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Association of smoking with postoperative atrial fibrillation in patients with cardiac surgery

A PRISMA-compliant article

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Abstract

Background: Cigarette smoking is an important modifiable risk factor for incident atrial fibrillation. However, the impact of smoking on postoperative atrial fibrillation in patients undergoing cardiac surgery remains controversial. We performed this meta-analysis to explore the association of smoking with postoperative atrial fibrillation in patients with cardiac surgery.

Methods: We systematically searched 2 computer-based databases (PubMed and EMBASE) up to July 2019 for all relevant studies. A random-effects model was selected to pool the odds ratios (ORs) and 95% confidence intervals (CIs). In this meta-analysis, the protocol and reporting of the results were based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

Results: A total of 36 studies were included in this meta-analysis. Overall, smoking was not associated with an increased risk of postoperative atrial fibrillation in patients undergoing cardiac surgery (odds ratio [OR] = 0.89; 95% confidence interval [CI] 0.79–1.02). The corresponding results were stable in the subgroup analyses. Specifically, smoking was not associated with an increased risk of postoperative atrial fibrillation regardless of the type of cardiac surgery: coronary artery bypass grafting (OR = 0.91; 95% CI 0.77–1.07), valve surgery (OR = 0.15; 95% CI 0.01–1.56), and coronary artery bypass grafting+valve surgery (OR = 0.91; 95% CI 0.70–1.18).

Conclusions: Based on currently published studies, smoking was not associated with an increased risk of postoperative atrial fibrillation in patients undergoing cardiac surgery.

Abbreviations: CABG = coronary artery bypass grafting, CI = confidence interval, LVAD = left ventricular assist devices, OR = odds ratio, POAF = postoperative atrial fibrillation, RCT = randomized controlled trial.

Keywords: atrial fibrillation, cardiac surgery, risk factor, smoking

1. Introduction

Postoperative atrial fibrillation (POAF) is a commonly encountered complication arising from cardiac surgery, which may greatly increase surgical mortality and morbidity, resulting in a lot of unnecessary medical waste and an additional cost of care.[1] While the exact etiology and pathophysiology of POAF remain unclear, several risk factors for POAF acting at preoperative, intraoperative, and postoperative levels have been identified.[2] Thereinto, cigarette smoking as a modifiable risk factor is associated with cardiovascular diseases (e.g., coronary artery disease).[3] The mechanisms of smoking-related coronary artery disease may be that smoking can lead to the injury and dysfunction in the endothelium of peripheral and/or coronary arteries, and the endothelial damage may further cause atherogenesis as well as acute cardiovascular events.[4]

To date, the incidence of smoking-related cardiac arrhythmias (in particular, supraventricular arrhythmias) has been shown a non-negligible tendency. A previous meta-analysis has reported that smoking is associated with a modestly increased risk of incident AF.[5] Another meta-analysis further reported the association of smoking with AF-related outcomes including thrombotic complications, bleeding, and death.[6] The mechanisms of smoking-induced AF may be that nicotine may increase the heart rate through stimulating the release of catecholamine, and nicotine may increase the electrical instability of the atria by

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blocking transient outward K^+ currents and influencing the cardiac repolarization and membrane transport processes. However, the impact of smoking on the development of POAF in patients undergoing cardiac surgery such as coronary artery bypass grafting (CABG), valve surgery, and left ventricular assist devices (LVAD) implantation remains controversial in the published studies. Interestingly, some studies have indicated that smoking has a protective effect on POAF potentially because smokers have higher baseline levels of sympathetic activity and higher adrenergic tolerance.[7] Given this conflicting issue, a comprehensive method may help clarify the assumed influence of smoking on POAF. This meta-analysis aimed to explore the association of smoking with POAF in patients undergoing cardiac surgery.

2. Methods

In this meta-analysis, the protocol and reporting of the results were based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[8] This was a meta-analysis of published studies, and thus no ethical approval was warranted.

2.1. Study search strategy

We systematically searched 2 computer-based databases (PubMed and EMBASE) up to July 2019 for studies that evaluated the effect of smoking on the risk of POAF in patients undergoing cardiac surgery. Three kinds of terms were combined by the Boolean operator "and." The first terms were linked to exposure of smoking (and similar terms). The second terms were linked to the outcome of POAF (and similar terms). The third terms were linked to cardiac surgery ("cardiac surgery" OR "coronary artery bypass grafting" OR "valve surgery" OR "aortic surgery" OR "ventricular assist device"). Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A217 provides a detailed description of the search strategies. We did not apply any language restrictions.

2.2. Selection criteria

Studies were included if they met the "PICOS" (population, intervention, comparison, outcomes, and study design) criteria: study subjects: adult patients undergoing cardiac surgery such as CABG, valve surgery, aortic surgery, and LVAD; risk factor: smoking; comparison and outcome: the relationship between smoking and POAF; and the design of study: randomized controlled trials (RCTs) and observational (prospective or retrospective) studies.

Reviews, letters, case reports, editorials, and comments were excluded. Studies with insufficient data were also excluded. If the study patients had a substantial overlap across the included studies, we included the study with the longest follow-up or largest sample size.

2.3. Data extraction and quality assessment

Two independent reviewers screened the titles/abstracts and full-texts for relevant studies. Discrepancies were resolved by discussion with each other. For each study, we abstracted the basic study characteristics and clinical factors such as the first author and publication year, country of origin, numbers of participants, sex, age, and types of cardiac surgery. Two researchers independently assessed the quality of cohort studies using the Newcastle-Ottawa scale[9] and assessed the quality of RCTs using the Cochrane Risk of Bias Tool.[10]

2.4. Statistical analysis

Data were abstracted by using predefined criteria and then pooled by Review Manager version 5.30 software (the Cochrane Collaboration, Copenhagen, Denmark). In this meta-analysis, odds ratios (ORs) and their corresponding confidence intervals (CIs) were used as the risk estimates. We calculated the natural logarithm of the ORs (log[ORs]) and their corresponding standard errors ($SE_{log[OR]}$). The heterogeneity inherent (both clinically and methodologically) across the included studies could not be neglected. To estimate the pooled results more conservatively, the log[OR] and $SE_{log[OR]}$ were pooled using a random-effects model. The consistency test was evaluated using the Cochrane Q test complemented with the I^2 statistic, where $P < .1$ or $I^2 > 50\%$ indicated high heterogeneity. The sensitivity analysis was performed to examine the influence of each study on the pooled results. The subgroup analysis was performed to explore the sources of heterogeneity. The publication bias was assessed using a funnel plot, and a visually significant asymmetry indicated major publication bias.

3. Results

3.1. Study selection

As shown in Table S2, Supplemental Digital Content, http://links.lww.com/MD2/A218, 36 studies were included in this meta-analysis. The basic characteristics of these studies were shown in Table 1. Overall, these included studies were published between 1996 and 2016. Thereinto, 11 studies were from Europe, 10 studies were from North America, 7 studies were from Asia, and 8 studies were from mixed regions. The reporting quality of all the included articles was acceptable.

3.2. Relationship between smoking and POAF

Overall, smoking was not associated with an increased risk of POAF in patients undergoing cardiac surgery (OR = 0.89; 95% CI 0.79–1.02; Fig. 1). The consistency test showed a high heterogeneity across the included studies ($I^2 = 89\%$). Nevertheless, in the sensitivity analysis, the pooled OR changed little after we omitted one study at a time.

To further explore the source of study heterogeneity, we performed the subgroup analyses based on several study characteristics and clinical factors (Figures S1–S5, Supplemental Digital Content, http://links.lww.com/MD2/A212, http://links.lww.com/MD2/A213, http://links.lww.com/MD2/A214, http://links.lww.com/MD2/A215, http://links.lww.com/MD2/A216). In all of these analyses, smoking was not associated with an increased risk of POAF (Table 2). Specifically, smoking was not associated with an increased risk of POAF regardless of the type of cardiac surgery: coronary artery bypass grafting (OR = 0.91; 95% CI 0.77–1.07), valve surgery (OR = 0.15; 95% CI 0.01–1.56), and coronary artery bypass grafting+valve surgery (OR = 0.91; 95% CI 0.70–1.18).

When the pooled analysis was confined to those studies with smoking as the main exposure,[11–15] smoking was associated

Table 1

Characteristics of the included studies in this meta-analysis.

Study (author-year)	Region	Design	Participants (N)	Age, y	Male ratio no. (%)	Adjusted for covariates (yes/no)	Type of cardiac surgery		
							CABG	Valve surgery	Others
Saskin-2016	Turkey	Retrospective (cohort)	1240	32–75	79.5	No	√	×	×
Tsai-2015	China	Prospective (cohort)	266	69.9±11.6	71.4	Yes	√	×	×
Masson-2015	Multicenter (United States, Italy and Argentina)	Prospective (cohort)	1516	66.0±11.3	74.0	No	√	√	√
Guenancia-2015	France	Prospective (cohort)	224	67.0±9.0	86.0	No	√	×	×
Tosello-2015	France	Prospective (cohort)	240	70.9±12.1	64.0	No	√	√	×
Sezai-2015	Japan	Prospective (RCT)	668	66.9±9.0	80.9	Yes	√	×	×
Melduni-2015	United States	Retrospective (cohort)	752	71.4±10.7	69.9	No	√	√	×
Onk-2015	Turkey	Prospective (RCT)	251	56.1±4.1	75.0	No	√	×	×
Ahin-2014	Turkey	Prospective (cohort)	597	63.5±8.5	67.0	No	√	×	×
Weidinger-2014	Multi-center (Austria and United States)	Prospective (cohort)	384	Mean 63.0	80.0	No	√	×	×
Erdil-2014	Turkey	Retrospective (cohort)	1040	64.1±9.4	73.6	No	√	×	×
Takahashi-2014	Japan	Retrospective (cohort)	63	78.5±6.1	34.0	No	×	√	×
Bidar-2014	Turkey	Prospective (RCT)	148	66.5±9.8	81.3	Yes	√	√	×
Narducci-2014	Italy	Prospective (cohort)	38	Mean 71.0	64.0	No	√	×	×
Nishi-2013	Japan	Retrospective (cohort)	277	66.7±9.1	76.2	No	√	√	√
Chua-2013	China	Prospective (cohort)	418	61.5±16.9	67.9	No	√	√	×
El-Chami-2012	United States	Retrospective (cohort)	19,895	62.5±10.9	71.7	No	√	×	×
Nardi-2012	Italy	Prospective (cohort)	220	71.2±7.6	67.2	Yes	√	×	×
Kinoshita-2011	Japan	Retrospective (cohort)	912	70.6±10.2	79.2	No	√	×	×
Shen-2011	United States	Retrospective (cohort)	14,960	62.3±12.9	65.0	No	√	√	√
Tadic-2011	Serbia	Retrospective (cohort)	322	63.0±7.0	74.0	Yes	√	×	×
Al-Sarraf-2010	United Kingdom	Retrospective (cohort)	2,813	61.3±9.2	83.0	No	√	×	×
Shirzad-2010	Iran	Retrospective (cohort)	15,580	58.1±10.1	67.6	No	√	√	×
Heidarsdottir-2010	Iceland	Prospective (RCT)	170	mean 69.0	79.1	Yes	√	√	×
Mariscalco-2009	Sweden	Retrospective (cohort)	3,245	65.7±9.1	72.0	Yes	√	√	×
Magee-2007	United States	Retrospective (cohort)	19,620	67.6±9.6	75.2	No	√	×	×
Nisanoglu-2007	Turkey	Retrospective (cohort)	426	71.2±4.6	72.5	Yes	√	×	×
Arribas-Leal-2007	Spain	Prospective (cohort)	102	67.7±8.8	78.0	No	√	×	×
Wiggins-2006	United States	Retrospective (cohort)	377	65.9±9.0	NA	No	√	×	×
Zacharias-2005	United States	Retrospective (cohort)	8051	68.0±10.0	66.2	No	√	×	×
Villareal-2004	United States	Retrospective (cohort)	6475	67.9±9.6	73.3	No	√	×	×
Mahoney-2002	United States	Retrospective (cohort)	8709	71.0±9.0	67.0	Yes	√	√	×
Hakala-2002	Finland	Prospective (cohort)	100	66.0±9.0	73.0	No	√	×	×
Jideus-2000	Sweden	Prospective (cohort)	80	65.7±7.4	79.0	No	√	×	×
Almassi-1997	United States	Prospective (cohort)	4,184	66.8±8.3	29.8	No	√	√	×
Aranki-1996	United States	Prospective (cohort)	570	Mean 67.0	69.0	No	√	×	×

CABG = coronary artery bypass grafting, NA = not available, RCTs = randomized controlled trials.

with a decreased risk of POAF (OR = 0.65; 95% CI 0.58–0.72), and there was no evidence of heterogeneity ($I^2 = 0\%$).

3.3. Publication bias

As shown in Fig. 2, we observed no major publication bias by inspecting the funnel plot.

4. Discussion

This meta-analysis sought to examine the association of smoking with POAF in patients with cardiac surgery. We performed this meta-analysis by including 36 studies, and demonstrated that smoking was not associated with an increased risk of POAF in patients undergoing cardiac surgery. Specifically, smoking was associated with a decreased risk of POAF when analyzed as the primary exposure. The pooled results were stable in the sensitivity analyses and subgroup analyses.

Over the past few decades, the mechanisms of acute vascular events of smokers have been well studied, including induction of a hypercoagulable state, increased myocardial work, carbon monoxide-mediated reduction in the oxygen-carrying capacity of the blood, induction of endothelial dysfunction, coronary vasoconstriction, and catecholamine release.[4,16] In the present study, no positive association between smoking and POAF was observed, and smoking may have a protective effect on POAF. With a growing number of related studies, this phenomenon may be explained by that smokers have higher baseline levels of sympathetic activity and higher adrenergic tolerance. Nicotine can induce the release of catecholamine from peripheral sympathetic nerve endings and adrenal medulla to cause AF, while those smokers who are repeatedly stimulated by chronic nicotine exposure can down-regulate the expression of nicotine acetylcholine receptors, thereby decreasing the risk of AF.[7]

Of note, smoking might have been reported and defined differently in this meta-analysis, which could greatly skew the

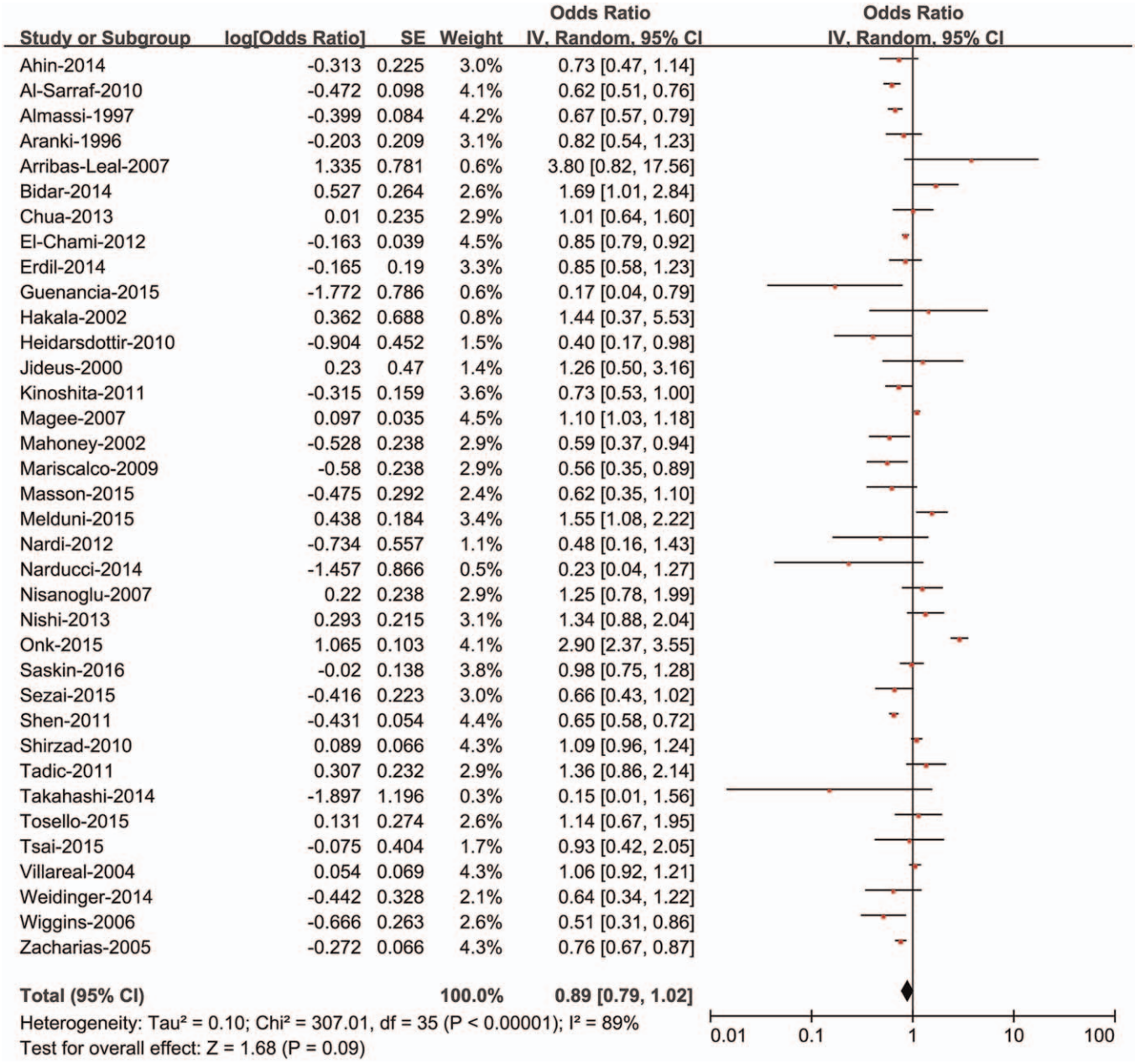

Figure 1. Forest plot of the association of smoking with POAF in patients undergoing cardiac surgery. CI = confidence interval, IV = inverse of the variance, POAF = postoperative atrial fibrillation, SE = standard error.

results of this study. Among the included studies, it is possible that they used different criteria when assessing the smoking status. For example, some studies could aggregate smoking status as positive even if the person is only a former smoker, while other studies might include only active smokers, meaning that no smoking was defined if a patient did not smoke for at least a month. In addition, result that smoking decreases the risk of AF after cardiac surgery is somewhat controversial and counterintuitive. While we proposed some mechanistic explanations, we have to respect the pathophysiology of AF which is quite complex. Further study should confirm whether smoking could play any role in the development of AF after cardiac surgery.

A previous meta-analysis reported that smoking was associated with a modestly increased risk of incident AF.[5] However, our present study showed no association between smoking and POAF. The mechanism of smoking resulting in AF is not enough to explain the discrepancy. As such, our findings do not mean to take encouragement for people to continue smoking. After all, smoking is associated with many cardiovascular diseases such as coronary artery disease. People should pay attention to the effect of smoking on post-operation malignant arrhythmias. Of note, the included studies of our meta-analysis were very different in terms of study design. The most important drawback in these studies was that there were only 5 studies with smoking as the main exposure. Since very few included studies that examined the

Table 2

Subgroup analyses of smoking and risk of POAF.

	Numbers of estimates	OR (95% CI)	I^2 values (%)
Overall	36	0.89 (0.79–1.02)	89
Geographic region			
Europe	11	0.77 (0.54–1.09)	64
North America	10	0.83 (0.71–0.98)*	92
Asia	7	0.93 (0.74–1.17)	56
Mixed	8	0.83 (0.71–0.97)*	81
Design of study			
Prospective	18	0.87 (0.60–1.25)	89
Retrospective	18	0.88 (0.77–1.00)	88
Adjusted for covariates			
Yes	9	0.83 (0.60–1.15)	67
No	27	0.91 (0.79–1.05)	91
Type of cardiac surgery			
CABG	23	0.91 (0.77–1.07)	89
Valve surgery	1	0.15 (0.01–1.56)	-
CABG+Valve surgery	9	0.91 (0.70–1.18)	83
CABG+Valve surgery+others	3	0.81 (0.50–1.31)	81
Smoking exposure			
As a main exposure	5	0.65 (0.58–0.72)*	0
As a confounder	31	0.95 (0.83–1.09)	89

CABG = coronary artery bypass grafting, CI = confidence interval, OR = odds ratio, POAF = postoperative atrial fibrillation.
* Indicated statistical significance.

influence of smoking on POAF as a primary outcome, further studies are needed to confirm our current findings.

4.1. Limitations

To the best of our knowledge, our meta-analysis first quantified the association of smoking with POAF arising from cardiac surgery. However, several limitations should be pointed out in this meta-analysis. First, we included several unadjusted data and performed a univariate meta-analysis in essence. This analysis was heavily unadjusted for many other baseline covariates that might have an important impact on AF onset after cardiac surgery. As such, a causal association of smoking with the risk of POAF was still unable to be concluded. Second, the high heterogeneity was observed and no obvious sources of heterogeneity were found. Thus, we still should interpret these findings cautiously. Third, cardiac surgery as an intervention was very heterogeneous and loosely defined in this meta-analysis. In this way, it is impossible to ascertain the true effect of cigarette smoking in this particular setting of cardiac surgery. Fourth, the protocol of our current meta-analysis was not registered in the PROSPERO database. Fifth, we excluded letters because of a lack

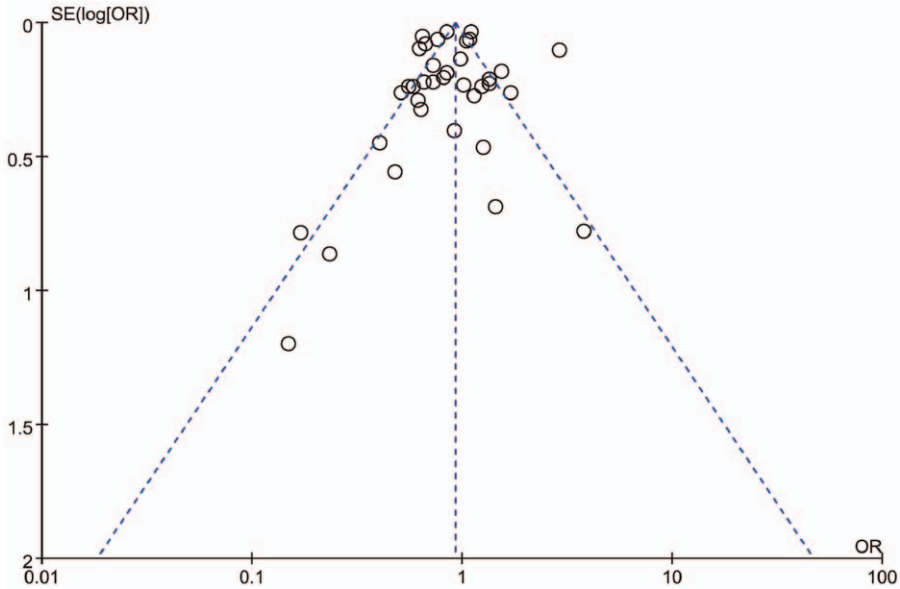

Figure 2. Funnel plot of the reported association of smoking with POAF in patients undergoing cardiac surgery. ORs = odds ratios, POAF = postoperative atrial fibrillation, SE = standard error.

of sufficient information for quality assessment. However, it would potentially delete some articles with available data. Finally, we only searched the studies in the PubMed and EMBASE databases, and some relevant articles in other databases might be missed. In addition, our analysis did not examine the dose–response relationship between smoking and POAF due to the limiting included studies. Further up-to-date meta-analysis could focus on this issue by including more relevant articles.

5. Conclusions

Our meta-analysis based on currently published studies demonstrated that smoking was not associated with increased risk of POAF in patients undergoing cardiac surgery. Our findings should be confirmed by further prospective studies.

Author contributions

Conceptualization: Jian Hu.
Data curation: Qin Wan, Siyuan Li.
Formal analysis: Qin Wan, Siyuan Li.
Investigation: Qin Wan, Siyuan Li.
Methodology: Qin Wan, Siyuan Li, Jian Hu.
Project administration: Qin Wan.
Resources: Qin Wan.
Software: Qin Wan, Siyuan Li.
Supervision: Jian Hu.
Validation: Siyuan Li.
Writing – original draft: Qin Wan, Siyuan Li.
Writing – review & editing: Jian Hu.

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