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Brief Communication

Incidence and risk factors for venous thromboembolism in patients with ovarian cancer during neoadjuvant chemotherapy: a meta-analysis

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Abstract: In recent years, there has been increasing recognition of the relationship between neoadjuvant chemotherapy (NACT) in ovarian cancer and the incidence rate of venous thromboembolism (VTE). Some studies have suggested that NACT may be associated with a high risk of VTE in patients with ovarian cancer. To investigate this, we conducted a systematic review and meta-analysis of the incidence of VTE during NACT and its associated risk factors. We searched PubMed, Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and the International Standard Randomized Controlled Trial Number Register (ISRCTN) from their inception to September 15, 2022. We calculated the incidence of VTE as the event rate (%) and used logistic regression analysis to investigate pooled VTE rates. Risk factors for VTE were presented as odds ratios (ORs), and pooled ORs was estimated using the inverse variance method. We reported pooled effect estimates with 95% confidence intervals (CIs). Our review included 7 cohort studies with 1244 participants. Meta-analysis of these studies revealed a pooled VTE rate of 13% during NACT (1224 participants; 95% CI, 9%-17%), with body mass index identified as a risk factor for VTE during NACT in 3 of the included studies (633 participants; OR, 1.76; 95% CI, 1.13-2.76).

Keywords: Risk factor, venous thromboembolism, ovarian cancer, neoadjuvant chemotherapy, meta-analysis

Introduction

Malignancy has been linked to venous thromboembolism (VTE), which includes deep venous embolism and pulmonary embolism. VTE is a leading cause of mortality in patients with gynecologic cancer [1]. Additionally, thromboembolic events in patients with cancer are associated with a poor prognosis [2]. Compared to other gynecologic cancers, ovarian cancer has a higher prevalence of VTE, and the incidence of preoperative VTE ranges from 13.4% to 36.4% [1, 3-5]. According to a meta-analysis, the pooled incidence of postoperative symptomatic VTE is 3%, while that of asymptomatic VTE is 8% [6]. Another meta-analysis revealed that the pooled prevalence of VTE in patients with ovarian cancer undergoing chemotherapy is 9% [7]. Risk factors associated with VTE in ovarian cancer include major pelvic surgery, chemotherapy, age, previous VTE, and advanced stage [8].

Ovarian cancer is considered the most deadly gynecological cancer because it is usually detected at a late stage of disease progression. This often results in patients presenting with poor disease status, rendering them unsuitable for surgery, or with tumors that cannot be resected. Such patients are recommended neoadjuvant chemotherapy (NACT) as an alternative treatment. In recent years, a link between NACT in ovarian cancer and the frequency of VTE has been suggested. VTE incidence was the highest in patients who underwent NACT in addition to surgery compared to those who underwent surgery alone [9]. Several studies have reported that NACT in patients with ovarian cancer is linked to an elevated risk of VTE [10, 11]. Furthermore, Black et al. reported that patients with ovarian cancer who developed

VTE during NACT showed a decrease in overall survival [12]. Based on such findings, many authors have recommended the use of anticoagulation treatment in patients with ovarian cancer who are receiving NACT [11-14].

As far as we know, there was no meta-analysis reporting the incidence of VTE during NACT for ovarian cancer in the literature. This study aimed to examine the occurrence of VTE in patients with ovarian cancer undergoing NACT and identify any associated risk factors. The findings of this study highlight the importance of offering anticoagulation treatment during NACT for ovarian cancer.

Methods

Protocol registration

This meta-analysis was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), and it was registered with the International Prospective Register of Systematic Reviews (CRD42022379835).

Eligibility criteria

Our study included only experimental studies written in English and published in peer-reviewed journals, such as randomized control trials. We excluded non-experimental studies, including commentaries and narrative reviews. If the data subsets were published in multiple articles, we only considered the largest sample size. Our inclusion criteria specified that only patients with ovarian cancer receiving neoadjuvant chemotherapy prior to cytoreductive surgery would be eligible. We excluded patients with a history of VTE or those receiving anticoagulation treatment for a different indication.

Search strategy and study selection

We conducted a comprehensive search of PubMed, Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and the International Standard Randomized Controlled Trial Number Register (ISRCTN) from their inception to September 15, 2022. Additionally, we reviewed the reference lists of published reviews and retrieved articles for any additional relevant trials. The following search terms were used: “thromboembolism”, “chemotherapy”, “NACT”, “ovarian cancer”, “ovarian carcinoma”, and “ovarian neoplasm”.

Two researchers (LH and HC) independently assessed the eligibility of the studies based on titles and abstracts. All potential articles were then independently reviewed in full by the same two researchers for further evaluation. Any disagreements between the authors were resolved through discussion with a third independent researcher (AZ).

Data extraction

Two independent reviewers (CL and LH) extracted the data in duplicate and recorded them in a standardized database using a pre-defined extraction form that included methods, study quality, participants, and outcomes. The reviewers extracted the data while blinded to the names of the authors and institutions, sources of funding, and acknowledgments of the included trials. Double data entry was conducted by another researcher, HC. The collected data included general information such as authors, year of publication, country, study type, detailed information about the included participants, and outcome indicators.

The primary outcome, as pre-defined, was the rates of VTE, while the secondary outcomes were the risk factors for venous thrombosis during NACT.

Quality assessment

The quality of the included studies was assessed independently by two reviewers (LH and HC) using the Joanna Briggs Institute’s critical appraisal checklist for studies reporting prevalence data. Any differences that arose were resolved by discussion, and if no consensus was reached, a third review author (AZ) was involved. The checklist consisted of nine items used to evaluate the quality of the studies: (1) whether the sample frame was appropriate for the target population, (2) if the study participants were sampled appropriately, (3) if the sample size was sufficient, (4) if the study participants and settings were described in detail, (5) if data analysis was conducted with sufficient coverage of the identified sample, (6) if valid methods were used to identify the conditions, (7) if the condition was measured in a standard and reliable way for all participants,

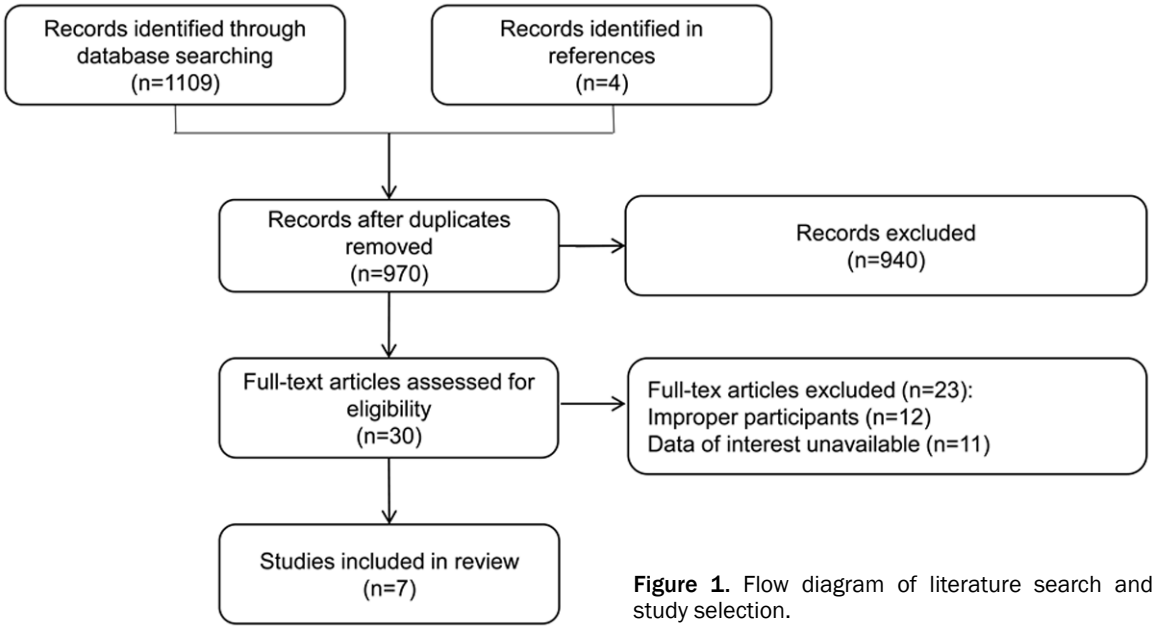

Figure 1. Flow diagram of literature search and study selection.

(8) if the statistical analysis appropriate, and (9) if the response rate was adequate and, if not, whether the low response rate was managed appropriately. Based on the percentage of "no" answers to the checklist, the studies were categorized as high-quality (≤ 49%), moderate-quality (50%-69%), or low-quality (≥ 70%). In a previous study, it was reported that higher total scores were associated with better quality and lower risk [15].

Statistical analysis

We used STATA 16.0 (Statacorp., College Station, TX) to conduct the meta-analysis. The incidence of VTE is presented as the event rate (%), and pooled VTE rates were investigated using logistic regression analysis. Risk factors for VTE were presented as odds ratios (ORs), and the pooled OR was estimated using the inverse variance method. Pooled effect estimates were reported with 95% confidence intervals (CIs), and statistical significance was set at $P < 0.05$. We assessed heterogeneity between studies using the I^2 test: $I^2 \leq 30\%$ was considered to indicate low heterogeneity, $30\% < I^2 < 50\%$ moderate heterogeneity, and $I^2 \geq 50\%$ high heterogeneity. Since there was moderate-to-high heterogeneity in most studies, we used a random-effects model to combine the data. Due to the small number of included studies, we did not use funnel plots to explore the possibility of small study effects. Although we planned to perform a subgroup analysis based on factors such as body mass index (BMI) and patient age, we could not do so because there were insufficient data for analysis.

Results

Study selection and characteristics

Figure 1 illustrates the process utilized for study selection. Initially, a total of 970 articles were identified, and removing duplicates, the titles and abstracts of the remaining articles were screened. Subsequently, 30 full texts were retrieved for further assessment. Of these, 23 articles were excluded due to inappropriate participant characteristics or unavailable data of interest. Eventually, 7 cohort studies involving 1244 participants were included in this review [10-14, 16, 17]. Among these, 4 studies were conducted in America, 1 in the UK, 1 in Canada, and 1 in China. The general characteristics of the 7 studies are summarized in **Table 1**. Moreover, all included studies were assessed as high-quality according to the critical appraisal checklist of the Joanna Briggs Institute (**Table 1**).

VTE rates during NACT

The meta-analysis of the included studies revealed that the pooled VTE rate in patients

Table 1. Characteristics of included studies

Study	Country	Age (median age)		Study span	Design	VTE during NACT	Total numbers of patients included	Stage	Quality assessment
		No VTE	VTE						
Black 2021 [12]	Canada	63.3	67.0	2013-2016	Single center retrospective cohort study	36	284	III-IV	High
Chokshi 2021 [16]	USA	63.13	64.08	2012-2018	Single center retrospective cohort study	25	90	III-IV	High
Oxley 2021 [13]	UK	63	67	2000-2015	Single center retrospective cohort study	33	259	III-IV	High
Chavan 2017 [17]	China	54.6		2012-2015	Single center retrospective cohort study	2	16	II-IV	High
Greco 2017 [14]	USA	No	70.1	2009-2014	Single center retrospective cohort study	13	112	III-IV	High
Basaran 2021 [10]	USA	69.1		2015-2018	single-center retrospective cohort study	27	233	III-IV	High
Salinaro 2020 [11]	USA	63.8	64.8	2000-2013	multicenter observational study	16	230	No	High

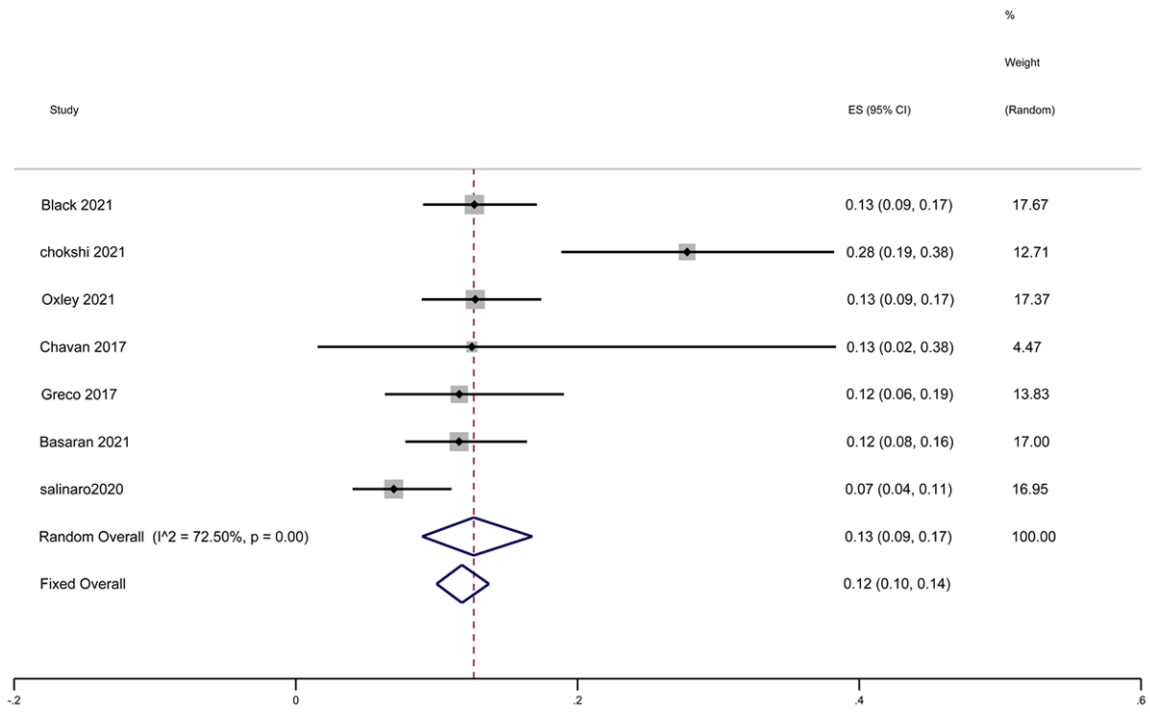

Figure 2. Forest plots of venous thromboembolism rate in patients with ovarian cancer during neoadjuvant chemotherapy.

undergoing NACT was 13% (1224 participants; 95% CI, 9%-17%; **Figure 2**).

Risk factors for VTE during NACT

According to the meta-analysis of the included studies, BMI was identified as a risk factor for VTE in patients undergoing NACT, based on data of 3 studies involving 633 participants. The OR was 1.76, with a 95% CI of 1.13-2.76 (**Figure 3A**). In contrast, age, smoking history, tumor stage, serous cancer, and CA125 levels did not show any significant association with VTE during NACT, as indicated by the respective studies included in the meta-analysis. The involved studies included 5 studies with 1,096 participants (OR=1.02, 95% CI 0.99-1.06; **Figure 3B**) for age, 2 studies with 349 participants (OR=0.77, 95% CI 0.34-1.74; **Figure 3C**) for smoking history, 3 studies with 633 participants (OR=0.93, 95% CI 0.62-1.41; **Figure 3D**) for tumor stage, 2 studies with 463 participants (OR=0.82, 95% CI 0.31-2.19; **Figure 3E**) for serous cancer, and 2 studies with 514 participants (OR=1.24, 95% CI 0.68-2.28; **Figure 3F**) for CA125 levels.

Discussion

Our meta-analysis found that VTE was a potentially common complication during NACT in women with ovarian cancer. Based on the 7 included studies, we estimated the pooled prevalence of VTE during NACT to be 13%. Additionally, our study analyzed the risk factors for VTE during NACT in women with ovarian cancer and found that BMI was associated with an increased risk of VTE.

Routine pharmacological thromboprophylaxis is recommended for all patients with malignant disease undergoing major surgical intervention and is suggested to commence preoperatively. However, the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update 2019 does not recommend routine pharmacological thromboprophylaxis for patients admitted solely for chemotherapy infusion [18]. The National Comprehensive Cancer Network and ASCO Clinical Practice Guideline Update 2019 recommend using the Khorana score to assess the risk of VTE in patients with cancer [18, 19]. The Khorana predictive model for chemotherapy-associated VTE in ovarian

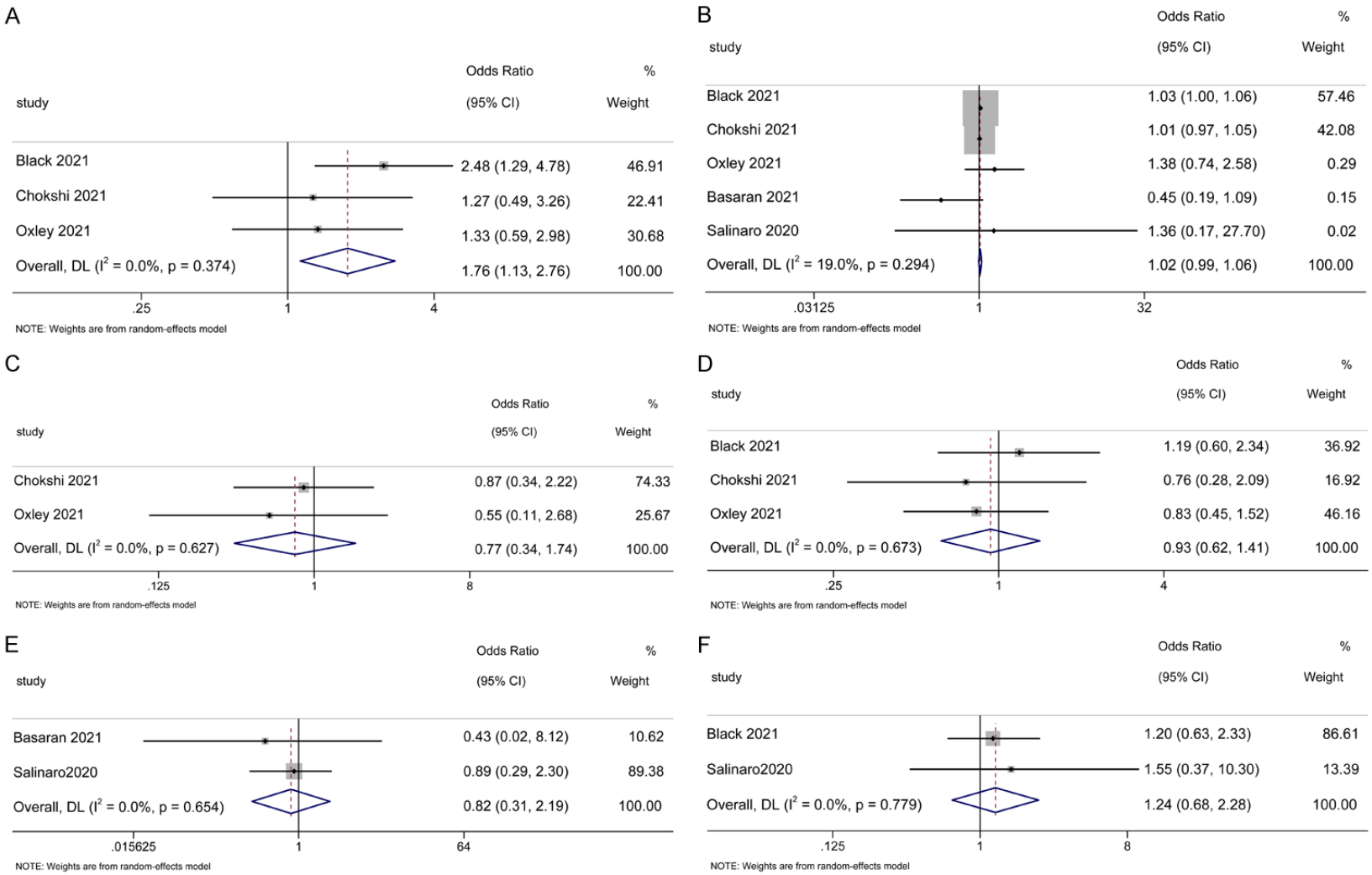

Figure 3. Forest plots of risk factors (A. Body mass index; B. Age; C. Smoking history; D. Tumor stage; E. Serous cancer; F. CA125) for venous thromboembolism in patients with ovarian cancer during neoadjuvant chemotherapy.

cancer assigns one point for the site of the primary cancer, and additional factors are assigned one point each, including pre-chemotherapy platelet count ≥ 350×10^9/L, hemoglobin level < 10 g/L, pre-chemotherapy leukocyte count > 11×10^9/L, and BMI ≥ 35 kg/m^2. A Khorana risk score of 0, 1-2, or ≥ 3 corresponds to a risk of symptomatic VTE of 0.3%-1.5%, 2.0%-4.8%, and 6.7%-12.9%, respectively [19]. A Khorana score of ≥ 2 before starting a new systemic regimen is recommended for anticoagulation treatment [18, 19]. Basaran et al. reported a 43.8% risk of VTE for patients with a score of 1 before chemotherapy; however, only 11.6% of patients with ovarian cancer developed VTE during NACT [10]. Based on our study's findings, which showed a high prevalence of VTE during NACT in patients with ovarian cancer, we suggest that the current anticoagulation treatment method may not be effective for these patients. The high VTE risk observed in our study (13%) is likely related to the high tumor burden and advanced age of patients undergoing NACT. Therefore, we recommend that the current anticoagulation treatment method be modified to better address the needs of patients with ovarian cancer undergoing NACT who are at a high risk for developing VTE.

A meta-analysis investigating the relationship between risk factors for perioperative VTE in patients with gynecological malignancies revealed that BMI was a significant risk factor for VTE [20]. Similarly, another meta-analysis reported a link between BMI and VTE risk during the postoperative period in patients with ovarian cancer [6]. However, previous studies exploring the association between BMI and VTE in patients with ovarian cancer receiving NACT have produced conflicting results. While Black et al. identified a BMI > 30 kg/m^2 as a high-risk factor for VTE in these patients on conducting a multivariate analysis, Oxley et al. and Chokshi et al. found no significant relationship between BMI and VTE in such patients. Our meta-analysis found a significant association between BMI and VTE risk in patients with ovarian cancer undergoing NACT. Obesity was identified as a major risk factor for VTE, resulting in a two- to three-fold increased risk [21], which is consistent with the findings of our study. The controversial results observed in previous studies may be attributed to the small size, and potential risk factors may not have reached statistical significance.

In our study, other factors were not found to be correlated with the risk of VTE in patients with ovarian cancer during NACT. The association between age with VTE during chemotherapy in ovarian cancer varies across different studies. For instance, Ye et al. conducted a meta-analysis that included 11 observational studies with 4759 patients with ovarian cancer and reported that advanced age was a potential risk factor for chemotherapy-related VTE [7]. Chokshi et al. also reported that older age was associated with an increased risk of VTE in patients with ovarian cancer undergoing NACT. However, Black et al., Oxley et al., Basaran et al., and Salinaro et al. concluded that age was not associated with VTE in such patients [10-13]. However, due to the small number of VTE cases in patients with ovarian cancer during NACT, these results should be interpreted with caution.

Previous studies have suggested that CA125 may be a risk factor for VTE in ovarian cancer, with different values of CA125 (> 500 IU/mL and > 760 U/mL) being reportedly correlated with the incidence of VTE [22, 23]. However, CA125 levels > 500 U/mL have not been found to be an independent risk factor for VTE in ovarian cancer during NACT [11, 12]. Further studies are needed to confirm the relationship between CA125 levels and the risk of VTE in ovarian cancer during NACT.

Regarding histology, previous studies have found no association between serous histology and the risk of VTE in ovarian cancer. A meta-analysis that included 20 cohort studies, including 6324 patients with ovarian cancer, concluded that serous histology was not a significant risk factor of VTE in ovarian cancer [24]. In our meta-analysis, two included studies also found no correlation between serous histology and the risk of VTE in ovarian cancer during NACT [10, 11].

A previous meta-analysis found that a history of smoking is associated with an increased incidence of postoperative VTE in patients with epithelial ovarian cancer [6]. However, two studies included in our study did not find a significant association between smoking history and the risk of VTE in patients with ovarian cancer

undergoing NACT [13, 16]. Due to the small number of VTE cases, further studies are needed to verify the relationship between smoking history and VTE risk.

In our study, cancer stage was not identified as a risk factor for VTE in ovarian cancer during NACT [12, 13, 16]. However, we hypothesized that advanced stage is associated with an increased risk of VTE in ovarian cancer [25, 26]. Since only two of the included patients with ovarian cancer had advanced stages (III and IV), advanced-stage disease did not act as a significant risk factor for VTE in ovarian cancer during NACT.

We rigorously followed the review protocol for study selection, data extraction, and data analysis. Two independent review authors conducted the study selection, data extraction, and risk of bias assessment, utilizing standardized data extraction forms. However, our review had several limitations. Certain critical information was unclear from some studies, and there was insufficient data for subgroup analysis on factors such as BMI and patient age. We attempted to contact the authors of the included studies to obtain additional information regarding missing data and individual patient data, but none of them responded. As a result, we relied only on data available in the published articles. We employed a random-effects model for our analyses, but it had some limitations, such as down-weighting large studies in the setting of statistical heterogeneity and assigning more equal weighting to the combined studies. Furthermore, all of the included studies were retrospective and thus had an increased risk of selection bias.

In conclusion, this systematic review and meta-analysis identified a pooled VTE rate of 13% (95% CI: 9%-17%) during NACT, particularly in those with a higher BMI. However, further research is needed through randomized controlled trials to investigate other potential risk factors for VTE during NACT.

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Disclosure of conflict of interest

None.

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