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REVIEW ARTICLE

Clear cell carcinoma of the ovary and venous thromboembolism: a systematic review and meta-analysis

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ABSTRACT

Objectives: As the second most common subtype of Epithelial ovarian cancers (EOCs), ovarian clear cell carcinoma (OCCC) is associated with a high rate of cancer-associated thrombosis. Previous studies revealed the wide range prevalence (6–42%) of venous thromboembolism (VTE) among OCCC patients. This study aimed to determine the prevalence of VTE among OCCC patients as well as factors affecting it.

Methods: PubMed, Scopus, Embase, and Cochrane Library databases were searched up to December 12th, 2022. Studies reporting venous thromboembolic events in women with clear cell carcinoma of the ovary were included. Demographic data, clinical, and paraclinical features of the patients were independently extracted by two reviewers.

Results: Out of the 2254 records, 43 studies were processed for final review. The qualified studies involved 573 VTE cases among 2965 patients with OCCC. The pooled prevalence of VTE among OCCC patients was 21.32% (95%CI=(17.38–25.87)). Most VTE events were reported in Japanese women (26.15%), followed by Americans (24.41%) and UK (21.57%), and Chinese (13.61%) women. VTE was more common in patients with advanced stages (37.79%) compared to those with early stages of the disease (16.54%).

Conclusions: Ovarian clear cell carcinoma is associated with a high rate of cancer-associated thrombosis. VTE events in OCCC patients were higher in advanced stages and Japanese women.

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Clear cell adenocarcinoma; venous thrombosis; thromboembolism; ovarian epithelial carcinoma; deep vein thrombosis

Introduction

EOCs have the highest mortality rate among all gynecologic cancers[1]. OCCC is the second most common subtype of EOCs, accounting for 25% and 10% of all EOC cases in the Japanese and Western population, respectively[2,3]. In Japan, the incidence of OCCC increased from 23.4% in 2002 to 29.1% in 2010[4]. OCCC is mainly manifested by a gross unilateral pelvic mass accompanied by thromboembolic events[5]. Compared to other histological subtypes of EOC, OCCC has a poorer prognosis, especially in advanced stages. It poorly responds to chemotherapy and platinum based regimens[6,7]. It is important to evaluate the frailty status of women with gynecological cancers to predict adverse outcomes and customize treatment strategies. Frail patients have a higher risk for postoperative complications[8].

Ovarian cancer is strongly associated with VTE events, including pulmonary embolism (PE) and deep vein thrombosis (DVT). VTE can lead to morbidity and mortality, prolonged hospitalization, increased healthcare costs, and worsened prognosis[9,10]. Furthermore, the risk of VTE in OCCC is 2.5 to 4 times higher than in other EOCs[5,11]. Previous studies revealed the wide range (6–42%) of the prevalence of VTE among OCCC patients, which may be due to differences in study design, methods used for VTE diagnosis, and heterogenicity in the studies[12,13]. Most VTE events are explored at the first examination of OCCC patients previous to the operation. Postoperative VTE could be a clue for the recurrence of the disease[5].

Tissue factor (TF) is an inflammatory cytokine with high expression in OCCC patients, which triggers the extrinsic pathway of blood coagulation and interleukin-6 (IL-6) production. These crucial components increase the risk of cancer-associated hypercoagulation[14,15].

This research hypothesized that other factors such as the disease stage, study type, surgery, and diagnosis methods of VTE might affect the prevalence of VTE in OCCC patients. Therefore, a meta-analysis was conducted to determine the prevalence of VTE among OCCC patients and explore factors affecting it.

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Methods

This systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [16]. This study was registered in the Systematic Review Registration: PROSPERO (ID: CRD42021287318). Studies reporting venous thromboembolic events in women with clear cell carcinoma of the ovary were included.

Search strategy

PubMed, Scopus, Embase, and Cochrane library were searched for cohort and case-control studies reporting venous thromboembolism in women with ovarian clear cell carcinoma published up to December 12th, 2022. The search strategy was as follows: ["Clear cell carcinoma" OR "Clear cell" OR "Clear cell adenocarcinoma" OR "Clear cell adenocarcinomas"] AND ["Cancer" OR "Cancers" OR "Neoplasm" OR "Neoplasia" OR "Neoplasias" OR "Tumor" OR "Tumors" OR "Tumour" OR "Tumours" OR "Malignancy" OR "Malignancies" OR "Malignant" OR "Carcinoma" OR "Carcinomas"] AND ["Ovary" OR "Ovaries" OR "Ovarian"] AND ["Emboli" OR "Embolus" OR "Embolism" OR "Thrombosis" OR "Thrombotic" OR "Thromboembolism" OR "Thrombus" OR "Thromboses" OR "Venous thromboembolism" OR "Deep vein thrombosis" OR "Pulmonary thromboembolism"].

Study selection

The records found through searching the databases were merged, and the duplicates were removed by Endnote X7 (Thomson Reuters, New York, NY, USA). Two reviewers independently screened the records based on title/abstract and full text to exclude irrelevant ones. Included studies met the following criteria: patients diagnosed with ovarian clear cell carcinoma and venous thromboembolism. Ovarian clear cell carcinoma was diagnosed based on the pathologic reports. Venous thromboembolism, including pulmonary embolism, DVT, and other site thromboses, was diagnosed based on imaging. Systematic reviews, meta- analysis, conferences, abstracts, editorials, reviews, cross-sectional studies, and case reports were excluded.

Data extraction

Variables such as prevalence, geographic location, study type, age, sex, body mass index (BMI), signs and symptoms of the patients, diagnostic laboratory data, imaging findings, treatments, and stages of the disease were extracted from each paper by two reviewers. Any disagreements were resolved based on the opinion of another reviewer. The quality of studies was evaluated with the Quality in Prognosis Studies Instrument (QUIPS).

Statistical analysis

The effect sizes (ES) with 95% confidence intervals (CI) were assessed. The meta-analysis of the overall prevalence and subgroups was conducted by the Cochran-Mantel-Haenszel method. The weight of each study in the pooled effect is the inverse of its variance. The I-squared criteria with a cut point of 45% were considered to capture the heterogeneity of the studies. The formal test was conducted for the significance of heterogeneity, and the P-value less than 0.05 was taken as the significant level. Consequently, the random effect approach was chosen. Publication bias was evaluated by funnel plot ($p < 0.05$ was considered the statistically significant publication bias; funnel plot asymmetry also suggests the bias). The random effect model (REM) was used to handle this situation. The statistical analysis and graphical presentations were conducted using the R statistical package. In this manner, we used the 'metaprop' command in the 'meta' package written in the R environment.

Results

Search results

Electronic database search resulted in 102, 1900, 238, and 14 records from PubMed, Scopus, Embase, and Cochrane library, respectively. Of 2254 records, 268 duplicates were removed. Screening the titles and abstracts resulted in the exclusion of 1788 records. Thus, the full-text papers of the remaining 198 records were reviewed independently by two reviewers for eligibility. After the full-text assessment, 155 studies were excluded (other languages ($n = 4$), review articles ($n = 14$), irrelevant content ($n = 97$), letter/editorial/conference ($n = 8$), case reports ($n = 17$), and unavailable full text ($n = 15$)). Eventually, 43 studies were processed for final review and meta-analysis. The process of study selection is described in supplementary material 1.

Characteristics and quality of included studies

Table 1 illustrates the characteristics of eligible studies. Publication dates of included studies ranged from 1996 to 2022. The qualified studies involved 573 women with VTE in 2965 OCCC patients from nine countries: 13 studies from Japan[14,17–28], ten studies from the United States of America (USA) [12,29–37], five studies from China[38–44], four studies from the United Kingdom (UK) [45–48], and the remaining from Australia[49,50], Korea[13,51], Denmark[52], Germany[53], Canada[54], and Thailand[55]. We categorized the studies into two groups to determine the effect of study design on the prevalence of VTE (Figure 1). The prevalence of VTE in cohort studies (28 studies) was 20.00% (95%CI = (15.29–25.72)), (heterogeneity: I^2=81%, τ^2=0.4980, $p < 0.01$), while the prevalence for case-control studies (12 studies) was 24.47% (95%CI=(18.28–31.94)), (heterogeneity: $I^2 = 76\%$, $\tau^2 = 0.2823$, $p < 0.01$). A test was performed for subgroup differences. The results demonstrated no significant difference in the VTE prevalence of cohort and case-control studies (random effects): ${\chi_1}^2$=1.06, df = 1, ($p = 0.30$).

Bias assessment

According to the funnel plot figure, the studies are distributed symmetrically around the reference line. In addition,

Table 1. Characteristics of included studies.

First author	Country	Published time	Type of study	Time span (year)	Quality of studies (QUIPS)
Bakhru	USA	2012	Cohort – R	10	Moderate
Shimizu	Japan	2019	Cohort – R	7	Moderate
Wield	USA	2018	Cohort – R	21	High
Kumar	USA	2017	Cohort – R	8	High
Supoken	Thailand	2014	Cohort – R	10	High
Goff	USA	1996	Case-Control	10	High
Fotopoulou	Germany	2009	Cohort – R	6	High
Zhu	China	2021	Cohort – R	10	High
Shigemi	Japan	2017	Cohort – R	1	Moderate
Diaz	USA	2013	Cohort – R	–	High
Saadeh	UK	2016	Case-Control	1.5	High
Saadeh	UK	2013	Case-Control	4	High
Saadeh	UK	2013	Cohort – R	5	High
Recio	USA	1996	Case-Control	36	High
Eltabbakh	USA	2006	Case-Control	4	Moderate
Lee	Korea	2020	Cohort – R	20	High
Kahr	Denmark	2019	Cohort – P	3	Moderate
Komatsu	Japan	2020	Cohort – R	5	Moderate
Takano	Japan	2018	Cohort – R	11	High
Cohen	USA	2017	Case-Control	18	High
Uno	Japan	2007	Cohort – R	–	High
Takasak	Japan	2019	Case-Control	17	High
Matsuo	Japan, USA, UK	2015	Case-Control	12	High
Yamanoi	Japan	2012	Case-Control	5	Moderate
Duska	USA	2010	Case-Control	10	High
Sakurai	Japan	2017	Cohort – R	6	High
Lim	Korea	2010	Case-Control	7	High
Tasaka	Japan	2020	Cohort – R	3	High
Greco	USA	2017	Cohort – R	5	Moderate
Zhou	China	2020	Cohort – R	2.5	Moderate
Kawaguchi	Japan	2012	Cohort – R	1	Moderate
Pather	Australia	2005	Cohort – R	16	High
Liang	China	2020	Cohort – R	3	Moderate
Ye	China	2015	Cohort – R	12	High
Ye	China	2015	Cohort – R	10	High
Satoh	Japan	2007	Cohort – P	3	Moderate
Ebina	Japan	2018	Cohort – P	6	High
Matsuura	Australia	2007	Case-Control	16	High
Samuel G.Oxley	UK	2021	Cohort – R	14	Moderate
Ryo Tamura	Japan	2021	Cohort – R	15	High
Kristin A. Black	Canada	2021	Cohort – R	3	Moderate
Jiayi Li	China	2022	Cohort – R	34	High
Yuhan Wang	China	2022	Cohort – R	4	High

the result of Egger's test showed no significant evidence of publication bias ($p = 0.27$) (supplementary material 2).

Demographic data

Out of 43 studies, six reported the age of the patients with a mean equal to 52.4 years old[28,33,38,41,46,51]. Three studies mentioned BMI with a mean level of 24.7 kg/m^2 [12,36,51] in women with ovarian clear cell carcinoma experiencing VTE (Table 2).

Signs and symptoms

Among the eligible studies, only four papers reported 17 cases of ascites (fluid more than 0.5 liters in the abdomen) out of 59 women[28,38,41,51]. Two studies reported 12 patients with lower limb edema as a sign of VTE[41,51]. Furthermore, three patients had dyspnea[51], and two patients had VTE as the first manifestation of OCCC[32] (Table 3).

Staging

Of 136 patients with stage I OCCC, 27 (19.85%) had VTE[12,36,38,50,52]. Of 31 patients with stage II OCCC, ten (32.2%) experienced VTE[12,36,50]. Of 99 patients with stage III OCCC, 41 (41.41%) had VTE[12,32,35,36,38,50,52]. Additionally, of 18 patients with stage IV OCCC, 9 (50%) experienced VTE[12,36,38,50] (Table 3). A meta-analysis was conducted to compare the prevalence of VTE in the early stages (stage I + II) with advanced stages (stage III + IV). Test for subgroup differences (random effects): $\chi_1^2 = 9.59$, df $= 1$ ($p < 0.01$) demonstrated a significant difference in the prevalence of VTE between patients with early stages disease and those with the advanced stages. The prevalence of VTE in early stages was 16.54% (95%CI=(10.71–24.66)), (heterogeneity: I^2=71%, τ^2=0.3778, $p < 0.01$). Meanwhile, the pooled prevalence of VTE in advanced stages was 37.79% (95%CI=(26.90–50.07)), (heterogeneity: I^2=68%, τ^2=0.3538, $p < 0.01$) (Figure 2).

Prevalence of VTE

Of 2965 patients with ovarian clear cell carcinoma included in the main analysis, 573 experienced VTE. Significant

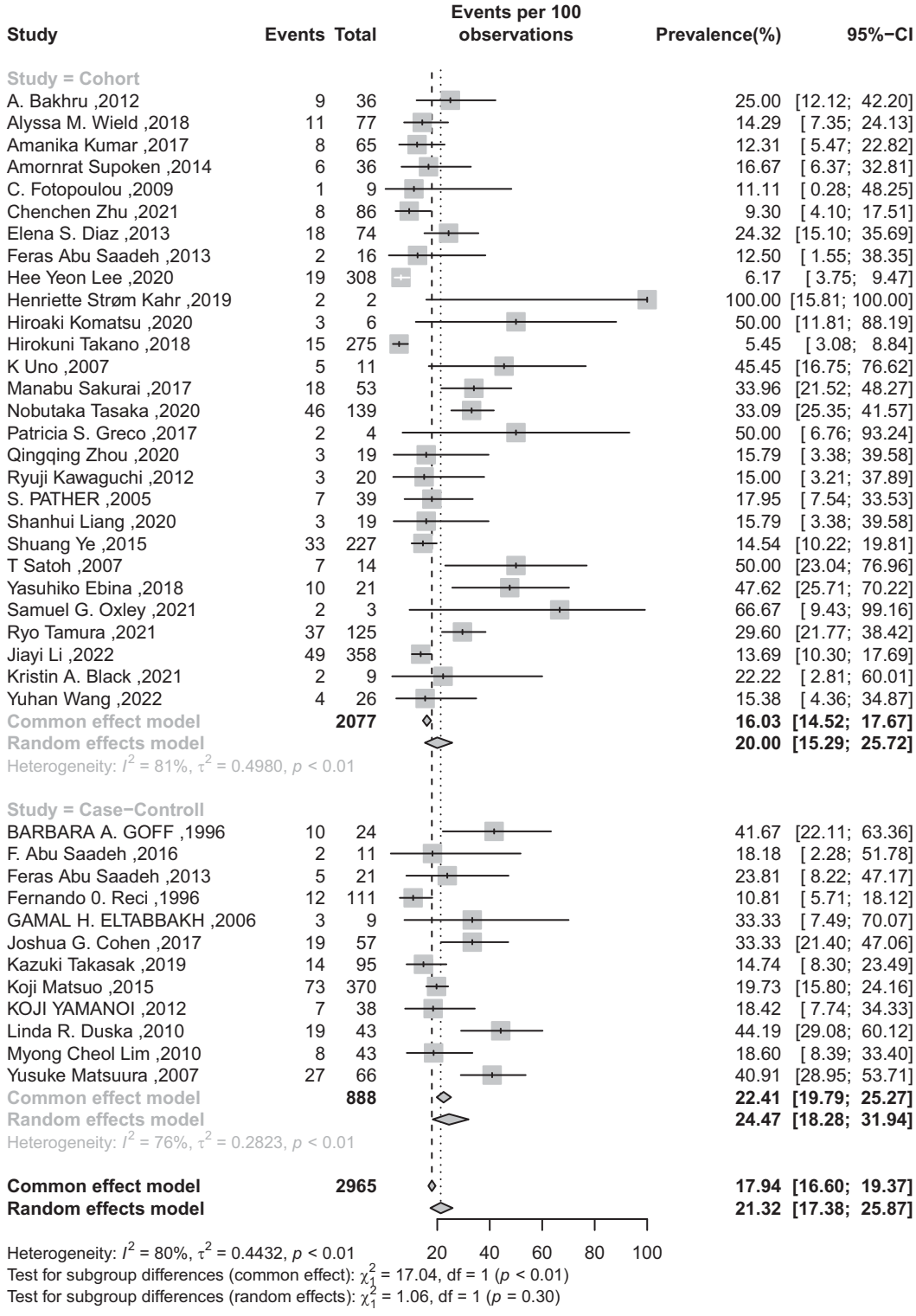

Figure 1. The prevalence of venous thromboembolism among OCCC patients based on the type of study.

Table 2. Characteristics of patients with OCCC and VTE based on evaluated studies.

Variable	No of study	
Mean age	6	52.4
Mean BMI (kg/m$^{2)}$	3	24.7 kg/m^2
Mean tumor size (cm)	3	11.01cm
Mean CA-125 (U/ml)	3	1023 U/ml

heterogeneity was observed among these studies (heterogeneity: I^2=80%, τ^2=0.4432, $p < 0.01$). The pooled prevalence of VTE in women with clear cell carcinoma of the ovary was 21.32% (95%CI=(17.38–25.87)). A random effect test was carried out for subgroup differences ($\chi_4{}^2$=14.92, df = 4, $p < 0.01$), which showed a significant difference between subgroups. Therefore, a subgroup analysis was performed based on the five geographic location (Figure 3).

Table 3. Different findings in patients with OCCC and VTE based on evaluated studies.

Sign and symptoms	Variable	No of study	[a]*n/N*	%
	Lower limb edema	2	12/41	29.26
	Dyspnea	1	3/8	37.5
	Ascites $>$ 0.5 L	4	17/59	28.81
	VTE as presenting symptom	1	2/10	20
Para clinic findings	Variable	No of study	*n/N*	%
	D-dimer $>$ 1 μg/mL	3	50/55	90.9
	DVT Alone	11	125/220	56.81
	PE Alone	9	45/215	20.93
Treatment options	Variable	No of study	*n/N*	%
	VTE before operation	7	42/106	39.62
	VTE after operation	6	34/101	33.66
Different Stages	Variable	No of study	*n/N*	%
	VTE in stage I	5	27/136	19.85
	VTE in stage II	3	10/31	32.2
	VTE in stage III	7	41/99	41.41
	VTE in stage IV	4	9/18	50

[a]n, number of patients with any variables; *N*, the total number of patients with OCCC and VTE.

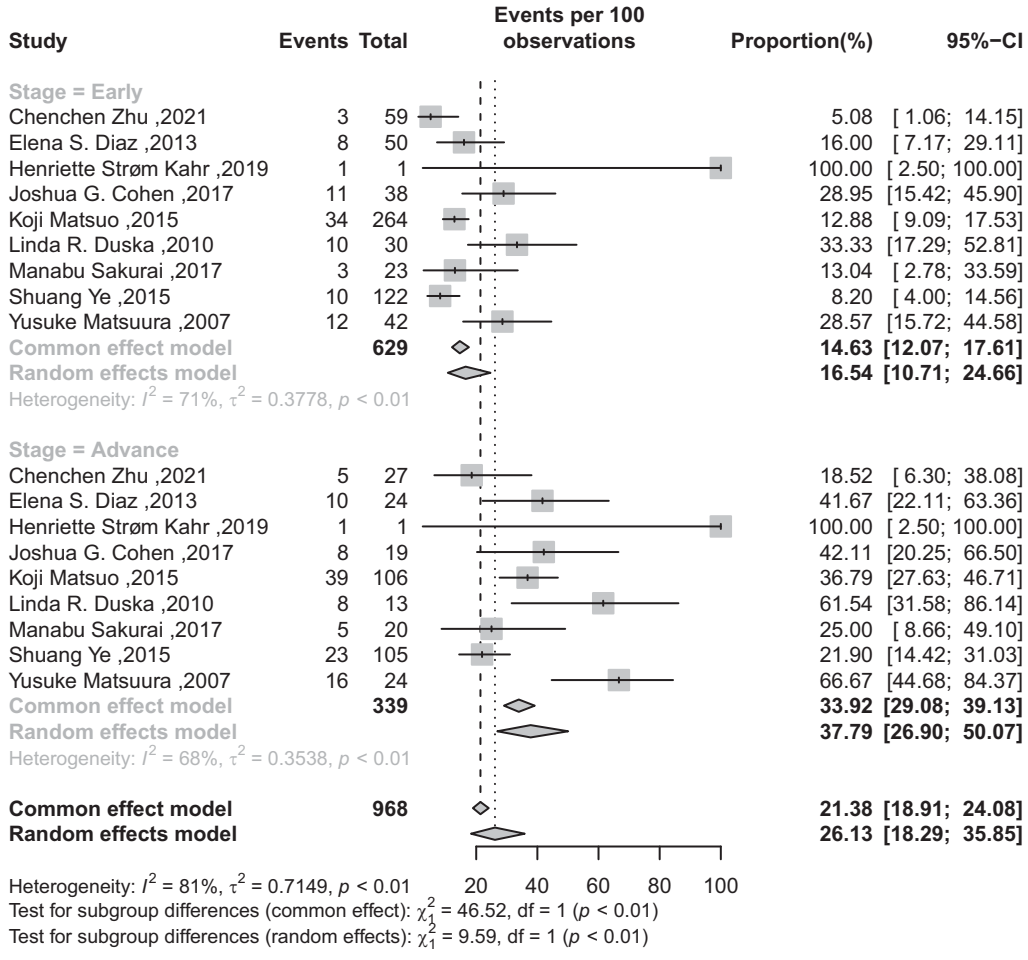

Figure 2. The prevalence of venous thromboembolism among OCCC patients based on the disease stage.

According to 10 studies from USA, 24.41% (95%CI=(17.13–33.54)) of American women with OCCC experienced VTE (I^2=75%, τ^2=0.3421, $p < 0.01$). Among 11 studies reporting Japanese OCCC patients, 26.15% (95%CI=(17.17–37.67)) had VTE (heterogeneity: I^2=86%, τ^2=0.6257, $p < 0.01$). The results from nine studies on the other geographic location showed that 19% (95%CI=(11.82–29.10)) of women with OCCC suffered from VTE (heterogeneity: I^2=83%, τ^2=0.4701, $p < 0.01$). Six Studies on Chinese population (heterogeneity: I^2=0%, τ^2=0, $p = 0.89$) revealed that 13.61% (95%CI=(11.31–16.28)) of Chinese women with OCCC had VTE. Based on four studies conducted in UK (heterogeneity: I^2=14%, τ^2=0, $p = 0.32$), 21.57% (95%CI=(12.37–34.89)) of UK women with OCCC experienced VTE.

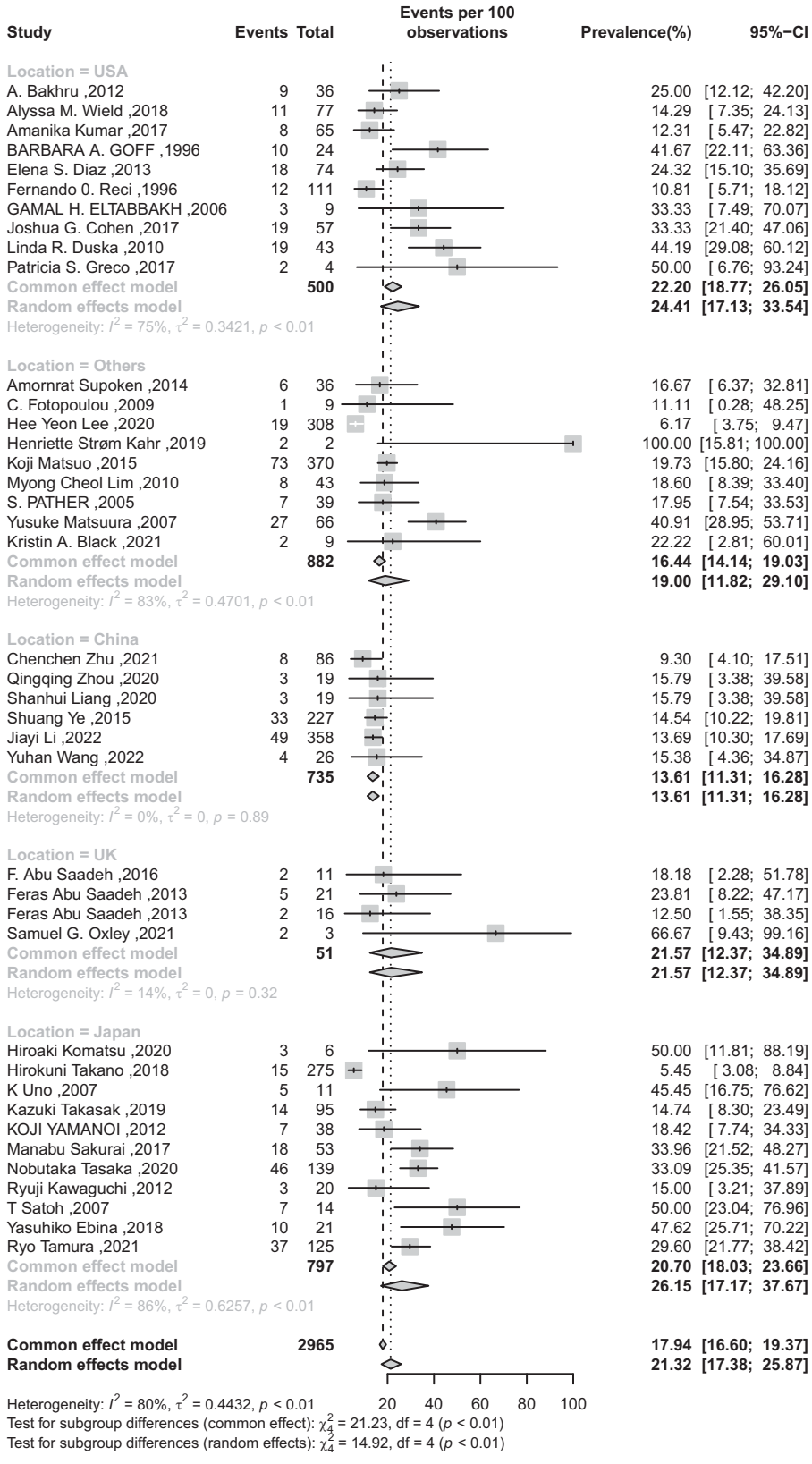

Figure 3. The prevalence of venous thromboembolism among OCCC patients based on geographic location.

Miscellaneous findings

The mean serum level of CA-125 was 1023 U/ml in 40 OCCC patients with VTE[38,41,51]. Furthermore, 50 out of 55 (90.9%) OCCC patients with VTE had D-dimer levels $>$ 1 μg/mL[14,28,38]. The size of clear cell tumors was reported for 46 cases with a mean value of 11.01 cm[28,41,51]. VTE presented as isolated DVT in 125 of 220 (56.81%) patients, while isolated PE occurred in 45 of 215 (20.93%) cases. Furthermore, nine studies indicated concurrent DVT and PE in 56 of 180 (31.11%) cases[12,27–29,36,38–41,49–51,56]. In terms of VTE occurrence time,

seven studies reported that 42 of 106 (39.62%) OCCC patients had VTE before the operation, while six studies showed that 34 of 101 (33.66%) OCCC patients had VTE events after the surgery (Table 3).

Discussion

In this comprehensive systematic review and meta-analysis of 43 studies, The pooled prevalence of VTE, severe medical condition that can lead to morbidity and mortality, was 21.32% among OCCC patients. Clear cell carcinoma of the ovary is a subtype of EOCs with a higher incidence of VTE than other ovarian malignancies[57]. The increased risk of VTE may be due to the higher expression of IL-6 and TF in OCCC compared with other ovarian tumors[14]. Tumor secretions, including TF and other coagulant components, are induced by activated oncogenes or inactivated tumor suppressors[58]. Despite a general agreement on the higher prevalence of VTE in women with OCCC compared to the other ovarian malignancies, the range widely varies in different studies. Duska et al. conducted a study in the USA[12] and reported the prevalence of VTE among OCCC patients as 42% [18/43], while Chenchen Zhu et al. (China) in a 10-year retrospective study reported a 9% prevalence of VTE in OCCC patients [8/86] [38]. Ryo Tamura et al. (Japan)[14] reported the prevalence of VTE among OCCC patients as 29.6% [37/125], while Hee Yeon Lee et al. (South Korea)[13] reported the prevalence of VTE among OCCC patients as 6.2% [19/308]. The VTE prevalence among OCCC patients varies in a wide range, whose result is obscure. Multiple aspects such as differences in the study design, early or advanced stages of the disease, prophylactic anticoagulotherapy, major pelvic surgery, geographical location, the method of VTE diagnosis, the time of diagnosis, and the heterogeneity between the studies might be involved.

Therefore, multiple analyses were performed based on the geographic location of studies, the tumor stage at the incidence of VTE, and study types. Among all locations, the pooled prevalence of VTE among OCCC patients was higher in Japan (26.15%), which was two times higher than China (13.61%). A meta-analysis by Kristin S. Weeks on the VTE risk in ovarian cancer patients[59] demonstrated that Japanese women with ovarian cancer had a higher risk of VTE events (20%) compared with Chinese women (8%). However, most studies demonstrating VTE events in OCCC were performed in Japan, while few studies were carried out in China. A study revealed that amplification of Zinc Finger Protein 217 (ZNF217) was noticeably higher in Japanese clear cell tumor samples as compared with Korean and German specimens. ZNF217 may promote neoplastic transformation by promoting cell survival during the telomeric crisis, leading to the survival of tumor cells and promoting later stages of malignancy[60]. VTE prevalence was higher among patients with advanced stages almost in all studies. Shuang Ye et al.[41] revealed the higher prevalence of VTE in the advanced stages of OCCC (21.9%) than in the early stages (8.2%). Moreover, Matsuura et al.[50] showed that VTE was more common in the advanced stages of OCCC (66.66% [16/24]) than in the early stages (28.57% [12/42]). These findings indicate a possible connection between the amplification of ZNF217 and the promotion of clear cell carcinoma to advanced stages in Japanese women compared to others. More VTE events are expected at more advanced cases.

In our finding, the pooled prevalence of VTE among patients with early and advanced stages of OCCC was 16.54% and 37.79%, respectively. This discrepancy could be due to the more extended hospitalization period, comorbidities, extra blood transfusion, extensive use of erythropoiesis-stimulating agents, and central venous catheters in advanced stages[58]. Furthermore, chemotherapy medications, such as bevacizumab, are a predisposing factor for VTE events[61]. Despite the higher prevalence of VTE in the advanced stages compared to the early stages, the expression of TF did not differ between the two stages[36,47]. Although cancer-associated thrombosis is a multifactorial phenomenon, the mechanism is still poorly understood. However, further studies are recommended to determine the association between the stages of clear cell carcinoma and VTE events.

Based on a study by Shuang Ye et al. 36% and 21% of OCCC patients experienced VTE before and after the operation, respectively[41]. Matsuura et al.[50] also reported the high prevalence of VTE before the operation due to pre-operative VTE prophylaxis. In contrast, Strøm Kahr et al. strongly suggest that surgery was associated with more than a three-fold VTE risk in patients with ovarian cancer[62]. We found that the prevalence of VTE before operation (39.62%) was not suggestively different from after operation (33.66%) which may be attributed to undiagnosed pre-operative thrombosis at the initial physical examination. Pre-operative VTE is mainly related to the type of EOC and comorbidities of the patient[44,63]. Severity of comorbidities can influence patient's general condition and consequently treatment outcomes[63]. In addition to the above parameters, postoperative VTE is affected by tissue damage secondary to the operation and poor conditions of the patient[44]. Moreover, pre-operative thrombocytosis is correlated with tumor stage and mortality. The interaction between platelets and cancer progression is bidirectional. Pro-inflammatory cytokines released by the tumors can lead to thrombocytosis. On the other hand, platelets release cytokines and chemokines, through which cancer cells extravasate from vessels in the metastatic niche and escape from the immune system[64]. It should be noted that platelets play a remarkable role in the VTE progression[65], a common cause of death in patients with ovarian cancer[41].

Strengths and limitation

Our study was comprehensive because we considered a more significant number of VTE events than in previous studies. The high heterogeneity of included studies remained high after subgroup analysis. Therefore, REM was utilized instead of the fixed-effect method for meta-analysis. The main advantage of REM is the aggregation of information,

which provides higher statistical power and more robust point estimates than estimates from a single survey.

Some relevant articles might be unintentionally excluded despite searching multiple databases with proper querie. Also, we included published articles written in English, so there is a possible issue of language bias. One of the limitations of the present study was the lack of adequate studies from all geographical location to compare with each other. Moreover, included articles had different study designs that can interfere with comparison and overall conclusions. Only few studies reported clinical (e.g. dyspnea, lower limb edema) and paraclinical (e.g. D-dimer, CA-125, and tumor size) features of the patients. Thus, due to the limited number of patients we could not consider the above variables in meta-analysis.

Conclusions

The pooled prevalence of VTE events among women with OCCC was estimated to be 21.32%. The highest rate of VTE events among women with OCCC was obtained in Japanese patients. The prevalence of VTE was higher in the advanced stages of the disease rather than in early stages. Further studies are required to determine the relationship between cancer-associated thromboembolism and multiple factors affecting the hypercoagulopathy states.

Transparency

Declaration of funding

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Declaration of financial/other relationships

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

S.Ramezani, K.Namakin collected the data. A.Sheidaei and K.Gohari analyzed data and interpreted the results. H.Najafiarab conceptualized the study, interpreted the results, and critically reviewed the manuscript. F. Farzaneh designed the study and reviewed the final approval of the version to be published. H. Didar, designed the study, interpreted the results, and drafted the manuscript. All authors agreed to be accountable for all aspects of the work.

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