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Are left ventricular ejection fraction and left atrial diameter related to atrial fibrillation recurrence after catheter ablation?

A meta-analysis

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Abstract

Atrial fibrillation (AF), the most common form of arrhythmia, is associated with the prevalence of many common cardiovascular and cerebrovascular diseases. Catheter ablation is considered the first-line therapy for AF; however, AF recurrence is very common after catheter ablation. Studies have been performed to analyze the factors associated with AF recurrence, but none have reached a consistent conclusion on whether left ventricular ejection fraction (LVEF) and left atrial diameter (LA diameter) affect AF recurrence after catheter ablation.

The databases PubMed, Embase, and the Cochrane Library were used to search for relevant studies up to September 2017. RevMan 5.3.5 software provided by the Cochrane Collaboration Network was used to conduct this meta-analysis.

Thirteen studies involving 2825 patients were included in this meta-analysis. Overall, the results revealed that elevated LA diameter values were significantly associated with AF recurrence in patients after catheter ablation (MD = 2.19, 95% CI: 1.63–2.75, $P < .001$), while baseline LVEF levels were not significantly positively associated with AF recurrence in patients after catheter ablation (MD = −0.91, 95% CI: −1.18 to 1.67, $P = .14$).

Overall, elevated LA diameter may be associated with AF recurrence after catheter ablation; however, there was no direct relationship between LVEF values and AF recurrence after catheter ablation when baseline LVEF values are normal or mildly decreased. Besides, because of publication bias, further studies should be performed to explore the mechanisms underlying AF recurrence.

Abbreviations: AF = atrial fibrillation, BNP = N-terminal pro-brain natriuretic peptide, CI = confidence interval, CRP = C-reactive protein, LA = left atrial, LVEF = left ventricular ejection fraction, MD = mean difference, NOS = Newcastle–Ottawa scale, RFP = restrictive filling pattern.

Keywords: atrial fibrillation recurrence, catheter ablation, left atrial diameter, left ventricular ejection fraction, meta-analysis

1. Introduction

Atrial fibrillation (AF), the most common form of arrhythmia, is associated with the prevalence of many common cardiovascular and cerebrovascular diseases, such as heart failure, myocardial infarction, stroke, extracranial systemic thromboembolism and dementia. According to the 2010 Global Burden of Disease Study, approximately 33 million people around the world suffer from AF,[1] leading to a heavy economic burden on society.[2] At present, although there are a variety of options for the treatment of AF, such as antiarrhythmic medication, surgical ablation, and catheter ablation,[3–5] catheter ablation is used as the first-line therapy by doctors and patients,[6,7] and it is increasingly being chosen as a therapeutic strategy for AF.[8] It is well known that AF

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recurrence is very common after catheter ablation and may decrease the probability of long-term success.[9] Studies have reported that several factors are related to AF recurrence after catheter ablation, such as obstructive sleep apnea, hypertension, age, sex, and obesity.[10–13] However, whether left atrial (LA) size and left ventricular ejection fraction (LVEF) affect AF remains controversial. Some studies have reported that LA size and LVEF are risk factors of recurrence of AF after ablation,[14,15] while other studies have failed to reach a consistent conclusion.[16,17] Therefore, we performed this comprehensive meta-analysis to investigate the effect of LVEF and LA diameter on AF recurrence after catheter ablation.

2. Materials and methods

2.1. Ethical statement

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.2. Inclusion and exclusion criteria

The selected studies had to conform to the following inclusion criteria: patients with a clinical diagnosis of AF; availability of baseline LVEF data before catheter ablation for both the AF recurrence and nonrecurrence groups; catheter ablation was performed in patients with AF; the follow-up period was not shorter than 6 months. The exclusion criteria were as follows: patients with AF treated with drugs or treatments other than catheter ablation; no report of baseline LVEF data in patients; articles with only abstracts without full texts; articles included patients with AF who had been treated previously with catheter ablation or other surgical procedures for the treatment of atrial fibrillation.

2.3. Literature search

This meta-analysis was performed according to the guidelines of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.[18] The relevant studies were independently searched by 2 reviewers (JX and PJK) using the databases PubMed, Embase, and the Cochrane Library up to September 2017. Searches combined free terms and medical subject headings (MeSH) related to "left ventricular ejection fraction" or "LVEF"; "left atrium diameter" or "LA diameter"; "recurrence of atrial fibrillation"; and "catheter ablation". In addition, we manually examined relevant new articles from the latest periodicals and conference papers. Articles containing only abstracts, unpublished reports, and non-English articles were excluded.

2.4. Data extraction

Two researchers (JX and PJK) independently selected the studies and extracted information according to the inclusion and exclusion criteria. The extracted data included the first author's name, publication year, sample size, mean age of the patients, ablation strategies, outcome measures, follow-up period, endpoint evaluations (the definition of recurrence of AF), baseline values of LVEF, and LA diameter in the AF recurrence and nonrecurrence groups, and blanking period. Disagreements were resolved by discussion or consultation with a 3rd or 4th reviewer (DPX and HLW). When the results were not clear or were questionable, we consulted the author by e-mail.

2.5. Statistical analysis

The RevMan 5.3.5 software provided by the Cochrane Collaboration Network was used for this meta-analysis. The baseline values of LVEF or LA diameter in the AF recurrence and nonrecurrence groups were presented as continuous variables and used to calculate the mean difference (MD) and 95% confidence interval (CI). The significance of pooled MD was tested by a Z-test ($P<0.05$ was considered significant). Cochran's Q and I^2 statistics were used to evaluate the heterogeneity among the studies. $I^2\leq 50\%$ indicates a lack of statistical heterogeneity or the presence of moderate heterogeneity in a study, and a fixed-effect model was used for the meta-analysis; otherwise, a random-effects model was used.[19] To determine the reasons for heterogeneity, subgroup analyses were carried out. Funnel plots were used to evaluate publication bias.

3. Results

3.1. Search results

According to the search criteria, 734 studies were identified. Among these, 236 identical studies were excluded. The remaining 498 abstracts were screened further, and 457 studies were excluded based on identified titles or abstracts. Of the remaining 41 studies, 16 studies did not access AF recurrence, 8 studies did not report data on LVEF and LA diameter, 2 studies evaluated drug therapy, and 2 studies only had abstracts without full text. Ultimately, 13 studies met the criteria and were included in our analysis (Fig. 1).

3.2. Baseline characteristics and quality assessment

The baseline characteristics of the included studies are illustrated in Table 1. Thirteen studies including 2825 patients met the inclusion criteria; the percentage of females in the included studies ranged from 47.3% to 86%; the mean age among the included studies fluctuated between 49.2±6.6 and 65±10 years; and the follow-up period also varied from 5.9±1.56 to 36 months. For the included nonrandomized studies, the Newcastle–Ottawa scale (NOS) was used to evaluate quality. The included studies were mainly evaluated in 3 respects according to the NOS, namely, selection of case and controls, comparability of cases and controls, and ascertainment of exposure (Table 2).

3.3. Outcomes

All included studies involving 2825 patients reported on LVEF values, and based on the random-effects model, the baseline LVEF values did not exhibit a significant positive association with AF recurrence after catheter ablation in patients (MD = −0.91, 95% CI: −2.25 to 0.43, $P=.18$) (Fig. 2).

Ten included studies reported the baseline values of LA diameter in the AF recurrence and nonrecurrence groups with moderate heterogeneity ($I^2=48\%$, $P=.04$); thus, a fixed-effects model was used for subsequent analysis. Based on the results, increased LA diameter values showed a significant relationship with AF recurrence in patients after catheter ablation (MD = 2.19, 95% CI: 1.63–2.75, $P<.001$) (Fig. 3).

3.4. Sensitivity analyses

The funnel plot graphed in this study did not indicate distinct publication bias (Fig. 4). However, the ablation strategies of the

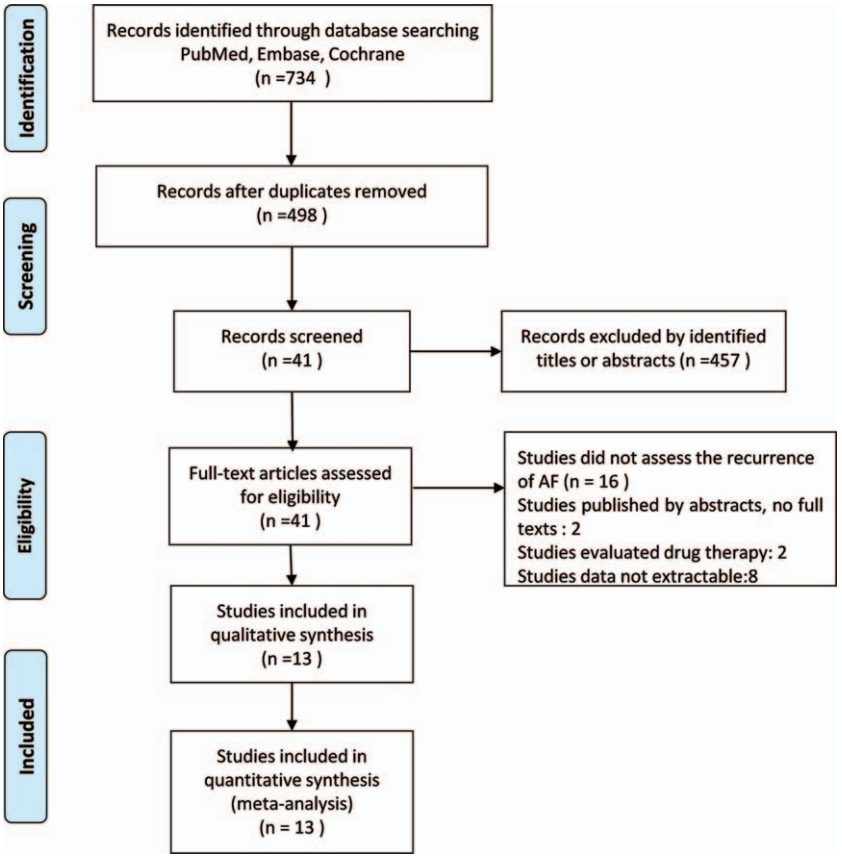

Figure 1. Flow diagram of the process of study selection.

included studies were different, and it was difficult for us to perform further sensitivity analyses. Consequently, we performed a subgroup analysis based on the mean follow-up duration (<12 months, 12 months and >12 months). There was a significant difference in mean LA diameter among patients with or without AF recurrence in the 3 subgroups (<12 months: MD = 3.27, $P < .00001$; 12 months: MD = 1.16, $P = .01$; and >12 months: MD = 2.32, $P < .0001$) (Fig. 5).

Table 1

Basic characteristics of the included studies.

Factors	Male (%)	Study population	Patients	Mean age	Ablation strategy	Follow-up period	Methods of AF detection	Blanking period
Pappone et al[20]	55.6	Italy	470	49.2 ± 6.6	CPVA	12 months	24- or 48-h Holter monitoring	NA
Emanuele et al[21]	65.5	Italy	245	61.4 ± 8.1	CAPV	18.7 ± 7.2 months	24-h Holter monitoring	3 months
Verma et al[22]	76	Canada	700	56 ± 13	PVAI	15.8 ± 7.8 months	12-lead ECG; 48-h Holter monitoring	NA
Liu et al[23]	70.2	China	100	56.7 ± 11.6	CPVA	18 months	12-lead ECG; 24-h Holter monitoring	NA
Cha et al[24]	84	USA	535	54 ± 10	CPVA; wide-area circumferential ablation	12 months	12-lead ECG examination; 24-h Holter monitoring	3 months
Lellouche et al[25]	79.5	France	302	55 ± 11	PV	12 months	24-h monitoring	3 months
Shin et al[26]	86	South Korea	68	51 ± 10	RFCA	6 months	24-h Holter monitoring; 12-lead resting ECG	1–3 weeks
Tzou et al[27]	80	USA	239	54 ± 11	PVI	5.9 ± 1.56 years	12-lead resting ECG; 24-h Holter monitoring	6 weeks
Hu et al[28]	64.7	Taipei	83	53.2 ± 12.4	PV	24 ± 12 months	12-lead ECG and 24-h Holter monitoring	2 weeks
Chang et al[15]	47.3	Taiwan	339	51.5 ± 10	PV	13 ± 5 months	24-h Holter monitoring	2 weeks
Cai et al[29]	66.13	China	186	55.12 ± 12.6	SPVI; CPVA	24 months	ECG; 24-h Holter monitoring	3 months
Pump et al[14]	78	USA	50	65 ± 10	PVAI	12 months	24-h Holter monitoring	3 months
Naruse et al[30]	65.6	Japan	153	60 ± 9	Extensive PVI	18.8 ± 10.3 months	24-h Holter monitoring	3 months

AF = atrial fibrillation, CAPV = circumferential anatomical pulmonary vein, CPVA = circumferential pulmonary vein ablation, ECG = electrocardiograph, PV = pulmonary vein, PVAI = pulmonary vein antrum isolation, PVI = pulmonary vein isolation, RFCA = radiofrequency catheter ablation, SPVI = segmental pulmonary vein isolation.

Table 2

Assessment of the quality of the included studies using the Newcastle–Ottawa scale.

		Selection					Exposure or outcome			
Factors	Study style	1	2	3	4	Comparability	1	2	3	No. of stars
Pappone et al[20]	Case–control study	*	*	*	*	*	*	*		7
Emanuele et al[21]	Prospective study	*	*	*	*	*	*	*		7
Verma et al[22]	Case–control study	*	*	*	*	*	*	*		7
Liu et al[23]	Prospective study	*	*	*	*	*	*	*		7
Cha et al[24]	Case–control study	*	*	*	*	*		*		6
Lellouche et al[25]	Prospective study	*	*	*	*	*	*	*		7
Shin et al[26]	Case–control study	*	*	*	*	*	*	*		7
Tzou et al[27]	Case–control study	*	*	*	*	*	*	*		7
Hu et al[28]	Prospective study	*	*	*	*	*	*	*		
Chang et al[15]	Prospective study	*	*	*	*	*	*	*		7
Cai et al[29]	Prospective study	*	*	*	*	*		*		6
Pump et al[14]	Prospective study	*	*	*	*	*	*	*		7
Naruse et al[30]	Case–control study	*	*	*	*	*	*	*		7

4. Discussion

In this study, we investigated the effect of LVEF and LA diameter on AF recurrence after catheter ablation using a meta-analysis to derive a powerful conclusion. Our meta-analysis illustrated that there was no direct relationship between LVEF values and AF recurrence after catheter ablation when baseline LVEF values of patients is normal or mildly decreased. However, the result revealed that the elevated LAD value is associated with an increased risk of AF recurrence.

A previous study confirmed that early recurrence of AF after catheter ablation was an accepted predictor of poor prognosis and indicative of long-term outcomes of AF.[31,32] A series of studies have reported the risk factors affecting AF recurrence, including the type of AF (paroxysmal), duration of AF, body mass index, surgical characteristics, sex, C-reactive protein (CRP), and N-terminal pro-brain natriuretic peptide (BNP) levels, and structural heart disease.[15,16,29,30]

LVEF has been treated as a routine prognostic parameter for systolic function, and patients with EF>50% have been

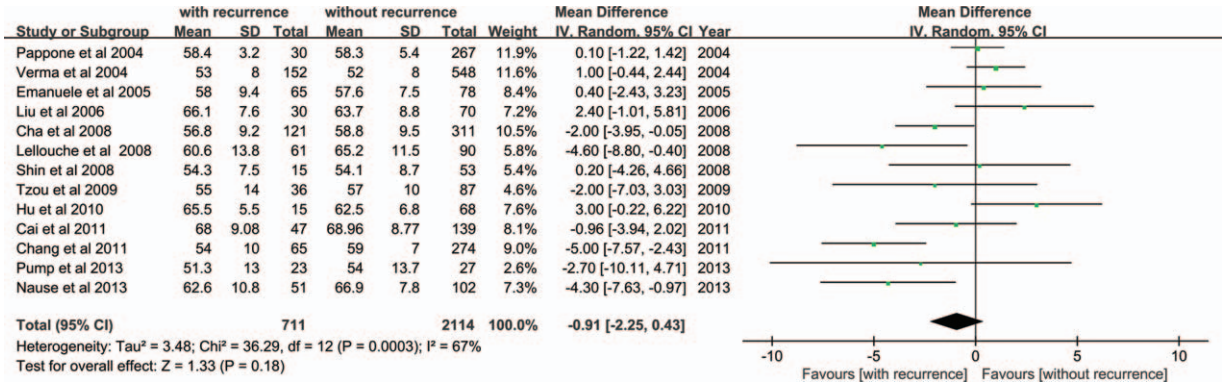

Figure 2. Comparison of LVEF values between groups with and without AF recurrence. AF = atrial fibrillation, LVEF = left ventricular ejection fraction.

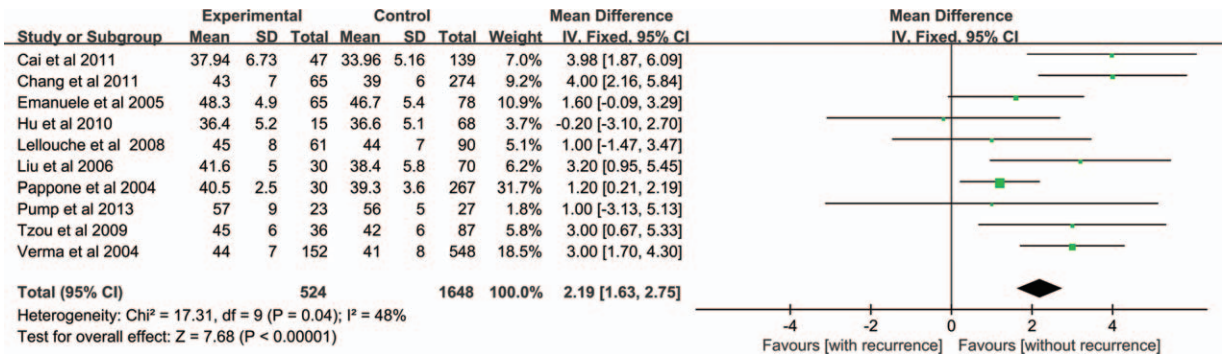

Figure 3. Comparison of LA diameter values between groups with and without AF recurrence. AF = atrial fibrillation, LA = left atrial.

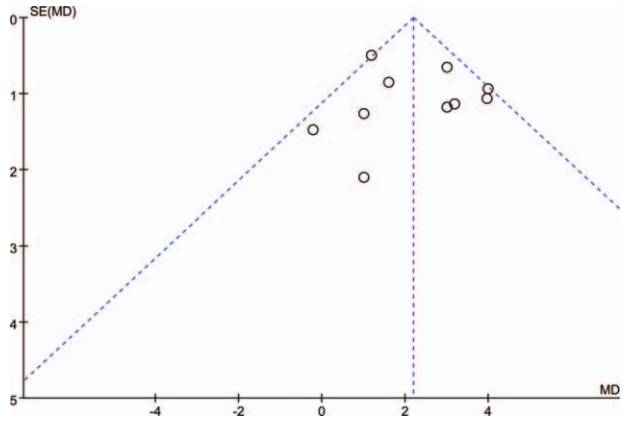

Figure 4. Funnel plot of the included studies.

considered to have normal systolic function.[33] Previous study revealed that patients with impaired LVEF pose a high risk of all-cause and operative mortality of patients, but this effect is less apparent among patients with EF>45%. Patients with LVEF ≤ 35% can be defined as low ejection fraction, which is related to heart failure and a high risk of all-cause and operative mortality of patients .[34] Consequently, LVEF ≤ 35% can be treated as a cut-off value of low ejection fraction. The fact that patients with low ejection fraction are at higher risk for AF and AF recurrence is well known; however, in this meta-analysis, we did not find that LVEF had a significant relationship with AF recurrence, consistent with previous studies.[14,15,17,24–29] All included studies assessed LVEF by multivariable analysis for AF recurrence; however, most included studies did not report the exclusion criteria of the subjects due to low LVEF. Of the included studies, only 3[15,25,30] studies reported statistically significant independent associations between lower EF and a higher rate of AF recurrence. The mean LVEFs ranged from 49% to 68% in the AF recurrence group, and in the nonrecurrence group, the mean LVEFs ranged from 51% to 69%. In short, the data pertaining to LVEF for most participants in the included studies were approximately normal (LVEF≥55%) or mildly decreased (LVEF ranged from 45% to 54%). Hence, we still cannot definitively conclude that LVEF has no relationship with AF recurrence from this meta-analysis. Further studies should be implemented to assess the relationship between low ejection fraction (LVEF ≤ 35%) and the recurrence of AF.

LA diameter is measured at the end-ventricular systole when the LA chamber reaches its greatest dimension. According to the results of a previous study, normal LA diameters range from 27 to 38 mm in females and from 30 to 40 mm in males, and LA diameters larger than 38 mm in females or 40 mm in males can be defined as enlarged LA diameters.[35] Among the included studies, 10 studies reported data pertaining to LA diameter. The mean LA diameter ranged from 38 to 50 mm in the AF recurrence group, and in the nonrecurrence group the mean LA diameter ranged from 36 to 47 mm. Consequently, the LA diameter in the AF recurrence group can be considered elevated.

Based on this meta-analysis, elevated LA diameter values were related to AF recurrence, although the pathophysiological mechanism of the occurrence and maintenance of AF is complicated and remains disputed. Studies have suggested that AF is closely related to atrial remodeling. However, several hypotheses have been proposed regarding this aspect. First, a previous study demonstrated that successful AF ablation is associated with LA reverse remodeling and an improvement in LV filling pressure.[36] Other studies have also revealed that the restrictive filling pattern (RFP) is closely related atrial fibrillation, although the mechanism has not been well explained.[37,38] RFP is characterized by advanced diastolic dysfunction, which can overload LA pressure and initiate LA remodeling; this effect can lead to structural and electrophysiological heterogeneity, which can create a substrate for AF occurrence.[39] In addition, the LA diameter can be caused by increased LA pressure. Hence, it is not difficult to understand that elevated LA measured by LA diameter is a risk factor for the recurrence of AF. Second, many studies showed that AF can lead to structural remodeling of the left atrium and left ventricle.[40] In contrast, Anthony et al[41]

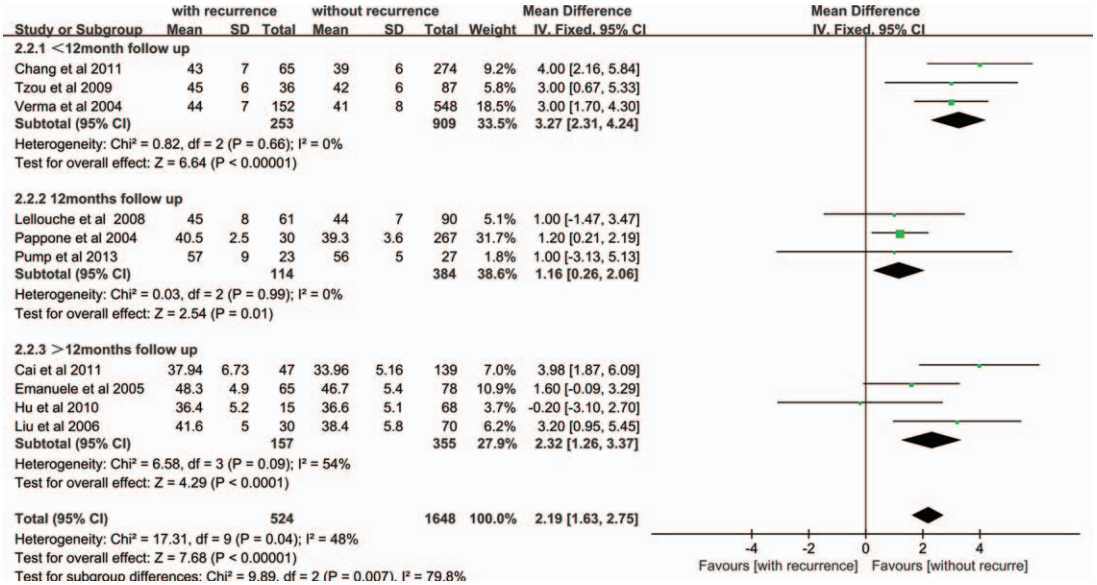

Figure 5. Subgroup analysis of LA diameter values based on different follow-up durations. LA=left atrial.

described that the enlargement and stretching of the left atrium could lead to AF. In addition, some scholars have suggested that LA enlargement can further promote the development and maintenance of AF. A cohort study has reported that as the volume of the left atrium increases by 30%, the incidence of AF increases by 43%.[41] Third, atrial fibrosis plays an important role in the pathophysiology of AF because of structural remodeling of the left atrium and consequent changes in conduction.[42] Other studies have suggested that the enlargement of the left atrium causes unequal stretching or dilation, leading to differences in the effective refractory period (ERP) between thick and thin regions and uncoordinated potential conduction between atrial myocytes, which may be conducive to the development of AF.[43] Furthermore, it is believed that during ablation, a large left atrium consumes more energy than a small left atrium and results in a greater extent of LA scarring. Verma et al[22] demonstrated that LA scarring is an independent predictor of AF recurrence and that it is associated with lower EF and higher levels of both CRP and BNP. Furthermore, evidence shows that obesity is strongly linked to LA size and is involved in electrostructural remodeling and the development of AF.[9]

4.1. Limitations

Our meta-analysis not only provides useful evidence regarding the associations between LVEF and AF recurrence in patients after catheter ablation, but also evaluated the relationship between LA diameter and the recurrence AF recurrence after catheter ablation. However, there are still some limitations to this meta-analysis. First, the definitions of AF recurrence in the included studies were not identical, and the follow-up period and type of AF investigated in the included studies were also different and may have contributed to publication bias. Second, the ablation strategies in the included studies varied, and we could not determine whether these variable ablation strategies had influenced the relationship between LA diameter and AF recurrence. Furthermore, LA size in most of the included studies was measured by LA diameter; however, an increasing number of studies have indicated that the left atrial volume index may be a better index of LA size than LA diameter and may thus lead to a stronger association with the occurrence of AF.[44] However, among the 13 studies included in this meta-analysis, only 1[26] study reported data about the left atrial volume index (LAVI); consequently, we could not further analyze the relationship between the left atrial volume index (LAVI) and atrial fibrillation. Hence, to arrive at more accurate conclusions, further studies should be implemented. The baseline LVEF values of the included studies were approximately normal or mildly decreased. Hence, we still cannot definitively conclude that LVEF has no relationship with AF recurrence from this meta-analysis. Further studies should be implemented to assess the relationship between low ejection fraction (LVEF $\leq$ 35%) and the recurrence of AF.

5. Conclusions

Elevated LA diameter may be associated with AF recurrence after catheter ablation; however, we did not find a relationship between LVEF and AF recurrence because the LVEF values in the included studies were approximately normal or mildly decreased. In addition, because of a series of factors contributing to publication bias, further studies should be performed to elucidate mechanisms underlying AF recurrence.

Author contributions

Conceived of and designed the experiments: XJ and DPX. Performed the experiments: XJ, JKP, and DPX. Analyzed the data: JKP and XJ. Contributed reagents/materials/analysis tools: JX, JKP and HLW. Wrote the paper: XJ and JKP. Revised the paper: HLW.
Formal analysis: Xiao Jin, Jianke Pan.
Methodology: Jianke Pan.
Software: Danping Xu.
Validation: Huanlin Wu.
Writing – original draft: xiao Jin.
Writing – review & editing: Danping Xu, Huanlin Wu.

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