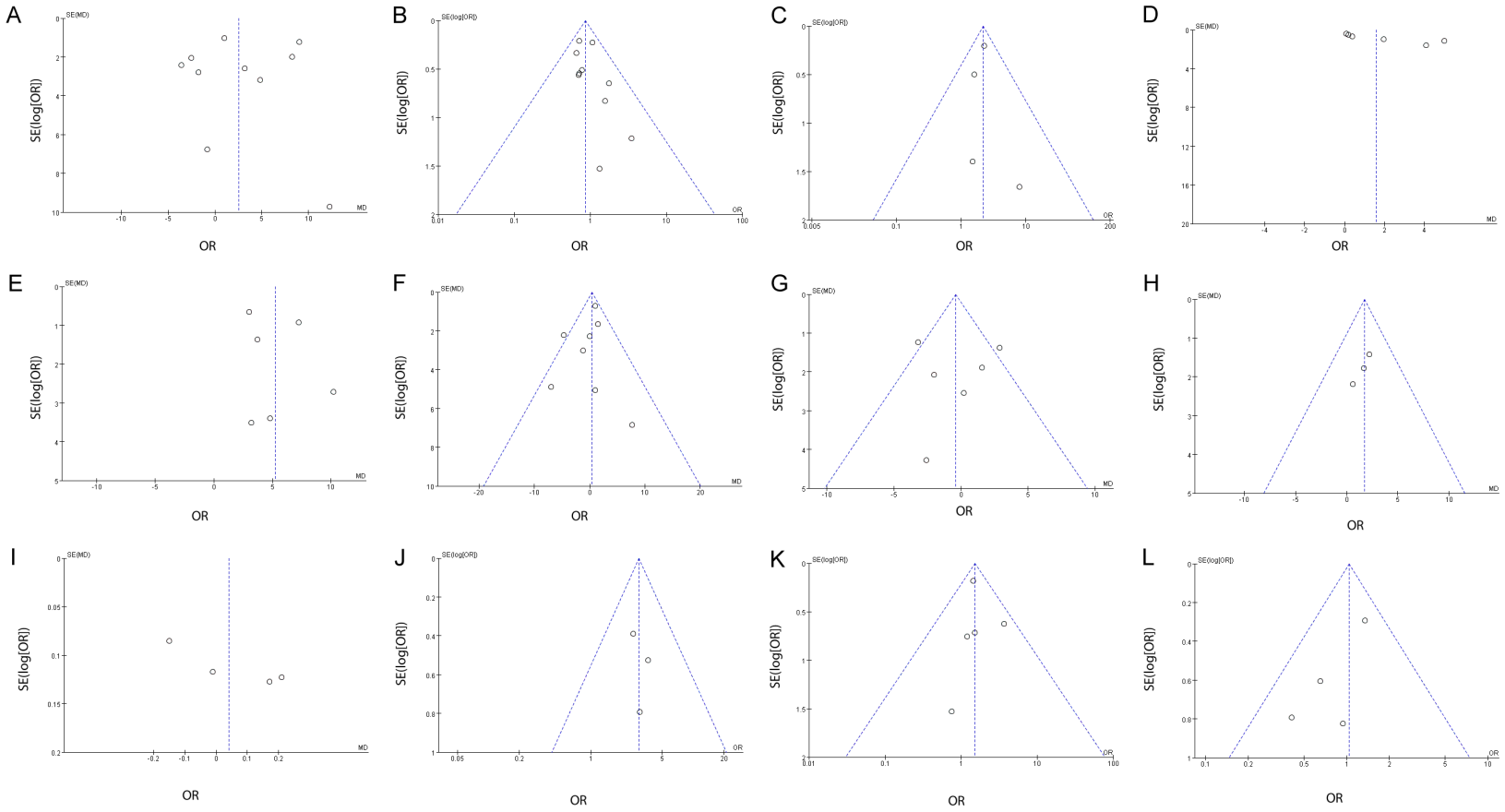

Figure 6. Funnel plot for each comparisons. A. Age; B. Gender; C. AF type; D. Duration of AF; E. Left atrial diameter; F. Left ventricular ejection fraction; G. LVEDD(left ventricular end-diastolic dimension); H. LVESD (Left Ventricular End Systolic Diameter); I. NYHA class; J. Tricuspid valve disease; K. Hypertension; L. Diabetes mellitus.

first time an association between AF recurrence after SA and left atrial diameter as well as tricuspid valve disease.

Longer duration of AF means that the patient was supposed to have longer period of exposure to organic stress causing AF, which leads a change of fibrosis and less elasticity in atrial wall [19].

Left atrial diameter may simply reflect preexisting AF burden, because atrial fibrillation itself causes structural changes within the atrium and results in structural remodeling [6], which can increase the rate and organization of depolarization waves emanating from focal sources [20], promoting formation of intraatrial rotors [21]. Thus, it is very plausible that the large left atrial diameter directly contributes to SA failure.

Preoperative more than moderate tricuspid regurgitation is related to left sided cardiac problem leading to right ventricular dilatation. More than moderate tricuspid regurgitation was due to functional regurgitation. In addition, it is well known that longer duration of AF or pulmonary hypertension can lead considerable regurgitation in tricuspid valve. Dreyfus et al. [22] commented that tricuspid anuloplasty should be considered according to presence of annular dilatation not degree of regurgitation in functional tricuspid regurgitation [7].

The clinical implications of our findings are potentially important. A significant proportion of recurrence of AF is currently classified as apparently unprovoked in the absence of major known risk factor such as longer duration of AF [23, 24]. Recognition of the other risk factors, if proven to be relevant for recurrence of AF after surgical ablation, may substantially lower recurrence rate and support new strategies for prevention of AF recurrence. For example, by identifying patients with large Left atrial diameter, operators can immediately predict a high chance of procedural failure. Based on this finding, it may be possible to alter therapy in this select group to maximize success. Patients with large Left atrial diameter may require routine detailed mapping of the scar with ablation of all potential isthmuses that can cause intraatrial reentry to minimize recurrence [25].

Our study has several limitations. A meta-analysis has inherent weaknesses in terms of combining heterogeneous data sets. Our analysis was by necessity restricted to individual risk factors. Therefore, the distinct possibility exists that the strength of association may be weaker with a multifactorial regression analysis. An additional limitation of our study lies in the fact that those potential factors reported in fewer than three studies could not be evaluated because of lack of sufficient clinical data. These factors included demographics (BMI [12, 15]), Cardiac conditions (LAA [7, 9]; RAA [7, 9]), Cardiac morbidity (Structural heart disease [12, 16]; CHD [7, 14]; RHD [3, 7]); Comorbidities (Renal dysfunction [8, 15]). Future studies should specifically address the studies on these factors. Besides, no multifactorial model was used because it could not be calculated due to the available dataset.

Major risk factors for sinus rhythm maintenance after surgical ablation in concomitant AF are significantly associated with duration of AF, left atrial diameter and tricuspid valve disease. AF patients with large left atrial diameter, long duration of AF, along with tricuspid valve diseases, are more likely to cause recurrence of AF after surgical ablation in concomitant AF patients. Future prospective studies should further investigate the underlying mechanisms of this relationship.

Disclosure of conflict of interest

None.

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