Incidence and Risk Factors for Postoperative Venous Thromboembolism in Patients with Endometrial Cancer: Systematic Review and Meta-analysis

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Research Article

Keywords: thromboembolism, endometrial cancer

Posted Date: October 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-915807/v1

Abstract

Background: Venous Thromboembolism (VTE) is a leading reason of morbidity and mortality in endometrial cancer patients. There is no meta-analysis available on this topic so far. In order to identify relevant risk factors contributing to VTE and form strategies to prevent VTE, we conducted the present study to quantitatively analyze the data from studies with the incidence and risk factors among cases with endometrial cancer.

Methods: PubMed, Embase and CNKI were searched for papers containing the key words “thromboembolism” “endometrial cancer” and their variants. Studies selection, data extraction, quality assessment of eligible studies were performed independently by two reviewers. Meta-analyses were conducted to determine postoperative VTE incidence rate and risk factors in endometrial cancer. Sensitivity analysis was used to verify the robustness of the results in the present study.

Results: 8 studies were included in this meta-analysis totally. The pooled incidence rate for postoperative VTE was 7% (95% CI, 0.04 –0.09).The presence of age>60 (OR, 2.26), tumor size in uterine cavity(≥60mm) (OR, 5.68), tumor extension (CT/MRI) (OR, 5.59), FIGO stage (OR, 2.92), massive ascites (OR, 3.78), clear cell cancer (OR, 4.78) and CA125(≥35U/ml) (OR, 5.05) increase the likelihood of having postoperative VTE remarkably.

Conclusions: The present study revealed that VTE is a prevalent complication in postoperative patients with endometrial cancer. The patients with the following risk factor including female elderly, large size of tumor, advanced endometrial cancer，massive ascites , elevated CA125 and special histology should be altered VTE occurrence.

Introduction

Endometrial cancer (EC) was the fourth leading malignant disease in women [1]. A major of post-menopausal women were affected by endometrial cancer and diagnosed in a localized stage, whose treatment were hysterectomy with or without adjuvant chemotherapy [2–3]. Staging operation was the main treatment of endometrial cancer, which is on the basis of pathological evaluation. The operative treatment for the majority of endometrial cancer patients includes laparoscopy or laparotomy removal of the uterus, cervix, fallopian tubes and ovaries and a sentinel lymph-node evaluation [4].

The correlation between malignant disease and venous thromboembolism (VTE) was covered by Armand Trousseau in the 19th century [5].The occurrence rate of VTE in cancer patients is associated with cancer type. Patients suffered with cancer originating from pancreas, stomach, brain, kidney, uterus, lung and ovary had great incidence of VTE [6].The reason of venous thromboembolism is related to several risk factors, including being female, undergoing pelvic surgery, over 60 years of age, and operation time≥3 h [7]. VTE accounts for the second reason leading to death among malignant disease [8–9].The treatment and other risk factors including obesity and history venous thromboembolism could significantly increase venous thromboembolism (VTE) risk among patients suffered with endometrial cancer [10].

The reported incidence of VTE in endometrial cancer patients varies from 1% - 11% [11–18].To our best knowledge, there was no meta-analysis focus on the incidence rate and risk factors for venous thrombus embolism among endometrial cancer patients. The association between endometrial cancer surgery-related risk factors and VTE were controversial. Therefore, we conducted this systematic review and meta-analysis, aiming to address two relevant questions: (1) what is the incidence of postoperative VTE among women with endometrial cancer? (2) which factors can effectively predict postoperative VTE in endometrial cancer?

Methods

The present study was conducted in accordance with the guideline of the Meta-analysis of Observational Studies in Epidemiology checklist and the Cochrane Handbook.

1. Literature search

The eligible studies were identified by systematic search electronic databases including PubMed, Embase and CNKI. Two reviewers searched articles by the following keywords including “thromboembolism,” “endometrial cancer” and their variants. The initial study was researched in 2013 and the latest was conducted in 2021. In addition, the relevant references listed in articles were manually searched to obtain more eligible data.

2. Study selection

We defined the inclusion criteria to screen the eligible studies as the follows: (1) the original studies published until 2021. (2) English language and Chinese articles published at peer-reviewed journals. (3) The articles we included were observational studies which investigated the prevalence and risk factors of VTE in endometrial cancer patients.

3. Data extraction and quality assessment

Two investigators (Xing Zheng and Xiaoying Hou) reviewed the relevant articles to extract the following data: name of first author, year of publication, country, the type of study design, study span, sample size, incidence rate of VTE. The studies included were assessed by Newcastle–Ottawa Quality Assessment Scale. Selection criteria of participants, comparability, exposure, and outcome were contained in the score system and each dimension was scored 3points.The maximum score of NOS is up to 9. The researches scored more than 7 were preferred to be high quality. When there was any disputation in two reviewers, the final results were settled by a senior reviewer.

4. Statistical Analysis

This meta-analysis was conducted by using the Review Manager (RevMan 5.3). The pooled incidence rate of VTE in patients with endometrial cancer was calculated by Revman. The pooled ORs of risk factors were estimated with inverse variance methods and the effects were assessed with 95%

confidence intervals (CIs). What's more, *Q*-test and I^2 statistic were assessed to evaluated heterogeneity between the enrolled researches. If the *P*-value was <0.05 or I^2 was greater than 60%, we applied the random-effect model for analyses. Otherwise, data were pooled with fixed-effects model and corresponding 95% CIs. In addition, we conducted subgroup analysis to explore the reason of heterogeneity. What's more, sensitivity was imitated by removing one study at a time. The publication bias was evaluated by simulating the asymmetry of funnel plot.

Results

1. Included studies

After English database including the "Pubmed" and "Embase" were reviewed, we found 102 English articles. And 42 Chinese articles were found in CNKI. After read the abstract and titles, 67 records were excluded because of irrelevant information. Due to the research did not report the incidence of VTE and other relevant information interested, 32 studies were excluded. As we failed to obtain the original data, 37 studies were discarded. In the end, 8 studies [11–18] were included in present meta-analysis. 6 articles were published in English and 2 studies were Chinese. The flow chart was displayed in figure 1. The NOS score of included studies were above 7. And the characteristics of the studies were summarized in Table 1.

Table 1
Characteristics of included studies

Study	Year	Country	Study span	Sample size	Rate of VTE	NOS SScSSScorescscore
Satoh T	2008	UK	2004-2007	171	17	7
Matsuo K	2013	USA	2000-2001	516	42	8
Emma L	2016	USA	2008-2013	9948	127	6
Huang M	2019	China	2010-2018	1062	29	7
Tasaka T	2020	Japan	2004-2017	862	97	8
Pin S	2020	Canada	2014-2016	442	26	9
Habu Y	2021	Japan	2009-2017	455	50	7
Xia W	2021	China	2004-2012	589	23	7

2. Prevalence of VTE

The included studies investigated the accidence of VTE. The pooled accidence of VTE was 7% (0.04-0.09) after calculated with substantial heterogeneity (I^2 = 97%), which was showed in figure 2. Considering the huge heterogeneity, we performed subgroup analyses according to the human race. Despite the study was subgrouped, the heterogeneity didn't reduce. The pooled accidence of VTE of Caucasian and yellow

race were 1% (0.01–0.02) and 5% (0.04–0.05), respectively, which was showed in figure 3. The funnel plot was applied to evaluate whether existed publication bias influence the results, and the funnel plot appeared to be asymmetrical. The trim-and-fill method was applied to explored sensitivity analysis. By removing any study in the analysis verify the effect of “missing studies” on the pooled prevalence of VTE. Interestingly, the new pooled estimate was basically consistent with the previous one.

3. Risk factors for the VTE among patients with endometrial caner

In summary, there are 8 studies reported the risk factors for the accidence of VTE in endometrial cancer. The univariate mata-analyses were conducted for risk factors (Table 2).

Table 2
Risk factors for postoperative VTE in patients with endometrial cancer (univariate analysis)

Risk factor	No.of studies	Model of meta-analysis	OR	95% CI	P	I^2 (%)
BMI>30	6	Random-effects	0.74	0.49-1.13	0.16	62
Age>60	3	Fixed-effects	2.26	1.71-2.98	0.00	24
Smoking history	3	Fixed-effects	1.14	0.51-2.54	0.76	0
Menopause	2	Fixed-effects	1.77	0.81-3.86	0.15	0
Tumor size in uterine cavity(≥60mm)	2	Random-effects	5.68	2.29-14.1	0.00	92
Tumor extension (CT/MRI)	2	Fixed-effects	5.59	3.86-8.08	0.00	57
Type of surgery (Laparoscopy *vs* Laparotomy)	3	Random-effects	1.55	0.53-4.51	0.42	83
FIGO stage(III+IV *vs* I+II)	6	Random-effects	2.92	1.42-6.04	0.004	88
Massive ascites	2	Fixed-effects	3.78	2.36-6.05	0.00	38
Histology: clear cell	3	Fixed-effects	4.78	3.28-6.98	0.00	59
CA125(≥35U/ml)	3	Random-effects	5.05	1.07-23.78	0.04	91
Diabetes mellitus	3	Fixed-effects	0.86	0.4-1.86	0.70	0

3.1 BMI

In general, six studies [11–15, 18] covered that the increased body mass index (BMI) was a risk factor for the occurrence of VTE among patients with endometrial cancer. But the results in the included studies were controversial. The result in the present meta-analysis showed the pooled OR of big BMI was 0.74 (95% CI, 0.49-1.13), indicating the BMI have no correlation with VTE.

3.2 Age

Five studies [11–13, 15, 18] explored the relationship between age and the occurrence of VTE in endometrial cancer patients. The pooled OR was 2.26 (95% CI, 1.71-2.98), indicating the older patients may have more probability to suffer VTE in postoperative time.

3.3 Smoking history

After calculating the pooled OR in the included three studies [11, 12, 17], we found the result showed that smoking history didn't relate with postoperative VTE in endometrial cancer (OR, 1.14; 95% CI, 0.51-2.54).

3. 4 Menopause

The meta-analysis of two studies [11, 16] proved that patients with menopause were associated with increasing the risk of postoperative VTE after operation (OR, 1.70; 95% CI, 0.55-5.22).

3.5 FIGO stages and type of surgery

Of note, advanced stages of disease [12–14, 16–18] was associated with high risk of postoperative VTE in EC. While type of surgery (laparoscopy *vs* laparotomy) [14, 16, 17] were not. The pooled ORs were 2.92 (95% CI, 1.42 –6.04) and 1.55 (95% CI, 0.53, 4.51) respectively.

3.6 Tumor size in uterine cavity and tumor extension (CT/MRI)

The presence of tumor size in uterine cavity [11, 13] increased the likelihood of having postoperative VTE in endometrial cancer (OR, 5.68; 95% CI, 2.29, 14.10). And the tumor extension (CT/MRI) [11, 13] was also associated with high risk of postoperative VTE in endometrial cancer (OR, 7.20; 95% CI: 2.73-18.98).

3. 7 Massive ascites and histology

The massive ascites [11, 13] was correlated with high risk of VTE in endometrial cancer after operation (OR, 4.53; 95% CI, 1.76, 11.69). Of note, the pooled OR of the histology type of clear cell was 5.57 (95% CI: 2.72-11.43).

3.8 Surgery related risk factors

The present study found that the level of CA125 [11, 14, 18] was associated with VTE in postoperative endometrial cancer patients. However, the pooled OR (OR, 0.86; 95% CI: 0.40-1.84) of diabetes mellitus [2, 6, 7] was not corrected with VTE.

Discussion

After VTE occurred in malignant disease was reported, the likelihood between VTE and a variety of cancer including endometrial cancer was extensively investigated. The recent study reported that endometrial cancer patients with high incidence of VTE were corrected with an increased risk of death [19]. In addition, researchers investigated that VTE in endometrial cancer was related with tumor invasion and cause

undesirable influence on the quality of economy and life due to its complications [20].Therefore, it is essential to identify the relevant risk factors contributing to VTE, which can help to form strategies to prevent VTE and improve the survival prognosis of women with endometrial cancer.

The present study was conducted on the basis of 8 observational studies, indicating that VTE was a relatively common complication in endometrial cancer patients after surgery. The results revealed that the pooled accidence of VTE in endometrial cancer was about 7% in endometrial cancer patients with substantial heterogeneity. In view of the huge heterogeneity may weaken the quality of the pooled estimate, we subgroup the study based on the human race. The heterogeneity didn't reduce due to the other confounding factor such as sample size, publication time and NOS score.

The associated risk factors for developing VTE in cancer patients can be grouped into patient-related factors, tumor-related factors, treatment-related factors, and biomarkers [21]. The present study identified relevant risk factors associated with postoperative VTE in endometrial cancer patients including age>60, tumor size in uterine cavity(≥60mm), tumor extension (CT/MRI), massive ascites, clear cell cancer, advanced stage and CA125(≥35U/ml), which can help clinical physicians to make decision to help manage the specific population of relevant specific risk. For the prevention of postoperative VTE, physician guided patients wear elastic stockings after surgery or applied anticoagulant treatment by low molecular weight heparin [22].

We identified advanced age as patient-related factors associated with VTE after operation in endometrial cancer. A number of researchers have found that the age was an effective predictor for VTE in endometrial cancer patients. Krantz [23] and colleagues reported that increasing age were independent predictors of receiving unfractionated heparin. Bhayadia showed that age was a risk factor causing vascular damage, as aging and senescence induced by telomere shortening lead to endothelial dysfunction and increased the accidence of VTE [24].With increased age, women inevitable experienced menopause, which was the last menstrual period and indicated the end of women reproductive potential ability [25]. The research conducted by Huang [16] indicated the OR of menopause for VTE was 2.90 (95%CI: 1.028-8.19).However, the present meta-analysis showed that menopause was not associated with VTE in endometrial cancer patients, which need more researches included to explore exact the relationship between menopause and VTE. Another patient-related factor, the obesity not only impacts the body weight but also influences insulin resistance as well as blood coagulation [26]. Although a number of studies [8–10] have reported that the elevated body mass index (BMI) is a danger signal of venous thromboembolism in population, the present data in our study reveal that the BMI was not a certain factor of VTE for patients with endometrial cancer after operation. Considering the heterogeneity in current systematic review, the potential role of BMI should further be investigated.

Tumor-related factors including extensive tumor lesion,massive ascites, clear cell cancer and advanced stage were identified associated with VTE. The volume of ascites indicated the inflammatory conditions in tumors, which contribute to the development of venous thromboembolic events [27]. Moreover, the patients with malignant disease usually suffered with hypercoagulable state, which may be the reason of

massive ascites and contribute to VTE after operation [28]. Besides Nakamura [29] reported that plasma D-dimer level was significantly higher in advanced endometrial cancer patients (FIGO classification III and IV) than in early stage patients (FIGO classification I and II). The clinical value of D-dimer has been widely recognized as exclusion of VTE. We hypothesized that the D-dimer associated with advanced endometrial cancer, contributing to VTE formation in endometrial cancer. Histologically, clear cell carcinoma significantly increased the odds of VTE in endometrial cancer patients. Tissue factor (TF) is a trans-membrane glycoprotein which can trigger thrombosis and extensive expressed by clear cell carcinoma [30]. Cuff reported that transcription factor hepatocyte nuclear factor 1-beta (HNF1B) was a biomarker of clear cell carcinoma and contributed to cytoplasmic prothrombin expression, which ultimately increased thromboembolic events [31].The above finding illustrate the reasons of clear cell carcinoma increased the odds of VTE on cellular-level mechanism.

CA125 was identified as a biomarker leading to VTE in the present study. Not only it is a tumor marker but also an inflammatory marker, which could also reflect the inflammatory response [32]. As such, patients with higher levels CA125 are associated with more advanced cancers, which could explain the reason why advanced cancer correlated with postoperative VTE.

The treatment of post-menopausal women affected by endometrial cancer was hysterectomy, which can be conducted by laparoscopy or laparotomy. Compared with conventional laparotomy, laparoscopy can shorten operation time and increase postoperative recovery ability. If patients maintained for a long time with the intraoperative lithotomy position or stayed in bed for a long time, it can weaken the muscle pump of both lower limbs and the cause venous reflux disorder. However, the results revealed that the type of surgery didn't relate with VTE, which need more credible results to verify the authentic correlation between operation type and postoperative VTE.

There were a few disadvantages in the present research. First of all, although we did not apply any restrictions in the research area when we conduct literature search, the study only included researches in Asia, North Africa and UK. As a consequence, the results may not suitable for the non-involved areas, such as South Africa and Australia. Secondly, in spited of the well-rounded literature search, the underlying publication bias can't be neglected in this study. What's more, due to the inconsistent description of risk factors such as BMI>30, tumor size in uterine cavity(≥60mm) and CA125(≥35U/ml) in the included studies, so the relevant risk factors showed significant heterogeneity. Finally, the other influence factors such as peritoneal dissemination, operative time histology grade may be associated with VTE, which can't be identified.

Conclusion

The present study indicated that the pooled incidence of VTE after operation was approximately 7% in endometrial cancer patients. A number of factors were effective predictors for surgery-related VTE including female elderly, large size of tumor, advanced endometrial cancer,massive ascites, elevated CA125 and special histology. Further superior quality studies should be noticed to investigate the

effective strategies for surgery-related VTE in endometrial cancer patients. It is possible that the factors identified in our study could ultimately be used in a predictive model to identify patients with endometrial cancer who are at high risk for VTE.

Abbreviations

VTE
Venous Thromboembolism
FIGO
The International Federation of Gynecology and Obstetrics
EC
Endometrial cancer (EC)
CI
Confidence interval
CNKI
China national knowledge infrastructure
NOS
Newcastle–Ottawa Quality Assessment Scale
OR
Odds ratios
BMI
body mass index.

Declarations

Ethics approval and consent to participate

Local ethics committee ruled that no formal ethics approval was required in the present meta-analysis.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

XZ wrote the manuscript and performed data analysis. XH and QW performed data search. YZ performed the study design and manuscript amendment. All authors corrected and proofed the final text. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

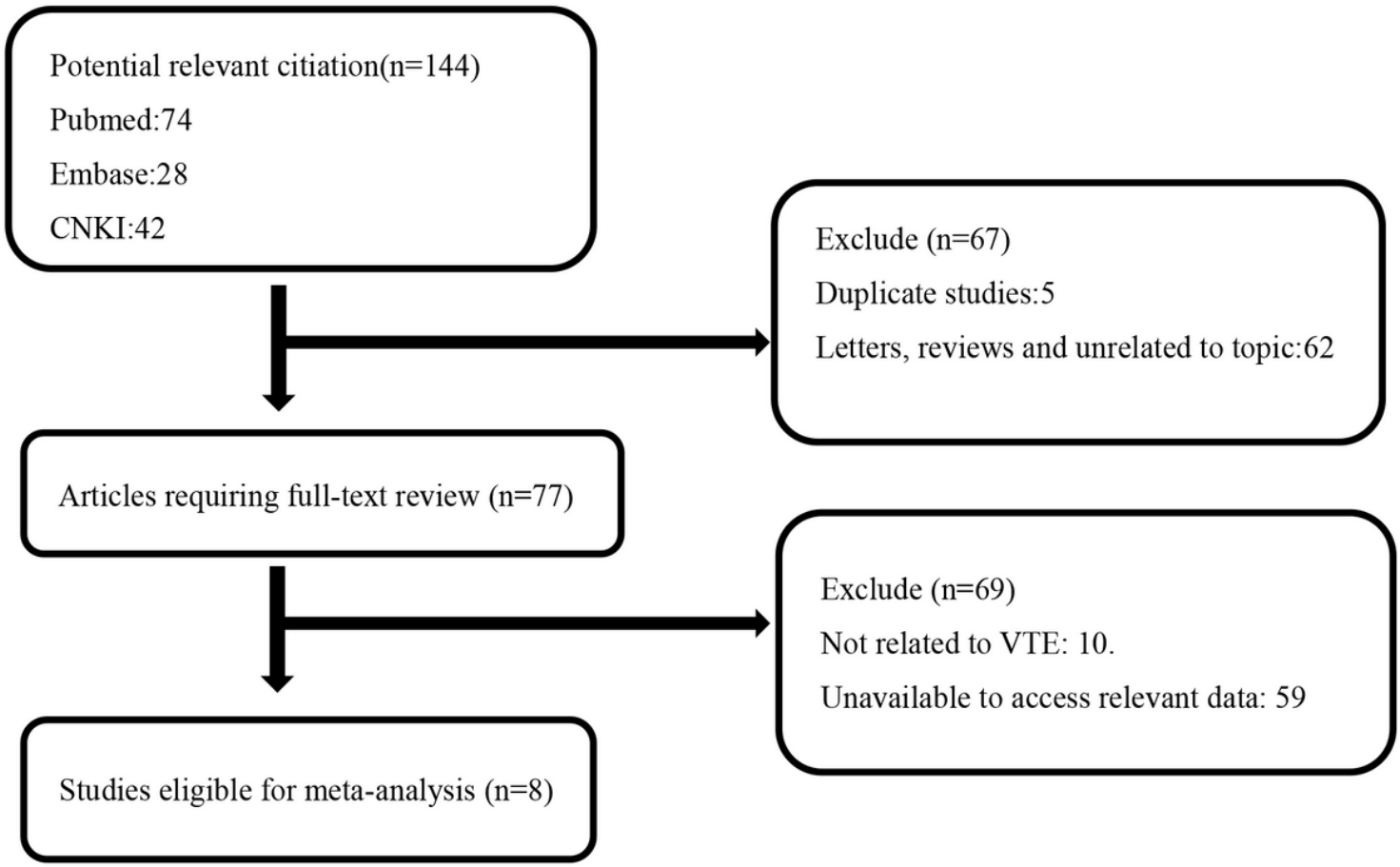

Figure 1

Flow diagram of the selection of relevant studies included in the meta-analysis

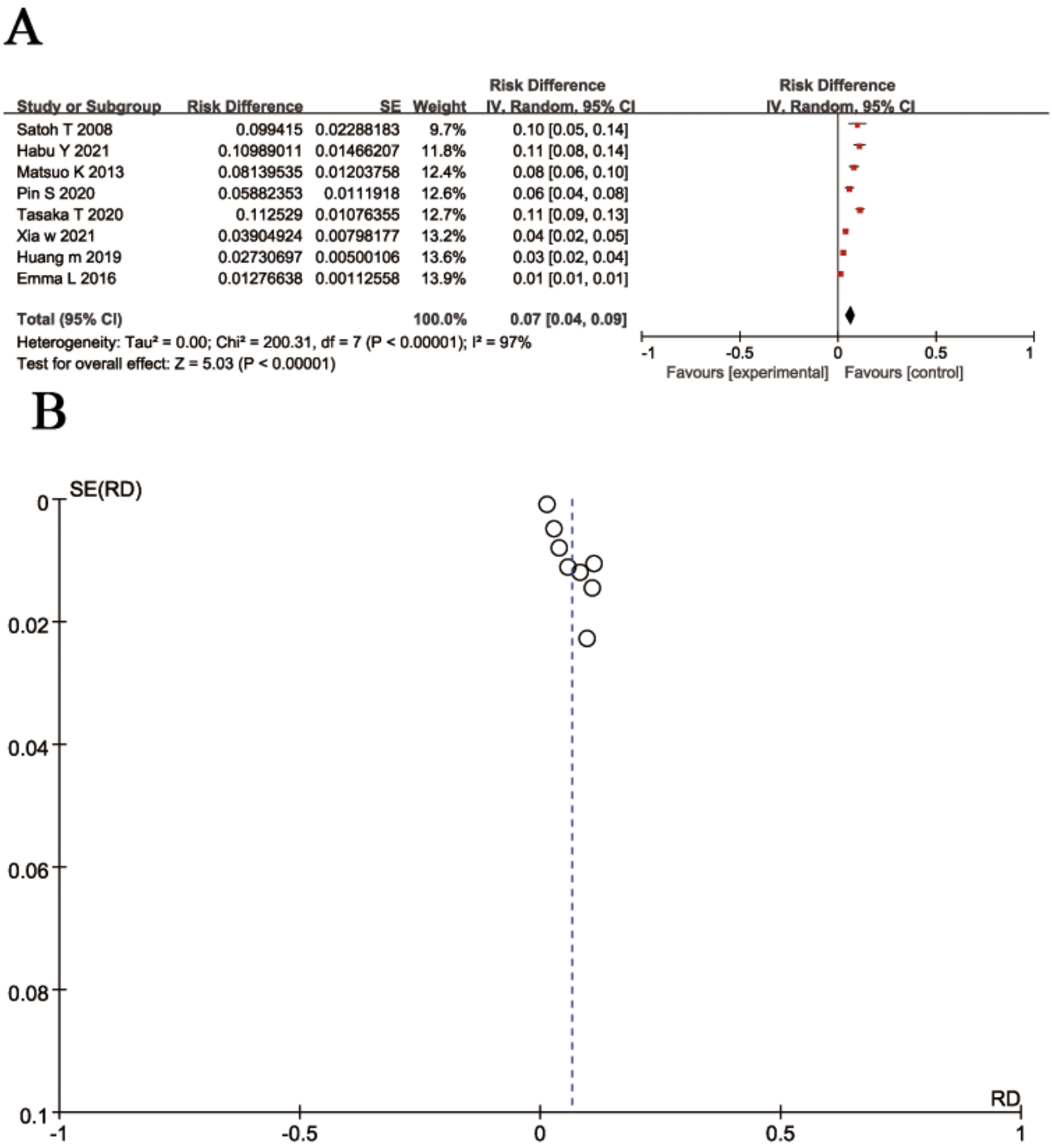

Figure 2

A Forest plots of postoperative VTE in endometrial cancer. Weights were from fixed-effects model. B Funnel plot was used to estimate publication bias from enrolled analysis.

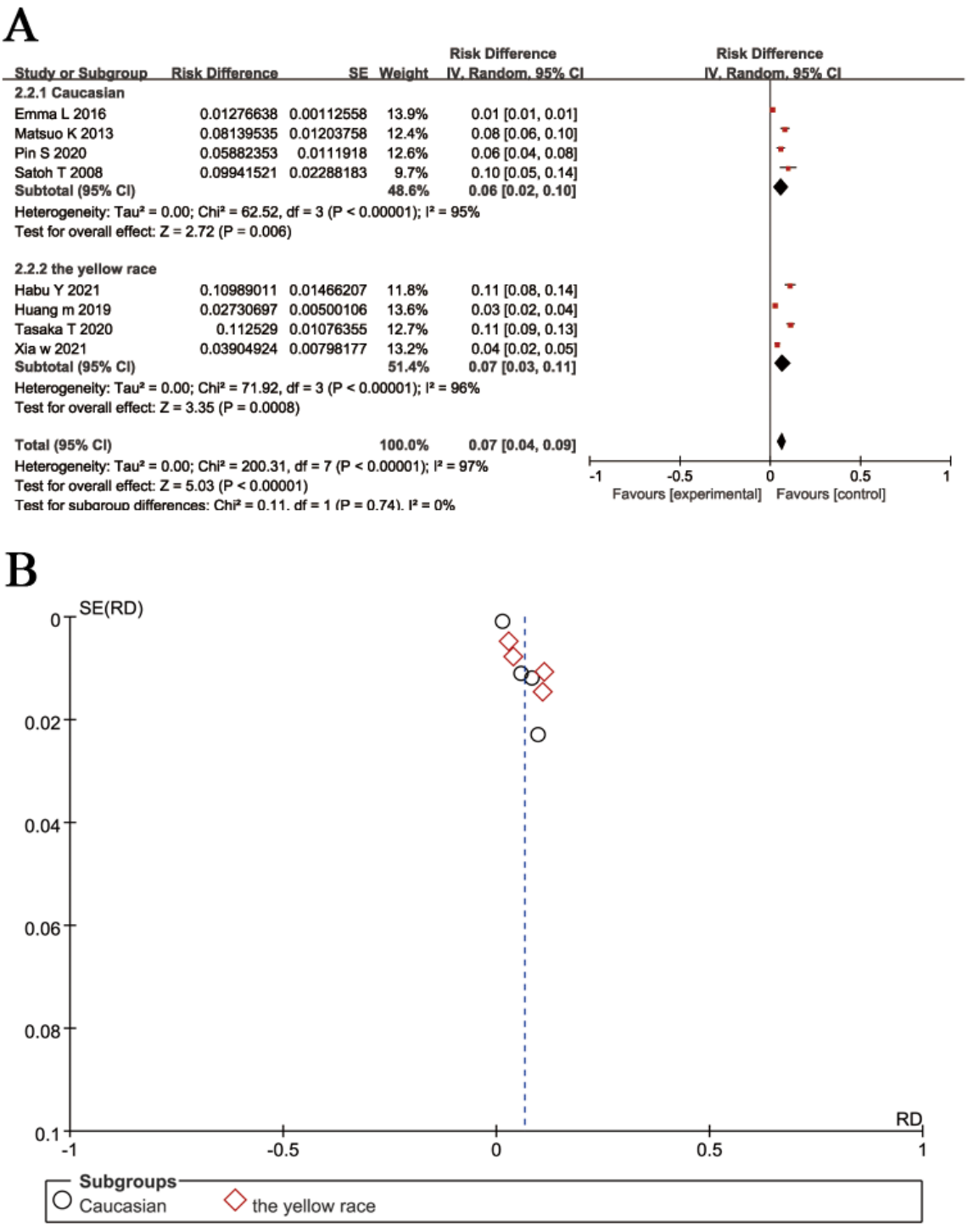

Figure 3

A Forest plots of subgroup analyses according to the human race (Caucasian and yellow race). Weights were from random-effects model. B Funnel plot was used to estimate publication bias from enrolled analysis.