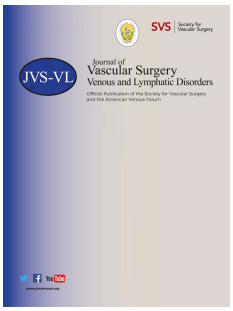

Effect of inferior vena cava filters on pulmonary embolism-related mortality and major complications: a systematic review and meta-analysis of randomized controlled trials

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Effect of inferior vena cava filters on pulmonary embolism-related mortality and major complications: a systematic review and meta-analysis of randomized controlled trials

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Inferior vena cava filters and Venous thromboembolism

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Abstract

Objectives: Inferior vena cava (IVC) filters are commonly used. However, there is no clear consensus on the benefits and risks from randomized, controlled trials (RCTs). Therefore, we aimed to investigate it.

Methods: PubMed and Cochrane libraries were searched from inception to 31st OCT 2019 to identify RCTs to perform meta-analyses. The primary outcome was mortality related to pulmonary embolism (PE). The secondary outcomes were overall mortality, occurrence of PE, deep vein thrombosis and major bleeding. Risk ratios were pooled using the Mantel–Haenszel method with the fixed effect mode for low heterogeneity, otherwise, with the random effect model. Risk differences were considered as a candidate of effect size if some data could not be pooled in the calculations.

Results: Seven articles with 1274 patients were included. There was no significant difference in mortality related to PE between the IVC filter group and the control group within 3 months (risk difference −0.01, 95% confidence interval [CI] −0.03 to 0.00, *P*=0.11) and during the whole follow-up time with low heterogeneity (I^2=0%). The rates of new occurrence of PE within 3 months and during the whole follow-up period were lower in the IVC filter group than those in the control group (0.81% versus 5.98%, risk ratio 0.17, 95% CI 0.04 to 0.65, *P*=0.01; 3.2% versus 7.79%, risk ratio 0.42, 95% CI 0.25 to 0.71, *P*=0.001, respectively). There were no

significant differences in the rates of new occurrence of deep vein thrombosis,major bleeding and mortality rates during the whole follow-up period between the groups (P>0.05).

Conclusions: There is insufficient evidence to conclude that IVC filters could reduce mortality. However, filters decrease the new occurrence of PE without increasing deep vein thrombosis and major bleeding.

Keywords Inferior vena cava filter, Deep venous thromboembolism, Pulmonary embolism, Mortality

Introduction

Venous thromboembolism, which mainly presents as deep venous thromboembolism (DVT) and pulmonary embolism (PE), is an important potentially fatal disease with a high incidence [1] and causes a huge burden[2]. In most cases, PE might be caused by thrombus embolization to the lungs. Besides anticoagulation, application of inferior vena cava (IVC) filters is commonly used in patients with contraindications to anticoagulation therapy (e.g., being injured, high risk of bleeding)[3-8] or patients with a high risk of occurrence of embolism [9, 10]. However, there is no clear consensus on the benefits and risks of IVCs from randomized, controlled trials (RCTs)[5, 11-13]. Systematic reviews have shown that IVC filters appear to reduce the incidence of subsequent PE, while appearing to increase the chance for DVT, and they have a limited effect on overall mortality[5, 14]. However, data in half of the included trials were not pooled into the effect size (odds ratio), which weakens the evidence of the conclusion[14]. Therefore, we performed a systematic review and meta-analysis of RCTs with more appropriate effect measures and more trials to investigate the effect of IVC filters on PE-related mortality and complications.

Methods

This research was carried out according to the PRISMA-P statement[15] and the prespecified protocol,which was registered in PROSPERO （CRD42020160628）. Ethical approval and patient's consent were not required for this systematic review. Adult patients received IVC filters

as an intervention and they were compared with no IVC filters as a control strategy. The primary outcome was mortality related to PE in the short term (within 3 months) and in the whole follow-up. The secondary outcomes were overall mortality in the short term and the whole follow-up time overall mortality, and complications, including the rate of the new occurrence or recurrence of PE, DVT, and major bleeding.

Search strategy and eligibility criteria

The authors YL and HL performed the literature search. Electronic databases, including PubMed and Cochrane library, were searched from inception to 31st OCT 2020 to identify the relevant studies. The search strategy was a combination of keywords and terms as follows: vena cava filters AND deep vein thrombosis OR deep venous thromboembolism OR pulmonary embolism. The searches were limited to studies on humans without language restriction. The references of all articles were checked and screened manually to identify additional potentially eligible studies. Duplicate papers were identified and deleted. The inclusion criteria for studies were as follows: (i) adult patients (≥16 years); (ii) designed as a RCT; (iii) the main purpose was to compare the effect of IVC filters with no IVC filters; and (iv) at least one outcome of interest could be extracted. The exclusion criteria for studies were as follows: (i) recruited patients were younger than 16 years; (ii) there was marked difference in anticoagulation therapy between the experimental and control groups if anticoagulation was adopted; (iii) an observational study; (iv) a cross-over study; (v) editorials, case reports, letters, reviews, news, comments, guidelines, or meta-analyses; (vi) conference papers or abstracts; and (vii) no response after contacting the corresponding author for the full text.

Data extraction and quality assessment of the studies

Independently, YL and HL extracted the data, which included the authors' names, publication year, characteristics of the patients and studies, and the outcomes of interest. If discrepancy occurred, it was solved by checking the original data again and discussion with HB. HB made the final arbitration. To assess the possible risk of bias, we applied the Cochrane Collaboration tool for RCTs, which contains six items[16]. Each item was rated as a "high", "low " or "unclear" risk of bias according to a method described in our previous studies. Evaluation was independently performed by YL and HL. In case of disagreement, it was discussed and then HB was consulted for the final decision

Statistical analysis

Data were analyzed with RevMan 5.3 software (Cochrane Collaboration, Oxford, UK). Numbers of events and patients in each group were identified and recorded. Risk ratios (RRs) with 95% confidence intervals (CIs) were pooled using the Mantel–Haenszel method. Risk differences (RDs) and 95% CIs were considered as a candidate of effect size if some studies could not be pooled in the calculations. The analyses were performed with the fixed effect model for low heterogeneity, and otherwise, the random effect model was used. Heterogeneity across the studies was tested by the I^2 statistic[17, 18]. The I square (I^2) value of 25% to 50% indicated low, 50% to 70% indicated moderate, and >75% indicated high heterogeneity[19].The sensitivity was analyzed by excluding each study and recalculating the I^2. Potential publication bias was assessed by visual inspection of a funnel plot. A *P* value <0.05 was considered to be statistically significant.

Results

Literature search and identification of studies

We found 2154 articles according to the search strategies. The flow chart of inclusion of RCTs is shown in Figure 1. A total of 2082 studies were excluded after screening titles and abstracts, and then 65 studies were excluded after further comment on the abstracts and full texts. Finally, six studies with 1274 patients (638 in IVC filter group and 636 in the control group) were eligible for this review[6, 20-25]. One of these studies involved two published articles at the end of different follow-up time durations[20, 21]. The research was performed in the USA[22-24], France[20, 21, 25], and Australia[6]. Two studies recruited injured patients[6, 22], two included patients with diagnosed DVT and symptomatic PE[20, 25], two reported patients with preexisting DVT[23, 24], and one reported patients with cancer[23]. Uninjured patients received consistent anticoagulant therapy in the intervention and control groups[20, 23-25]. The shortest follow-up time was three month[6] and the longest was eight year[21]. Detailed characteristics of the RCT are shown in Table 1.

Data extraction and quality assessment

All of the data were extracted according to a pre-specified method. Data for short-term outcomes from the Prévention du Risque d'Embolie Pulmonaire

par Interruption Cave (PREPIC) study were extracted from an article that was published in 1998[20] and data for the whole follow-up period was extracted from one published in 2005[21], more information in detail were uploaded as appendix (Supplemental Table 1 and Table 2). Most of the items were evaluated as a low risk of bias by the Cochrane Collaboration tool

(Supplemental Table 3). Notably, blinding of participants and personnel in these types of studies for the patients' safety and the large difference in strategies in the IVC filter and controlled groups, and for IVC filters was impossible. Performance bias was considered as a high risk in all of the studies. For the primary outcome of mortality, the outcome assessment was unlikely to be biased by blinding or not, and we estimated the detection bias as low risk.

Effect of IVC filters on mortality related to PE or overall mortality within 3 months

As shown in Figure 2A,there was no significant difference in mortality related to PE within 3 months between the IVC filter group and the control group (0.94% versus 1.10%,RD −0.00, 95% CI −0.01 to 0.01, *P*=0.81) with low heterogeneity (I^2=0%, *P*=0.36). The overall mortality rate within 3 months was similar in the IVC filter group and the control group (9.22% versus 6.73%, RR 1.37, 95% CI 0.91 to 2.06, *P*=0.13) (Figure 2B).

Effect of IVC filters on mortality related to PE or overall mortality during the whole follow-up

The mortality rate during the follow-up period was reported in all of the included trials. However, data in one study could not be extracted since they were reported in a Kaplan–Meier survival curve[23]. There were no significant differences in PE-related mortality (1.32% versus 1.49%, RD −0.00, 95% CI −0.02 to 0.01, *P*=0.81, I^2=0%) (Figure 2C) and overall mortality (22.73% versus 21.72%, RR 1.05, 95% CI 0.87 to 1.26, *P*=0.61, I^2=0%) between the IVC filter group and the control group (Figure 2D).

Effect of IVC filters on the rate of major complications

There was significant difference in the rate of new occurrence of PE within the first 3 months between the IVC filter group (0.81%) and the control group (5.98%) (RR 0.17, 95% CI 0.04 to 0.65, Z=2.58, *P*=0.01) with low heterogeneity (I^2=0%, *P*=0.47 Figure 3A),but the overall effect was non-significant when the data of reccurence PE being pooled together. The overall rate of new occurrence of PE during the whole follow-up period was lower 3.2%(18/562) in the IVC filter group compared with 7.79%(43/552) in the control group (RR 0.42, 95% CI 0.25 to 0.71, *P*=0.001, I^2=42%, Figure 3B) Subgroup analysis showed filters decreased occurrence of PE during the whole follow-up period in patient with both a high risk of PE and an absolute contradiction to anticoagulant therapy (P=0.01 and 0.04,respectively) . There was no significant difference in the rate of new occurrence of DVT between the IVC filter group and the control group either (11.91% versus 9.12%, Z=0.56, *P*=0.58), with high heterogeneity (I^2=72%) (Figure 3C).Sensitivity analysis showed the high heterogeneity was attributed to the PREPIC study[21] . Additionally, there was no significant difference in the rate of major bleeding between the IVC filter group and the control group (20.39% versus 20.29%, RR 0.99, 95% CI 0.83 to 1.18,Z=0.15, P=0.88, I^2=0%) (Figure 3D).

Publication bias

Visual inspection of the funnel plot was nearly symmetrical for the effect of IVC filters on PE-related mortality within 3 month (Figure 4). Begg's and Egger's tests were considered as unnecessary, and therefore, they were not performed.

Discussion

We performed a meta-analysis on the basis of RCTs to investigate the effect of IVC filters on short-term and long-term PE-related mortality and complications. We found that the benefit of IVC filters in reducing mortality might be limited. However, IVC filters decreased the occurrence of PE in 3 months and during the whole follow-up period without increasing DVT and major bleeding.

IVC filters are commonly used in clinical medicine, although the current guidelines cautiously recommend them [26-29] and there is no sufficient evidence to prove the compelling benefits of IVC filters. A few studies have indicated that IVC filters reduce the risk of recurrent PE[5, 14, 20, 21], while others have shown little effect [6, 30]. More importantly, few studies have shown that IVC filters reduce overall mortality[14, 26, 30]. Up to now, the strong evidence came from a meta-analysis with the most included studies including both RCTs and observational studies. However, data in several included studies could not be pooled in the effect size about mortality related with PE because of the limitation of the effects size (odds ratio) itself[14]. In addition, a study conducted in 1973 was also included [31].This was not a standard RCT study, patients in the study were grouped according to the patient's admission hospital number,odd or even. These two aspects weaken the evidence to some extent.

In this study, we adopted another effect size, SD,to ensure that all extracted data from included trials were pooled together , which made the evidence of IVC filters on the effect of PE related mortality more credible. It was shown that IVC filters could not reduce the PE related mortality within three months and the entire follow-up time with low heterogeneity. Long-term

prognosis was similar between the IVC filter and control groups in PE-related or total mortality. This finding was explainable because most of the patients received retrievable IVC filters, which were removed in the short term, and the underlying diseases themselves determined the final survival time of patients. According to the PREPIC study, PE only occurred in nine patients in the IVC filter group versus 24 in the control group during 8 years of follow-up[20, 21]. However, the overall number of deaths was 98 versus 103 during the same period, which indicated that chronic disease was the main determinant of long-term survival. A non-significant effect of IVC filters on overall long-term mortality does not exclude a potential effect on short-term PE related mortality if more trials were performed with selected patients cohorts.

A retrospective cohort study of 461,974 patients showed that filters might have a limited effect on reducing the occurrence of PE in injured patients who were absolute contradicted to early anticoagulant adoption[32]. Another study showed that filters did not reduce the incidence of PE in patients with venous thromboembolism[30]. The current study showed that IVC filters reduced the new occurrence of PE within 3 months and during the whole follow-up period. However, this effect could not be translated into a reduction in mortality,which may be attributed to the lower reported incidence of fatal PE. A few studies showed that filters did not reduce and even increased the risk for DVT[11, 14],which is different from the result in our study. In one study, the negative conclusion about DVT was driven by observational studies, but more powerful evidence from a RCT subgroup indicated that filters did not increase the rate of DVT (P=0.10) with low heterogeneity[14],which was consistent with the result in our study. Another study of patients with cancer showed that filters did not prevent recurrent DVT, but the pooling analysis met with high heterogeneity (I^2=76%), and only one RCT was included[11]. We found that IVC

filters did not increase the risk of DVT and the rate of major bleeding on the basis of pooled results of RCTs. In view of the controversial effect of IVC filters on mortality, we do not recommend that IVC filters be inserted regularly. The aim of inserting filters is mainly to mechanically prevent venous clots reaching the pulmonary vessels from the lower limbs. IVC filters should be considered in patients with a high risk of PE after balancing the benefits and risks.

There are some limitations in this study. First, patients who were recruited in the included trials were not completely consistent regarding the disease conditions. Some patients suffered from injury with contraindications to anticoagulant therapy,some patients suffered from DVT with a high risk of recurrence of thromboembolism, but this diversity didn't produce high heterogeneity .Second, performing subgroup analyses was limited because of the paucity of trials, which suggests that more studies , especially RCTs, with the selected patients need to be performed. Third, performance bias was a high risk, which was attributed to the dramatic difference in therapy between the two groups, with or without surgery to insert an IVC filter. This made participants and personnel blinding from the intervention strategy impossible, and might have affected the outcomes to a certain extent.

Conclusions

This meta-analysis indicates that caution should be used for conclusion of an effect of IVC filters on mortality. There is insufficient evidence to prove that IVC filters can reduce PE-related mortality and overall mortality. However, IVC filters decrease the occurrence of PE without increasing DVT and major bleeding. IVC filters should be considered after balancing the

benefits and risks for the patients with contraindications to anticoagulant therapy or high risk of PE. Large RCTs are still required to provide more robust evidence.

Author contributions

QL conceived and designed the study; YL and HL searched databases, identified the relevant studies, extracted and analyzed the data statistically; HB and QL assisted in identifying the relevant studies and interpreted the results; YL, HL and QL drafted the manuscript; RC helped conceive ,design the study and explain the results; all of the authors reviewed, revised and approved the manuscript to be submitted.

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Table 1 Characteristics of randomized, controlled trials included in the meta-analysis

Author year	Patients characteristic	IVC filters Strategy	Control strategy	Sample size		Major Outcomes
				IVC filters	Control	
Ho 2019[6]	Severely injured patients with a contraindication to anticoagulant agents,≥18 years old, ISS >15	Retrievable IVC filters +intermittent pneumatic compression +prophylactic anticoagulation 72 hours after admission for the injury	intermittent pneumatic compression +prophylactic anticoagulation 72 hours after admission for the injury	122	118	Composite of symptomatic PE or death from any cause, major or nonmajor bleeding at 90 days
PREPIC 1998,2005 [20,21]	Acute proximal DVT with or without symptomatic PE, > 18 years old, high risk for PE	Permanent IVC filters + anticoagulation +compression stockings ≥3 months	Anticoagulation +compression stocking	200	200	PE within the first 12 days，recurrent DVT, death, major filter complications, major bleeding
Rajasekhar 2011[22]	High risk trauma patients > 18 years old admitted within 96h	Retrievable IVC filters +anticoagulation when it was considered to be safe	Anticoagulation when it was considered to be safe	15	15	Incidence of PE, DVT and death
Barginear 2012[23]	Patients with cancer and venous thromboembolism, ≥18 years old with an acute DVT	Permanent IVC filters with anticoagulation	Fondaparinux sodium	31	33	Recurrent thromboembolism, Resolution of thromboembolism, survival rates, complications
Sharifi 2012 [24]	Acute proximal DVT	IVC filters+ PEVI +anticoagulation	PEVI + anticoagulation	70	71	Occurrence of PE, recurrent venous thromboembolism and filter integrity, mortality
PREPIC II 2015[25]	Symptomatic PE associated with lower-limb DVT or SVT,≥18 years old, at least 1 additional criterion for severity	Retrievable IVC filters plus anticoagulation	Anticoagulation alone	200	199	Symptomatic recurrent PE, DVT, major bleeding, death at 3 and 6 months, and filter complications

IVC, inferior vena cava; ISS, injury severity score; PE, pulmonary embolism; DVT, deep venous thrombosis; SVT, superficial vein thrombosis; PEVI, percutaneous endovenous intervention

Figure 1 Flow chart of inclusion of studies for the meta-analysis.

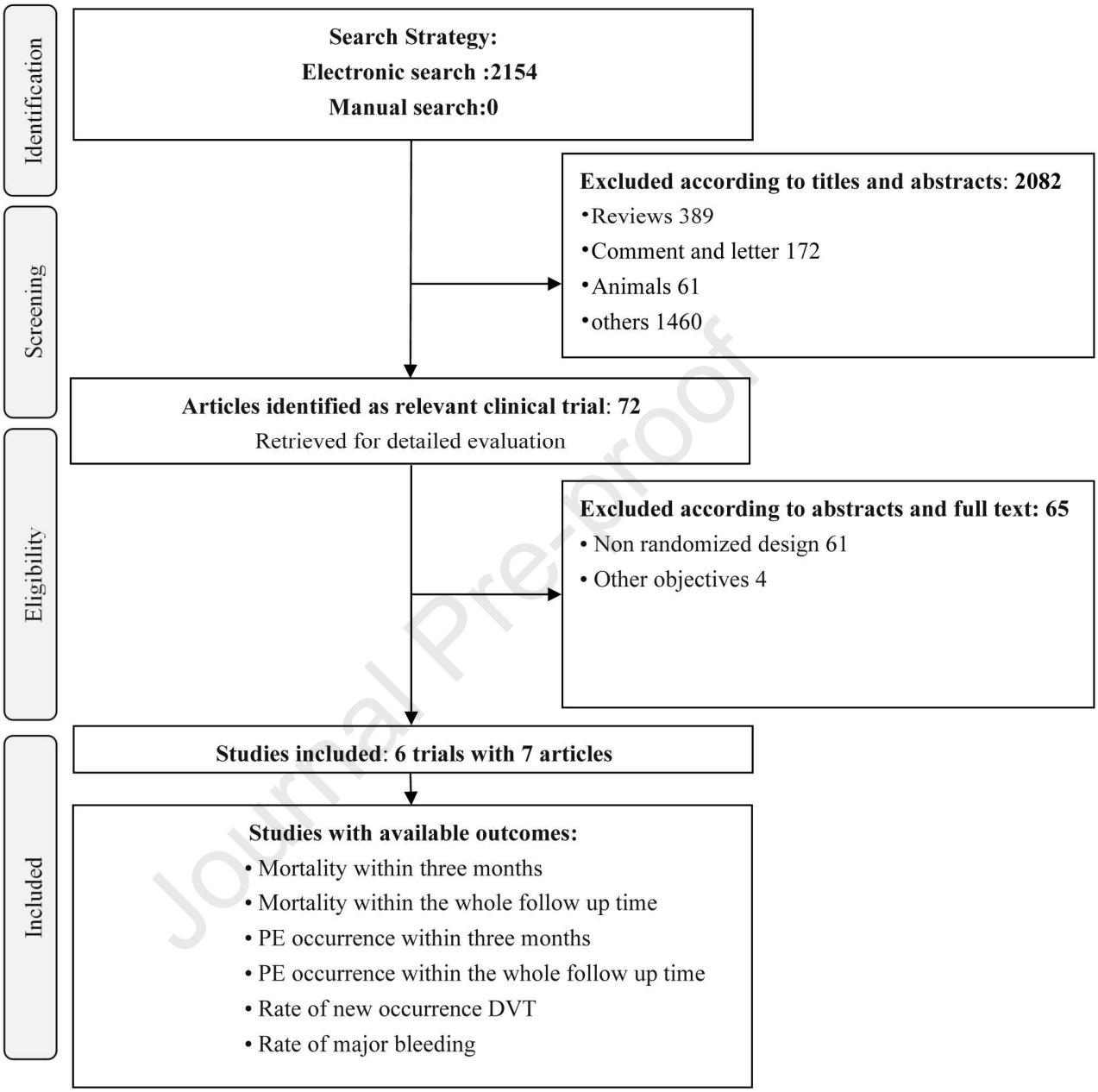

Figure 2 Effect of IVC filters on mortality within 3 months and during the whole follow-up time

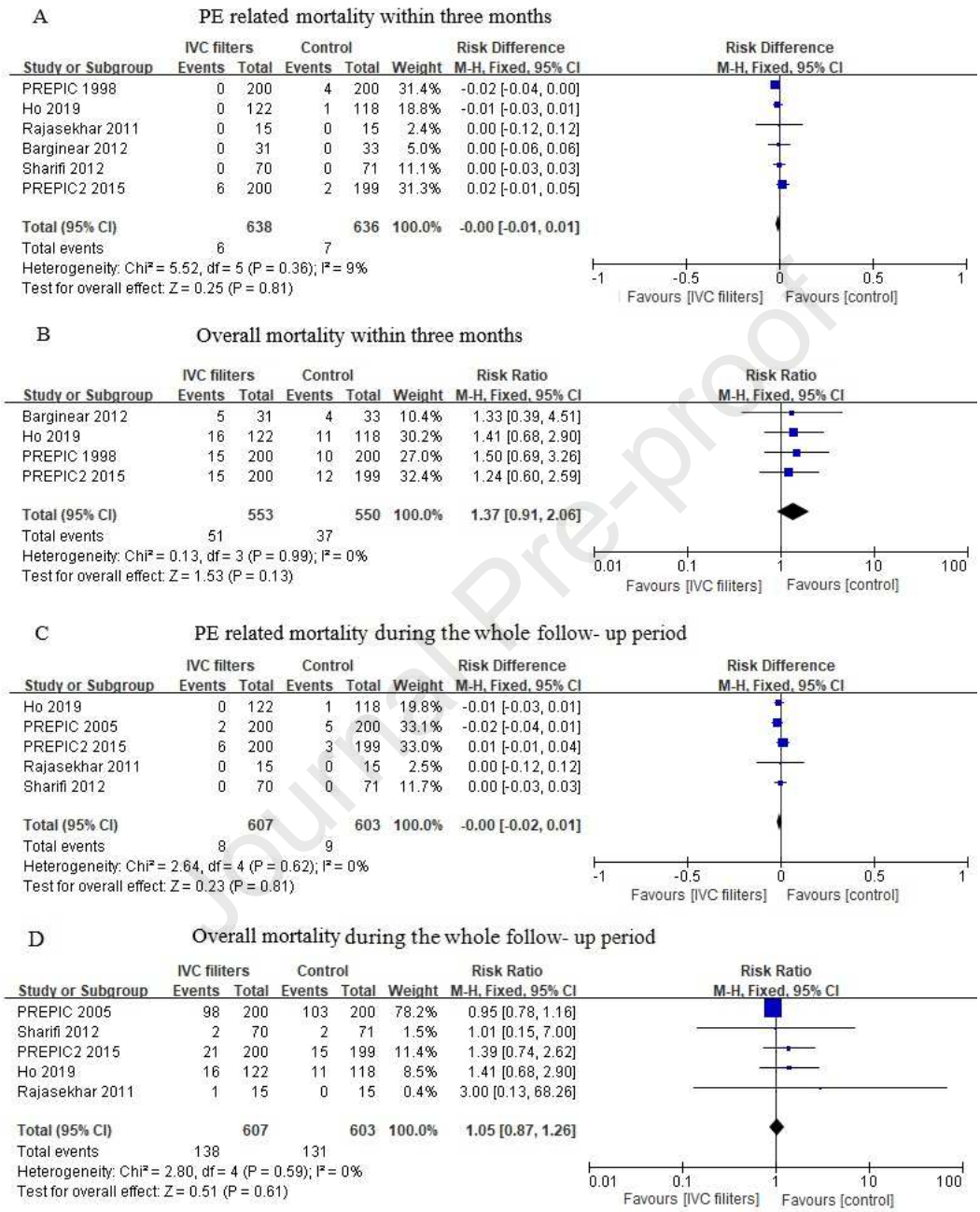

Figure 3 Effect of IVC filters on the rate of major complications

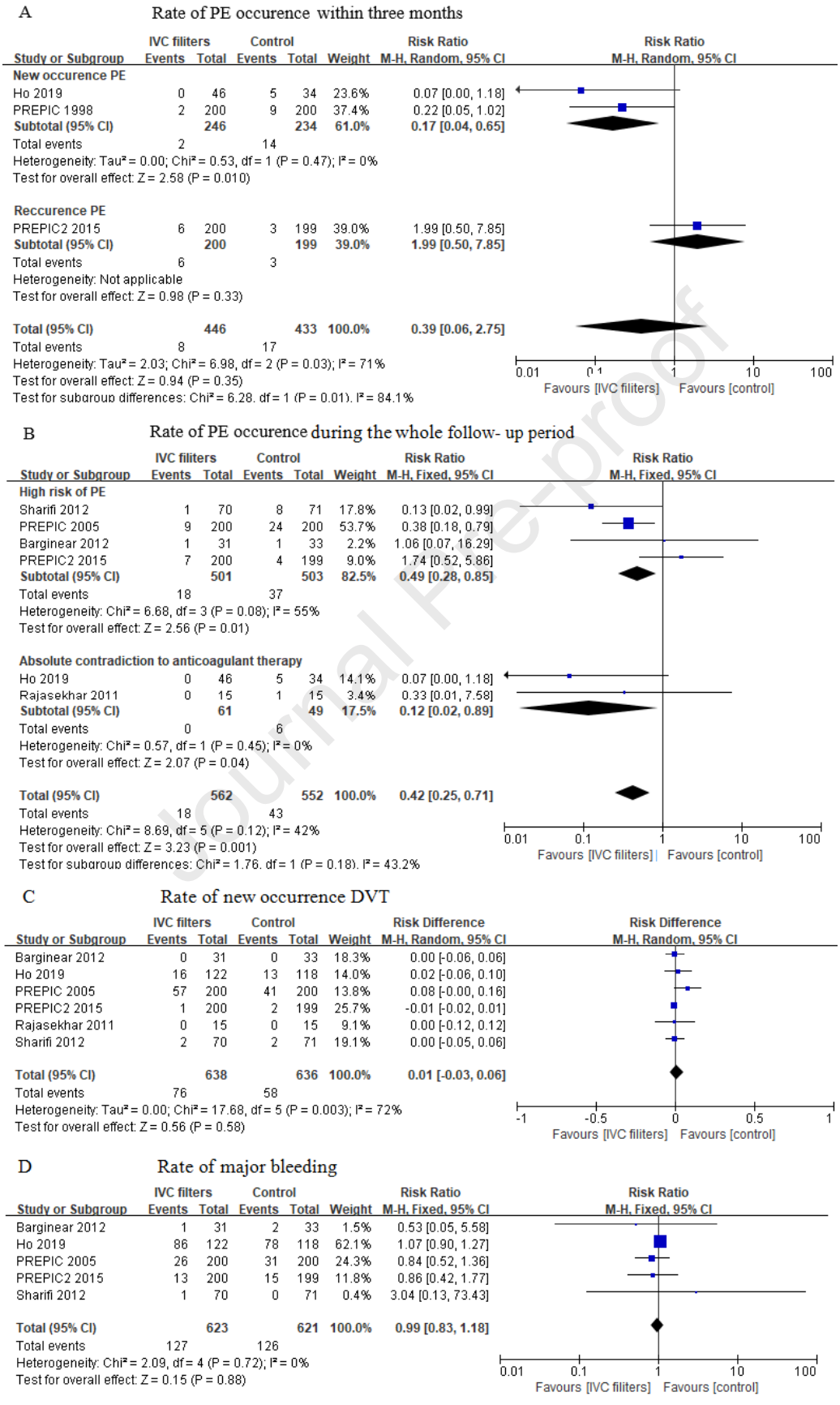

Figure 4 Funnel plot for estimating the publication bias for the effect of IVC filters on PE-related mortality within three month

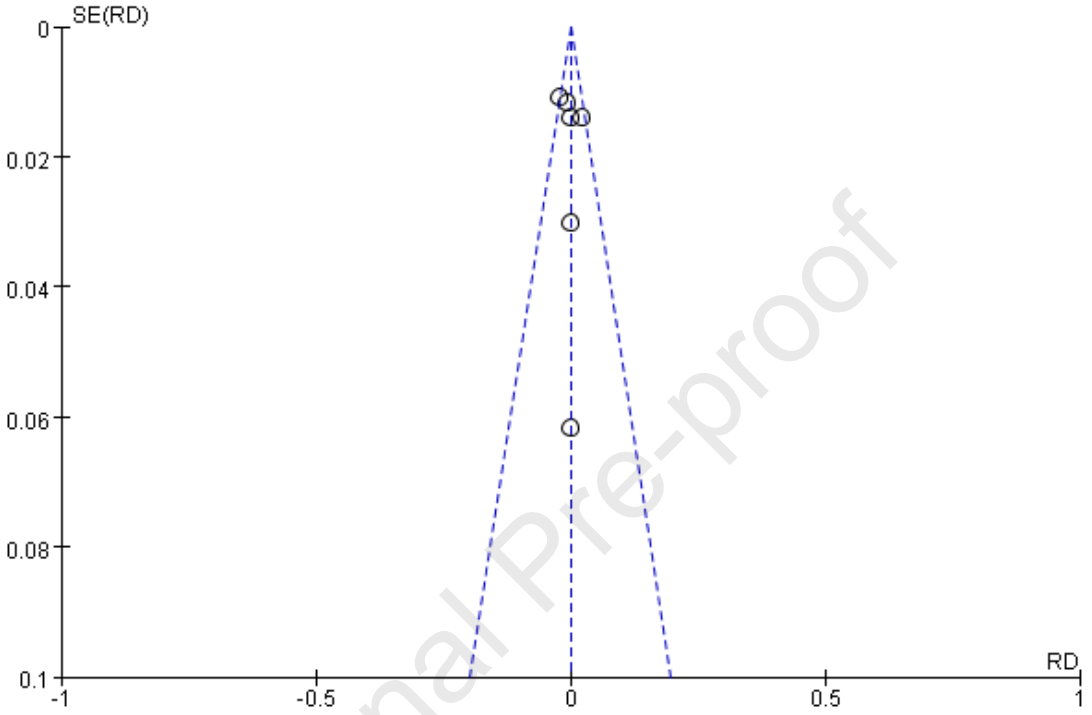

Figure 1 Flow chart of inclusion of studies for the meta-analysis.

Figure 2 Effect of IVC filters on mortality within 3 months and during the whole follow-up time

The vertical solid line shows the null effect boundary, boxes and horizontal lines show the outcomes of included studies and the 95% CI, and filled rhomboid boxes show the overall effect size of the pooled results. IVC, inferior vena cava; PE, pulmonary embolism; M-H, method of Mantel–Haenszel; fixed, fixed effect model; CI, confidence interval.

Figure 3 Effect of IVC filters on the rate of major complications

The vertical solid line shows the null effect boundary, boxes and horizontal lines show the outcomes of included studies and the 95% CI, and filled rhomboid boxes show the overall effect size of the pooled results. PE, pulmonary embolism; M-H, method of Mantel–Haenszel; fixed, fixed effect model; CI, confidence interval; DVT, deep venous thrombosis.

Figure 4 Funnel plot for estimating the publication bias for the effect of IVC filters on PE related mortality within three months