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*Systematic Review*

# Left Atrial Low Voltage Areas Predicts Recurrence of Atrial Fibrillation after Catheter Ablation: A Meta-Analysis

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## Abstract

**Background**: Low voltage areas (LVAs) on left atrial (LA) voltage mapping correlate with atrial fibrosis. However, there is no uniform standard for the definition of LVAs, or mapping techniques and mapping rhythms, so that the predictive value of left atrial LVAs for recurrence of atrial fibrillation (AF) is uncertain. This study aimed to explore the relationship between the presence of pre-ablation left atrial LVAs and the risk of recurrent AF after catheter ablation. **Methods**: The databases of PubMed, Embase, Web of science, Cochrane library, Scopus, Wanfang Datebase, China National Knowledge Infrastructure, China Biology Medicine and China Scientific Journal Datebase were searched from inception to 31 July 2023. Relevant studies regarding left atrial LVAs prior to ablation to predict postoperative recurrence of AF were identified and analyzed. The efficacy endpoints were defined as the recurrence of atrial arrhythmia lasting over 30 s. **Results**: A total of 12 studies with 1070 patients were included. We found the presence of pre-ablation left atrial LVAs correlated with the risk of recurrent AF after ablation (hazard ratio (HR) = 2.87, 95% confidence interval (CI): 2.33–3.52). The presence of pre-ablation left atrial LVAs can predict the risk of recurrent AF after ablation both in the follow-up duration $\leq$12 months group and follow-up duration $>$12 months group (follow-up duration $\leq$12 months: HR = 2.93, 95% CI: 2.20–3.90; follow-up duration $>$12 months: HR = 2.80, 95% CI: 2.09–3.77). The presence of pre-ablation left atrial LVAs correlated with the risk of recurrent AF after ablation in paroxysmal AF (HR = 2.89, 95% CI: 1.97–4.24). **Conclusions**: The presence of pre-ablation left atrial LVAs correlate with the risk of recurrent AF after catheter ablation.

## Keywords

low voltage areas; atrial fibrillation; catheter ablation; recurrence risk; meta-analysis

## Introduction

Atrial fibrillation (AF) is one of the most common tachyarrhythmias and is associated with impaired quality of life, ischemic stroke, heart failure, and increased all-cause mortality [1]. The major techniques to treat AF include cryo-balloon ablation and radiofrequency ablation, which are superior to antiarrhythmic drugs [2–4]. Techniques studied to eliminate AF include ablation of complex fractionated atrial electrograms (CFAEs), empiric linear ablation, and autonomic denervation with targeting of ganglionated plexi. However, no ablation protocol is clearly superior, and still results in a significant incidence of recurrent AF [5,6]. Therefore, the prediction of the risk of recurrent atrial fibrillation is crucial for the selection of appropriate treatment options for the long-term management of AF patients.

Left atrial low voltage areas (LVAs) as a mark of left atrial fibrosis, which contributes to the maintenance of permanent AF [7]. Studies have shown that the presence of left atrial LVAs predicts the risk of recurrence of AF [8,9]. However, reported outcomes of the permanent elimination of AF following AF ablation differ based on the definition of LVAs, the type of AF, mapping techniques, mapping rhythms and duration of follow-up. Therefore, the predictive value of the presence of left atrial LVAs to predict the risk of recurrent AF is uncertain [10–14]. Therefore, this meta-analysis of the correlation between the presence of pre-ablation left atrial LVAs and the risk of recurrent AF after ablation was undertaken to investigate whether the presence of pre-ablation left atrial LVAs can predict the incidence of recurrence after AF catheter ablation.

## Methods

### *Data Sources and Search Strategy*

This meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for systematic Review and Meta-Analysis) guidelines. All studies of the role left atrial low voltage areas to predict recurrence of AF after catheter ablation of atrial fibrillation published before 31 July 2023 were included. PubMed, Embase, Web of science (WOS), Cochrane library, Scopus, Wanfang Datebase, China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM) and the China Scientific Journal Datebase (VIP) were searched by using different combinations of terms, including "low atrial voltage", "left atrial voltage", "low voltage areas", "low voltage zones", "low-voltage zone", "voltage mapping", "atrial fibrillation", "AF", "ablation", "catheter ablation" and "recurrence". We also manually searched reference lists of retrieved articles to identify any relevant studies. All results were imported into EndNote x9.3.3 (Clarivate Analytics, Thomson Scientific, USA) and duplicate results were identified and removed. There was no limitation regard to language and region.

### *Study Selection/Quality Assessment*

The quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) [15]. Two reviewers assessed the eligibility of the identified studies independently and in parallel to minimize subjective selection bias. Divergences were adjudicated by discussion with a third investigator. Inclusion criteria were: (1) the type of study was a cohort study (including retrospective and prospective studies); (2) the study subjects were all patients who underwent the first catheter ablation; (3) left atrial low voltage areas indicated by the endocardial electroanatomical mapping system (unlimited systems) before ablation; (4) end point: recurrence of AF or atrial tachycardia (blanking period of 3 months for recurrence was removed). Exclusion criteria were: (1) data unavailability; (2) except circumferential pulmonary vein isolation (CPVI) (excluding other ablation methods such as linear ablation, LVA targeted ablation and BOX ablation).

### *Date Extraction and Outcomes Definition*

Two authors independently extracted data on the year of publication, sample size, LVA areas and duration of follow-up (WZ and YW). The efficacy endpoints of interest was the recurrence of atrial arrhythmias. Any disagreement among reviewers concerning study selection, data extraction or quality assessment was discussed with a third reviewer and resolved by consensus (YG).

### *Statistical Analysis*

Statistical analysis was performed using ReviewManager5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane collaboration, 2014) and Stata18.0 (Stata, College Station, TX, USA). Publication bias was evaluated by visual inspection of funnel plots. If publication bias was identified, the trim-and-fill method was used for correction by conservatively imputing hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry [16]. All results were reported as number of cases, and statistical significance was considered for a two-tailed $p < 0.05$. The statistical model was selected based on the results of the heterogeneity test, if the heterogeneity test $I^2 \leq 50\%$ then the fixed-effects model is chosen to calculate the combined effect size; if the heterogeneity test $I^2 > 50\%$ then a random effects model is chosen. $I^2$ less than 25% indicated low heterogeneity, 25% to 50% indicated moderate heterogeneity, or greater than 50% indicated high heterogeneity [17]. Sensitivity analysis and subgroup analysis were performed to explore the source of heterogeneity and reduce the heterogeneity. The results of meta-analysis were presented using forest plots.

## Results

### *Search Results*

Our initial search strategy yielded 979 studies. According to the search strategy, twelve studies (two retrospective studies and ten prospective studies, with a total of 1070 patients) met our inclusion criteria (Fig. 1). 393 cases had low voltage areas and 286 cases had recurrent AF during the follow-up period. The basic information of the study is shown in Table 1 (Ref. [11,18–28]) and the characteristics of each study are shown in Table 2 (Ref. [11,18–28]).

### *Literature Quality Assessment*

The quality of the 12 studies was evaluated according to the NOS Cohort Study Rating Scale, including the selection of the study population, comparability between groups and outcome measurement, with total nine points. All 12 studies scored above 6 points, indicating that the quality of the included studies was high (**Supplementary Information 1**). Points were deducted for: failure to control for important confounding factors (1 item) and less than 12 months of follow-up (2 items).

### *Publication Bias*

Publication bias was assessd by Stata 17.0. A visual inspection of funnel plot for included studies is as follows (Fig. 2). Begg's test showed z = 2.47, $p = 0.014$, Egger's test showed $p = 0.001$ (**Supplementary Information 2**).

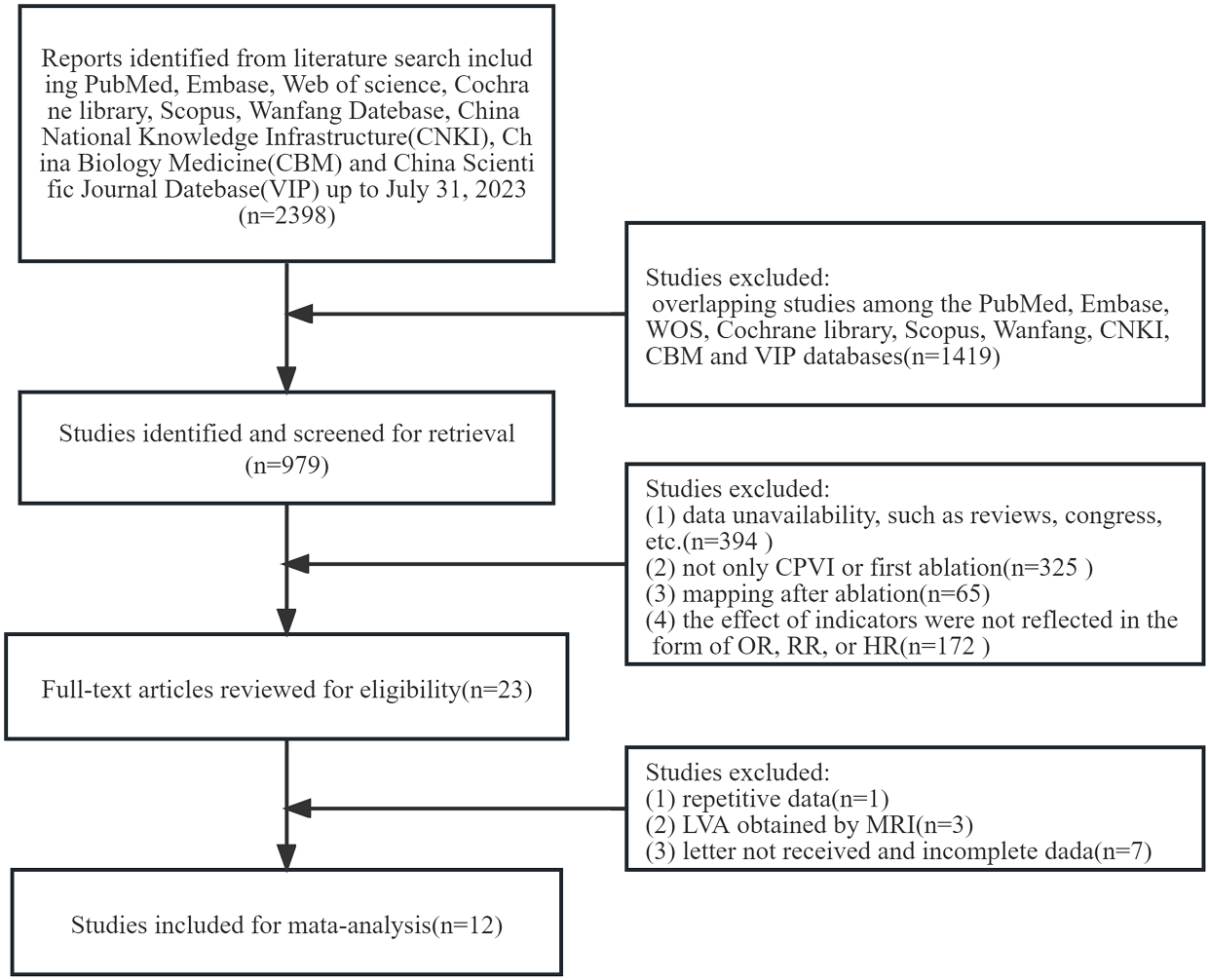


**Fig. 1. Flow diagram of studies screening.** LVAs, low voltage areas; MRI, magnetic resonance imaging; OR, odds ratio; RR, risk ratio; HR, hazard ratio; CPVI, circumferential pulmonary vein isolation.

The sample size included in this study was less than 20 and there are statistical analyses to show that the efficacy of Egger's test is higher than Begg's [29]. So there was publication bias in the included studies based on Egger's test. We used the trim-and-fill method to recalculate the pooled effect size. A total of 5 studies were added to the funnel plots, and the pooled effect size remain stable (risk ratio (RR) = 2.26, 95% confidence interval (CI): 1.89–2.71) (Fig. 3).

### *Meta Analysis of Left Atrial Low Voltage Areas Predicting Recurrence of Atrial Fibrillation*

Twelve studies with a total of 1070 atrial fibrillation patients were enrolled, 393 patients had pre-ablation left atrial low voltage areas and 286 patients had recurrent AF during follow-up. The test for heterogeneity was $I^2 = 36\%$, so fixed-effects model was used to combine the analysis. Forest plot showed that the presence of pre-ablation left atrial low voltage areas significantly increased the risk of recurrent AF following ablation (hazard ratio (HR) = 2.87, 95% CI: 2.33–3.52) (Fig. 4).

### *Sensitivity Analysis*

Sensitivity analyses were performed using a single study-by-study exclusion in Stata version 12.0 (Stata, College Station, TX, USA). The results showed no significant change in the results of the Meta analyses, indicating a more stable and reliable result for the combined effect (Fig. 5).

### *Subgroup Analysis*

Subgroup analysis according to follow-up duration: follow-up duration varied among the studies, which were divided into 2 groups ($\leq$12 months and $>$12 months). In 7 studies the follow-up duration was less than or equal to 12 months, and in 5 studies, it was more than 12 months, showing a significant effect in both groups ($\leq$12 months: HR = 2.93, 95% CI: 2.20–3.90; $>$12 months: HR = 2.80, 95% CI: 2.09–3.77) (Fig. 6).

**Table 1. Basic information.**

| Included in the study (first author/publication year) | Type of study | Region | AF patients (cases) | Paroxysmal AF (%) | Non-paroxysmal AF (%) | Have LVA (cases) | Recurrence (cases) | | Follow-up time (months) | NOS score (scores) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | with LVA | without LVA | | |
| Yamaguchi/2014 [19] | prospective | Japan | 76 | 65 (86%) | 11 (14%) | 24 | 15 | 10 | 24 | 9 |
| Wang/2018 [11] | prospective | China | 150 | 150 (100%) | 0 (0%) | 94 | 17 | 4 | 12 | 9 |
| Vlachos/2017 [20] | prospective | Greece | 80 | 80 (100%) | 0 (0%) | 43 | 18 | 6 | 18 | 9 |
| Moteleb/2018 [18] | prospective | Egypt | 28 | 28 (100%) | 0 (0%) | 6 | 5 | 1 | 6 | 8 |
| Kuo/2022 [21] | prospective | China | 50 | 50 (100%) | 0 (0%) | 12 | 8 | 4 | 11 | 8 |
| Gramlich/2019 [23] | prospective | Germany | 60 | 0 (0%) | 60 (100%) | 23 | 16 | 6 | 12 | 9 |
| Begg/2018 [22] | prospective | UK | 92 | 62 (67%) | 30 (33%) | 23 | 15 | 27 | 12 | 9 |
| Yagishita/2017 [24] | retrospective | USA | 100 | 73 (73%) | 27 (27%) | 43 | 16 | 4 | 28 | 7 |
| Tian/2014 [25] | prospective | China | 168 | 168 (100%) | 0 (0%) | 42 | 14 | 21 | 23 | 9 |
| Yan/2014 [26] | prospective | China | 50 | 32 (64%) | 18 (36%) | 16 | 9 | 5 | 12 | 9 |
| Jia/2022 [27] | retrospective | China | 99 | 49 (49%) | 50 (51%) | 45 | 19 | 9 | 10 | 8 |
| Chang/2007 [28] | prospective | China | 117 | 99 (85%) | 18 (15%) | 22 | 14 | 23 | 15 | 9 |

AF, atrial fibrillation; NOS, the Newcastle-Ottawa Scale.

**Table 2. Characteristics of included studies.**

| Included study (first author/publication year) | Inclusion of people | Definition of left atrial low voltage | Rhythms during mapping | Ablation method (region) | Mappling catheter |
|---|---|---|---|---|---|
| Yamaguchi/2014 [19] | symptomatic drug-refractory AF | <0.5 mV | SR | PV, PV external trigger, tricuspid valvular isthmus | 20 pole circular mapping catheter (HDTM) |
| Wang/2018 [11] | symptomatic drug-refractory PAF, 18–80 years, LA dimension <55 mm. | <0.5 mV | SR | PV, PV external trigger, tricuspid valvular isthmus | Decapolar circular mapping catheter (Lasso) |
| Vlachos/2017 [20] | symptomatic PAF | <0.4 mV | SR | PV, PV external trigger, tricuspid valvular isthmus | 20 pole circular mapping catheter (Lasso) |
| Moteleb/2018 [18] | symptomatic drug-refractory non-valvular AF | <0.5 mV | SR | PV, coronary sinus, cavo-tricuspid isthmus, right free wall accessory pathway, Mahaim pathway | Circular decapolar mapping catheter (Lasso) |
| Kuo/2022 [21] | symptomatic PAF | <0.5 mV | SR | PV, PV external trigger, tricuspid valvular isthmus | Advisor™ HD Grid Mapping Catheter (Abbott) |
| Gramlich/2019 [23] | symptomatic PsAF | <0.5 mV | SR | Cryoballoon ablation (PV) | Spiral catheter (Advisor FL, Inquiry AFocus II or Reflexion circular mapping catheter, Abbott) |
| Begg/2018 [22] | AF | <0.5 mV | SR or AF | RF ablation (PV, other region depended on operator) | Circular mapping catheter (Lasso) |
| Yagishita/2017 [24] | AF, LA voltage >0.5 mV | 0.5–1.5 mV | SR | RF ablation (PV) | Circular mapping catheter (Lasso) |
| Tian/2014 [25] | drug-refractory PAF | <0.5 mV | SR | RF ablation (PV, tricuspid valvular isthmus) | 10 pole mapping catheter (Lasso) |
| Yan/2014 [26] | drug-refractory AF | 0.05–0.5 mV | SR | RF ablation (PV, the roof of the left atrium, mitral annulus) | 10 pole mapping catheter (Lasso) |
| Jia/2022 [27] | AF | <0.5 mV | SR or AF | RF ablation (PV, the roof of the left atrium, coronary sinus) | 20 pole mapping catheter (Pentaray) |
| Chang/2007 [28] | symptomatic drug-refractory AF | ≤0.05 mV | SR | RF ablation (PV, tricuspid valvular isthmus) | 4-mm tipped ablation catheter (USA) |

SR, sinus rhythm; PV, pulmonary veins; LA, left atrial; PAF, Paroxysmal AF; PsAF, persistent AF; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; RF, radiofrequency.

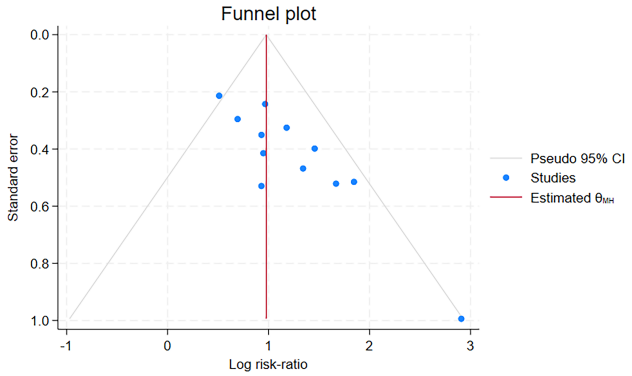


**Fig. 2. Funnel plot of the included studies.**

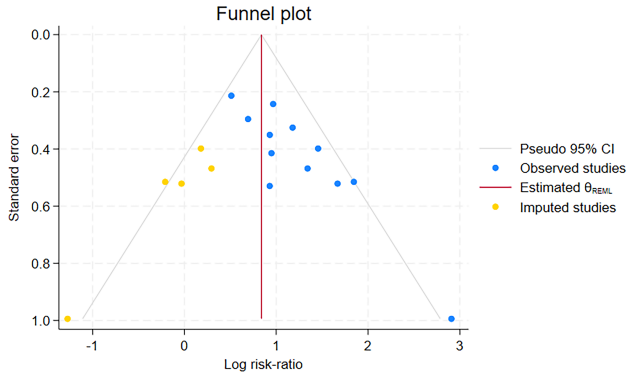


**Fig. 3. Trim-and-fill method for the included studies.**

Subgroup analysis according to atrial fibrillation type: atrial fibrillation type enrolled differed in the studies, 5 studies only included paroxysmal atrial fibrillation patients, 1 study only included non-paroxysmal atrial fibrillation patients, 6 studies included paroxysmal and non-paroxysmal atrial fibrillation patients. Meta analyses of the studies showed that the presence of pre-ablation left atrial LVAs correlated with the risk of recurrent AF after catheter ablation in paroxysmal AF and non-paroxysmal AF (paroxysmal AF: HR = 2.89, 95% CI: 1.97–4.24; non-paroxysmal AF: HR = 4.29, 95% CI: 1.97–9.36) (Fig. 7).

## Discussion

The current study demonstrated that the presence of pre-ablation left atrial LVAs correlate with the risk of recurrent AF after catheter ablation. Subgroup analysis demonstrated that neither the follow-up duration and AF type changes its effect on the recurrence of AF after catheter ablation.

Electrical and structural remodeling of the atrium occurs in patients with AF [30]. Studies have demonstrated that some patients with atrial arrhythmias have spontaneous atrial scarring characterized by discrete regions of low voltage [31]. In terms of clinical observations, McGann *et al.* [32] classify atrial fibrosis into four stages(<10%, 10%–20%, 20%–30%, ≥30%) according to the degree of fibrosis assessed by delayed enhancement magnetic resonance imaging (MRI). A retrospective analysis of 426 patients followed up for 1 year demonstrated that recurrent arrhythmia are strongly correlated with the degree of left atrial (LA) fibrosis, with stages I, II, III and IV having 21%, 29.3%, 33.8% and 71.4% of recurrent arrhythmia cases, respectively [32]. The presence of atrial fibrosis regarded as a predictor of AF recurrence after radiofrequency ablation [33]. In terms of mechanisms, atrial fibrosis reduces local voltage. Historically, atrial fibrous remodeling has been considered to result from AF, in turn perpetuating AF. However, electro-anatomical mapping suggest that fibrosis possibly precedes AF occurrence. In conclusion, however, there is a correlation between LVAs and atrial fibrosis [34]. AF can induce myocardial fibrosis and myocardial fibrosis can promote atrial fibrillation [35,36]. In addition, the atrial LVAs is a reflection of the electrical activity characteristics of atrial muscle cells. The electrical activity characteristics of cardiac muscle cells in patients with AF are altered, including a shortening of the refractory period, prolongation of the P-wave duration [37], and an increase in P-wave dispersion [38], to name a few. Explorations based on both clinical observations and basic mechanistic studies have shown that left atrial LVAs is associated with recurrence risk of AF. Therefore, in terms of theory and mechanism, the discovery of the presence of pre-ablation left atrial LVAs correlate with the risk of recurrent AF after catheter ablation is established.

Twelve high-quality studies with a total of 1070 atrial fibrillation patients were enrolled in this study. All 12 studies NOS scored above 6 points, indicating that the quality of the included studies was high (**Supplementary Information 1**). We conducted a heterogeneity analysis, the test for heterogeneity was $I^2 = 36\%$ indicating moderate heterogeneity. We further performed subgroup analyses related to duration of follow-up and type of atrial fibrillation. The results of the subgroup analyses demonstrated that the presence of pre-ablation left atrial LVAs correlate with the risk of recurrent AF after catheter ablation, and is independent of follow-up time and type of atrial fibrillation. We consider that the sources of heterogeneity may be the definition of low voltage areas (LVZs) and mapping techniques or mapping catheters. Vlachos *et al.* [20] defined ≤0.40 mV as LVAs through electrical anatomical mapping. Wang *et al.* [11] defined ≤0.50 mV as LVAs through electrical anatomical mapping. There is no clear definition of the threshold for LVAs, a large amount of the literature uses a cut-off value of 0.5 mV [18,39,40]. Furthermore, there are differences in the mapping techniques or mapping catheters used in different studyes to measure LVZs. Yamaguchi *et al.* [19] and Vlachos *et al.* [20] used 20 pole circular mapping

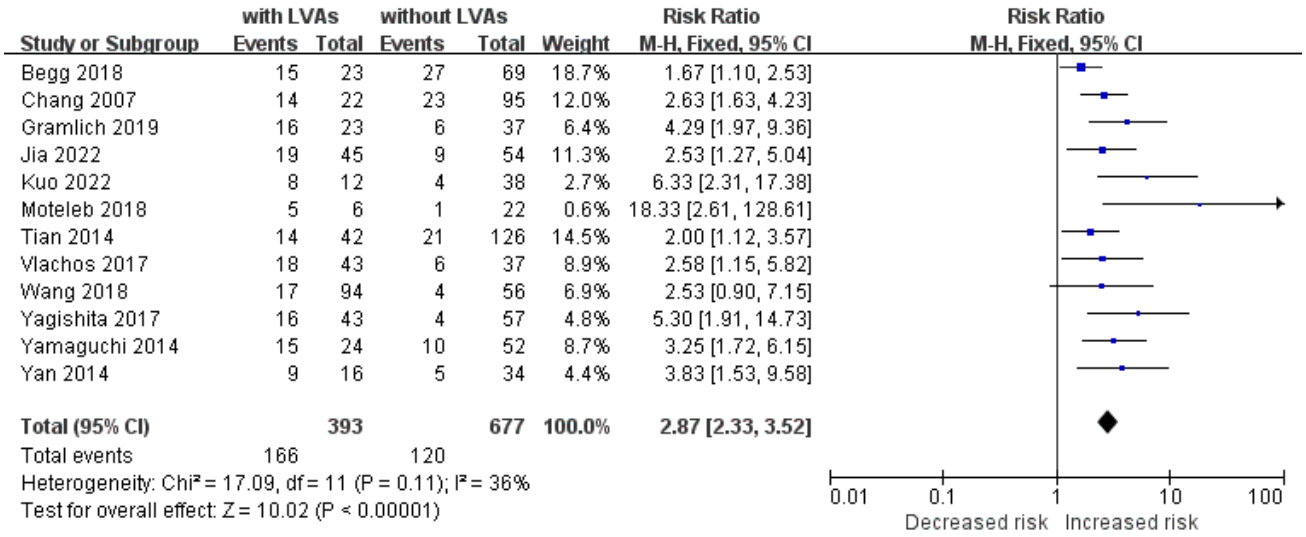


**Fig. 4. Forest plot of the presence of pre-ablation left atrial LVAs predicting the risk of recurrent AF.**

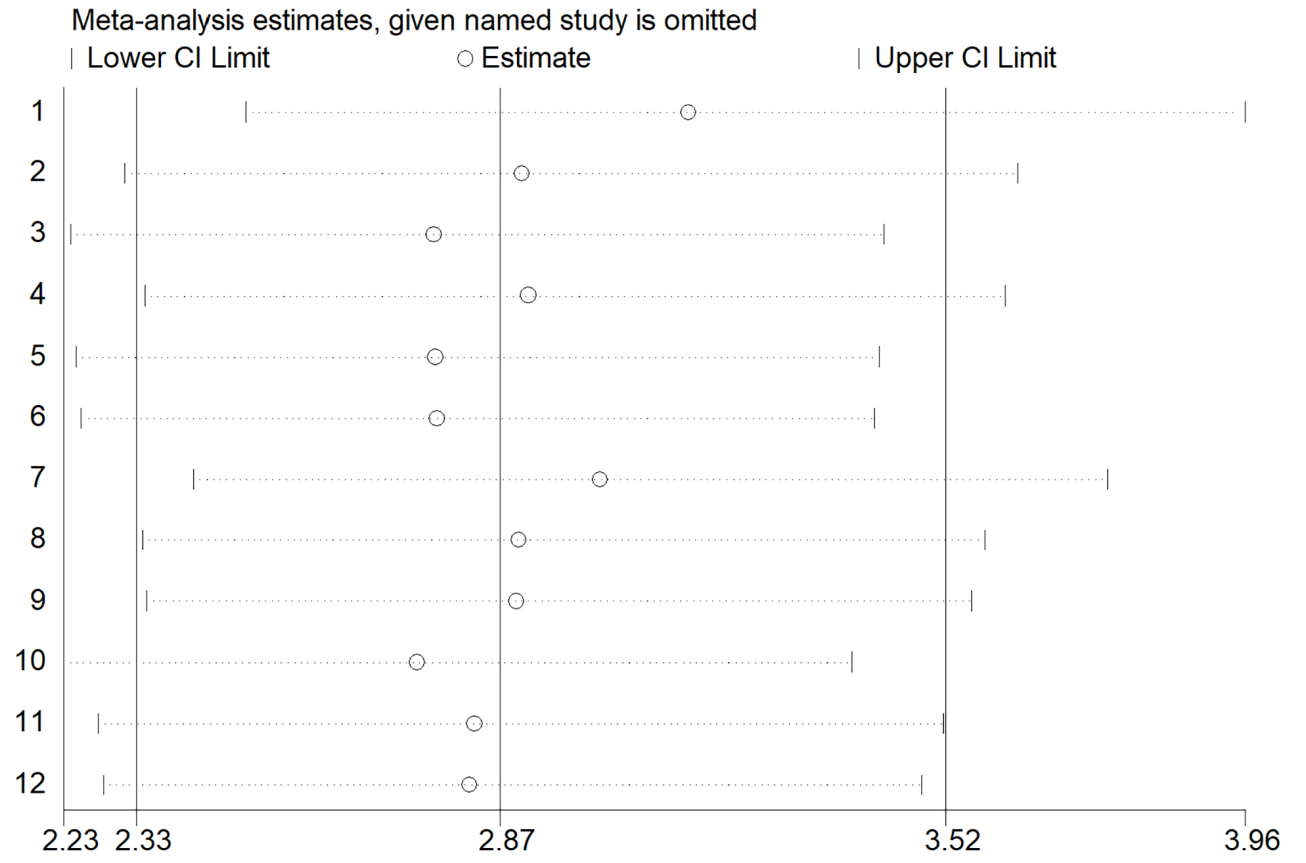


**Fig. 5. Sensitivity analyses of included studies.**

catheter. Kuo *et al*. [21] used a direction-independent grid catheter for mappings. Masuda *et al*. [41] found that the grid catheter took less time in collecting mapping points and had better tissue contact during voltage contact, which leads to higher voltages collected during mapping and therefore a decreased area of LVAs compared to the circular catheter. Of course, there may have been other important methodological differences in these studies which could have influenced the mapping of LVAs. These differences include the spacing distance of the mapping catheter electrode, tissue contact, signal filtering and the number of mapping points. However, with the constant understanding of LVAs and the

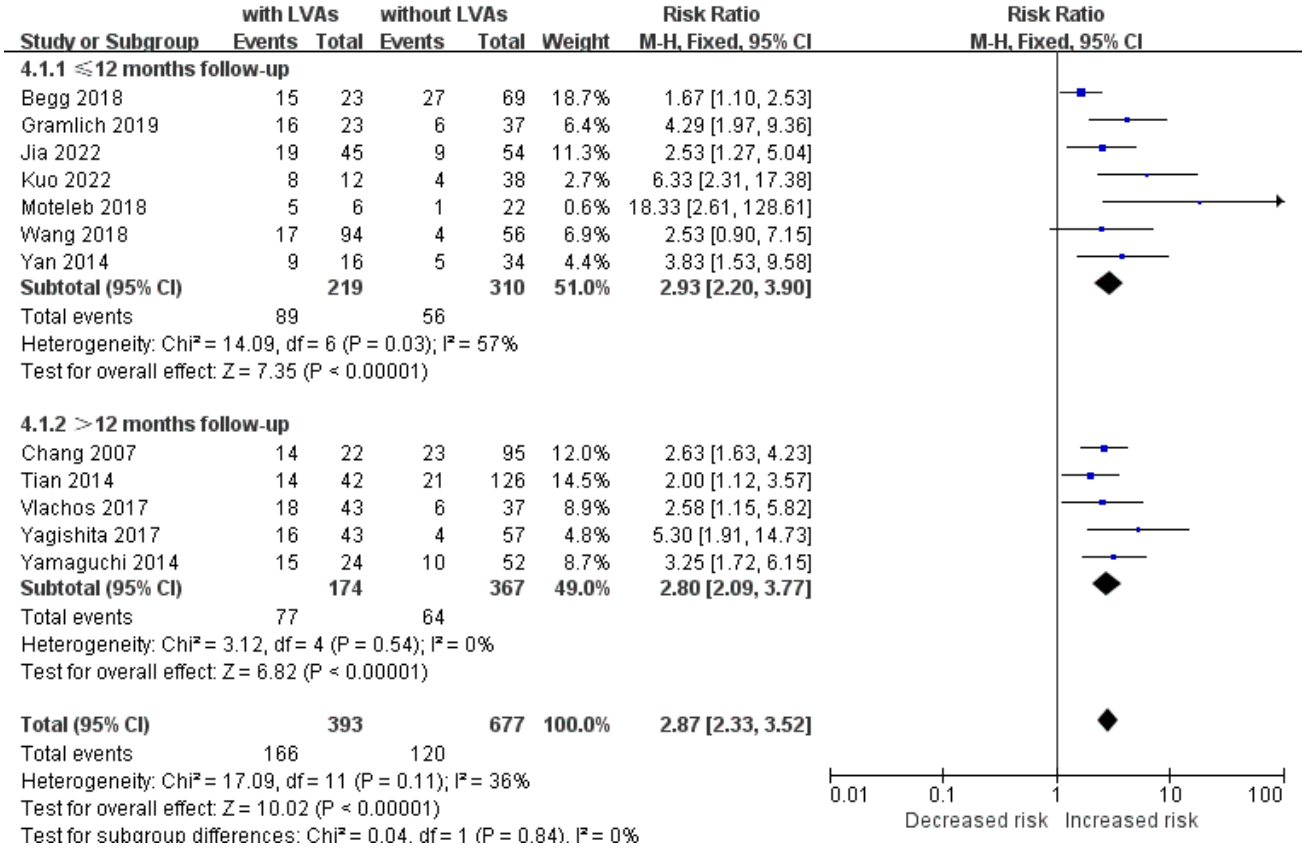


**Fig. 6. Subgroup analysis according to the follow-up duration (≤12 months *vs.* >12 months).**

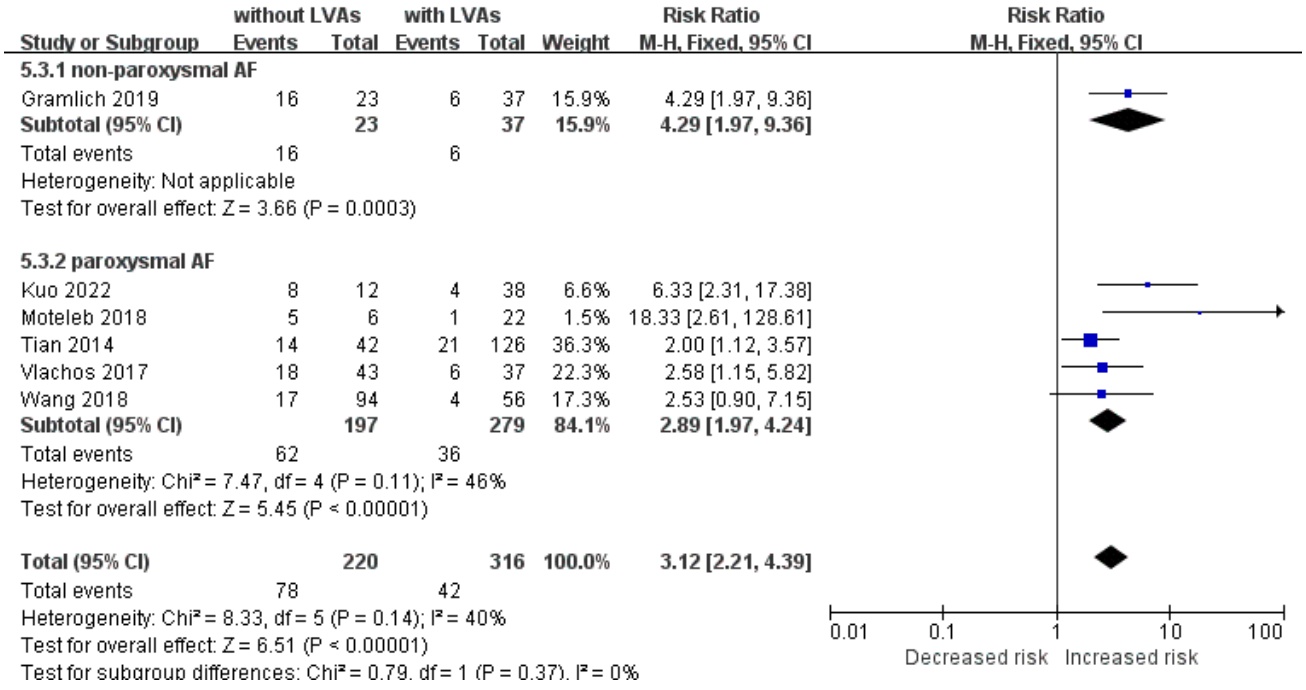


**Fig. 7. Subgroup analysis according to the type of AF (paroxysmal AF *vs.* non-paroxysmal AF).**

advancement of mapping techniques, there is currently no uniform standard for these factors, and it is hoped that a uniform standard can be established in the future, which will in turn validate the results of this study. In addition, individual differences in the study populations which may have produced clinical heterogeneity. Accordingly, as the

population is more widely distributed, we conducted subgroup analyses based on continent, and the results showed consistency (**Supplementary Information 3**). This clinical heterogeneity in a meta-analysis is unavoidable and is unable to be further defined, unless more detailed individual information could be provided by the original researchers. Egger's test showed a $p = 0.001$, suggesting that there was publication bias. We used the trim-and-fill method to recalculate the pooled effect size, and the pooled effect size remain stable. A total of 5 studies were added to the funnel plots, by the trim-and-fill method we found that the RR values were not greatly affected (RR = 2.26, 95% CI: 1.89–2.71). And even though there was publication bias, our results were stable. Publication bias possibly due to the fact that only published literature was searched and studies with positive results were more likely to be published. Another reason may be due to the small sample sizes of the individual included studies. However, this cannot be avoided, and the sample sizes of such studies are currently such that [10,11,21,22]. In addition, the potential for publication bias and heterogeneity that exists in the field interact when they occur simultaneously, which is not uncommon in many published meta-analyses [42]. Besides, sensitivity analysis also suggests that the model is more stable. Therefore, the conclusions reached in our article are stable and reliable.

Although we study the presence of pre-ablation left atrial LVAs correlate with the recurrence risk of AF after catheter ablation, unable to screen patients more suitable for PVA in advance. This finding will provide a basis for guiding clinical use of the drug postoperatively. As atrial electrical and structural remodeling of the atrium occurs in patients with AF. On the one hand changes in atrial electrical activity will guide the application of postoperative antiarrhythmic drugs. Controversy still exists over which class of anti-arrhythmic drugs to use after ablation in patients with AF and for what period of time. Xu *et al*. [43] included six randomised controlled trials (RCTs) studies with a total of 814 patients in a meta-analysis that showed that although the continued administration of anti-arrhythmic drugs (AADs) after catheter ablation for AF can decrease early atrial tachycardia, this treatment does not prevent late atrial tachycardia. Related research is also being further explored. On the other hand changes in atrial structural remodeling will guide the application of postoperative antiremodeling drugs. Sacubitril/valsartan as a representative of cardiac anti-remodeling drugs. Wang *et al*. [44] found that sacubitril/valsartan can decrease AF recurrence after catheter ablation in patients with persistent AF at the 1-year follow-up. Furthermore, there is no consistency in the findings of current studies for LVAs targeted ablation. For example, Liu *et al*. [45] found that linear targeted ablation based on LVAs in patients with non-paroxysmal atrial fibrillation was effective in reducing the rate of distant recurrence, and even reversal of left atrial remodeling by restoring sinus rhythm in these patients. However, Masuda *et al*. [40] who found no benefit of pulmonary veins isolation (PVI) + LVAs targeted ablation in patients with paroxysmal atrial fibrillation for recurrence-free rates at 1 year. Although there are no consistent findings for LVAs targeted ablation, the few positive results provide thought for LVAs targeted ablation. This may also be due to our lack of understanding of the mechanisms of AF, but knowledge of LVAs can guide postoperative medication in patients with AF, especially the use of anti-remodeling drugs. This would be in favour of the long-term management of AF patients and improves the quality of their life.

The results of this study are consistent with the results of a previous meta-analysis [46]. Only one relevant Chinese meta-analysis has been published so far. Tao *et al*. [46] only included articles where the effect indicator was in the form of OR, RR or HR. In contrast, we not only collected primary data, but also have a much wider scope, and our inclusion of patients is more refined. There were several limitations of this study. First, the study only included the presence of pre-ablation left atrial LVAs and all patients underwent only PVI ablation. Patients with postoperative LVA and different ablation methods were not analyzed. However, this avoids the effect of different procedures on the LVAs and the impact of different ablation methods on prognosis. Second, there was moderate heterogeneity and potential publication bias. But the results of subgroup analyses, validation of the trim-and-fill method and sensitivity analysis also suggests that the model is more stable. Third, due to the limitations of the included studies, the relationship between the site and extent of the LVAs and the risk of recurrence after AF ablation was not analyzed. In the future, large-scale, multicenter, randomized, high-quality studies are still needed.

## Conclusions

Our meta-analysis indicated that the presence of pre-ablation left atrial LVAs correlate with the risk of recurrent AF after catheter ablation. The postoperative management of these patients needs to be improved and they should be closely monitored for the presence of recurrent AF. Whether further interventions should be performed for LVAs to limit the incidence of recurrent AF following catheter ablation requires further clinical evaluation.

## Availability of Data and Materials

All data used in this study have been listed in Tables 1&2.

## Author Contributions

WZ and YW completed study searches, data collection, and quality assessment data. WZ, YG and HW performed statistical analyses and drafted the manuscript. SL, YS and QD contributed to study conception, study design, manuscript revision, and fund acquisition. All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

## Ethics Approval and Consent to Participate

Not applicable.


## Acknowledgment

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## Conflict of Interest

The authors declare no conflict of interest.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.59958/hsf.7043.

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