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Incidence and risk factors of silent deep venous thromboembolism before interval debulking surgery in ovarian cancer patients, a tertiary centre experience

Mohamed Abdelkhalek *, Basel Refky, Mohammed Zuhdy, Omar Hamdy, Mohamed Hamdy, Khaled Gaballa, Amr Elalfy

Surgical Oncology Department, Oncology Center Mansoura University, Mansoura, Egypt

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ABSTRACT

Objective: To determine the prevalence and risk factors for the development of asymptomatic venous thromboembolism (VTE) in ovarian cancer patients who underwent interval cytoreductive surgery after finishing neoadjuvant chemotherapy.

Methods: This is a prospective observational trial. Female patients with pathologically proven ovarian cancer who received neoadjuvant chemotherapy without clinical evidence of VTE were included.

Results: A total of 107 patients were enrolled in this study. The mean age was 53.37 years, and the mean body mass index (BMI) was 34.11 kg/m^2. Seven (6.5 %) patients suffered from silent VTE, as documented by bilateral Doppler ultrasound in the pre- and postoperative settings. The mean age of the patients in the VTE group was 56.17 years, and their mean body mass index was 31.71 Kg/m^2. Their median serum CA125 concentration was elevated (325.6 units/ml). On the other hand, the median D-dimer level was elevated by 678 ng/ml fibrinogen equivalent units (FEUs) in the same group of patients. In the present study, comorbidities did not influence the incidence of VTE, as the 7 patients who were diagnosed with VTE did not have any comorbidities. Most of the patients who were diagnosed with serous adenocarcinoma (71.4 %) or stage IIIc disease (57.1 %) were most likely to develop VTE.

Conclusion: Silent VTE is more prevalent in patients with advanced-stage ovarian cancer and serous carcinomas.

1. Introduction

Venous thromboembolism (VTE) and pulmonary embolism (PE) are multifactorial events that are affected by many variables (Zhang et al.,2018). Malignancy is deemed a strong risk factor for VTE (Salinaro, 2020). Among cancer patients, the second major cause of death is VTE (Zhang et al.,2018; Ikushima et al., 2016; Pookcharoen et al., 2018); which affects 25–38 % of gynaecological cancer patients with the highest risk reported in ovarian cancer patients (Salinaro, 2020; Shafa, 2023; Ye et al., 2021).

The association between neoplastic disease and thromboembolic disorders was first reported by Trousseau in 1865, who described thrombophlebitis that occurred with visceral malignancy; subsequently, it was termed Trousseau syndrome (Zhang et al.,2018; Chavan et al., 2017; Takano, 2018). Thereafter, VTE was considered to be a disastrous event that could be fatal. Although sincere efforts have been made to minimize its incidence in cancer patients, its incidence has increased in recent years (Zhang et al.,2018).

According to past studies, DVT and PE affect gynaecologic cancer patients by 7–45 % and 1–2.6 %, respectively (Zhang et al.,2018). The incidence of VTE in ovarian cancer patients is the highest, ranging from 10-22 % (Zhang et al.,2018; Pookcharoen et al., 2018; Ye et al., 2021; Greco, 2017).

Cancer-related VTE has been linked to several risk factors. These factors can be categorized as patient-related factors, cancer-related factors and treatment-related factors. Patient-related factors include age at diagnosis, increased BMI, and comorbidities, such as hypertension, diabetes mellitus, and cardiovascular diseases. Cancer-related factors include pathological type, serum levels of tumor markers, tumor size, and tumor site especially pelvic ones that can compress pelvic veins resulting in stasis which could increase the risk of VTE staging. On the other hand, treatment-related factors include increased

* Corresponding author.
E-mail address: mabdelkhalek@mans.edu.eg (M. Abdelkhalek).

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operative time, prolonged postoperative immobilization, chemotherapy, and radiation therapy (Pookcharoen et al., 2018).

Several studies have demonstrated that the D-dimer level (DD) is a chief prognostic factor for VTE in ovarian cancer patients before treatment, since d-dimer is a degradation product of fibrin, it has high specificity for fibrin production and stabilization as the confounding factor of thrombosis (Cho et al., 2020; Satoh, 2007).

Several consequential morbidity events can follow VTE, including prolonged hospitalization, diminished respiratory function, post-thrombotic syndrome, VTE recurrence, haemorrhagic complications due to anticoagulation therapy and delayed cancer treatment (Kuderer et al., 2009; Lyman and Edin, 2013). Moreover, the incidence of mortality increases among cancer patients with VTE (Kuderer et al., 2009; Lyman and Edin, 2013; Wang and Huang, 2019). In his retrospective study, Khorana reported that the in-hospital mortality rate was 2- to 5-fold greater in cancer patients hospitalized with thromboembolism than in patients without thromboembolism (Lyman and Edin, 2013). Patients with cancer related thromboembolism are at higher risk for recurrence and have poorer prognosis thanks to significantly lower median overall survival rates (Wang and Huang, 2019). This study aimed to detect the incidence and analyse the risk factors for VTE in ovarian cancer patients who were treated with interval debulking surgery after neoadjuvant chemotherapy.

2. Patients and Methods

A prospective observational trial was conducted in Oncology Center Mansoura University (OCMU), Egypt from May 2022 to May 2023. The study was approved by the ethical and institutional Research Board committee under the code number (R.21.11.1513), and fully informed consent was taken from all the participants. Throughout the study, patients with pathologically proven ovarian cancer who received neoadjuvant chemotherapy were included.

Patients who had a history of VTE, patients receiving anticoagulation therapy or who were diagnosed with non-gynaecologic cancer or concomitant malignancy at the time of study recruitment were excluded from the study.

We relied on Doppler ultrasound before surgical interval debulking to determine the incidence of DVT.

DVT was defined as radiological evidence of thrombosis by compression ultrasonography with Doppler imaging during the perioperative period (from 2 weeks preoperative to 6 weeks postoperative) in the absence of consistent signs and symptoms in admission history and physical examination.

The main outcomes of this study were the incidence and predictors of silent VTE after neoadjuvant chemotherapy for ovarian cancer.

2.1. Statistical analysis

We used IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. IBM Corp., Armonk, NY, for analysis of the study data. Qualitative data were described using numbers and percentage, while the quantitative data were represented using either the median and range for non-parametric data or the mean and standard deviation for parametric data after performing normality testing using the Kolmogrov-Smirnov test. The significance of the obtained results was judged at the 0.05 level.

Qualitative data were analysed by performing a chi-square test for comparisons of 2 or more groups, and Fisher's exact test was used as a correction for the chi-square test when more than 25 % of cells had a count less than 5 in 2*2 tables.

Parametric tests were used to analyse the quantitative data. We used Student's *t* test to compare two independent groups and the non-parametric Mann-Whitney *U* test to compare two independent groups.

3. Results

A total of one hundred seven patients were included in the study. The mean age was 53.4 +/- 14.1 years, and the mean body mass index was 34.1 +/- 7.7 kg/m^2 (Table 1). Thirty-nine (36.4 %) patients had associated comorbidities, including hypertension, diabetes mellitus and cardiovascular disease.

Histopathology according to the WHO 2020 classification revealed that most of the patients had high-grade serous carcinoma (74.8 %), dedifferentiated carcinoma (7.5 %), and 4 patients had mucinous carcinoma (3.7 %), as shown in Table 1.

According to the tumor staging results shown in Table 1, 6 patients had stage II disease (5.6 %), 82 had stage III disease (76.6 %), and 19 had stage IV disease (17.7 %). Among our cohort, there were 7 (6.5 %) cases of subclinical VTE. The relationship between tumor stage and the incidence of DVT among the studied patients is shown in Fig. 1.

In this study, the median CA125 concentration was 412.3 (range 27.7–2175) units/ml, and the median D-dimer concentration was 401 (range 286–874) ng/ml FEU in the study group.

Out of the 107 patients included in this analysis, only 7 (6.5 %) experienced VTE, as evidenced by pre- and postoperative bilateral venous Doppler ultrasound. The mean age of the participants was 56.2 +/- 7.1 years, and their mean body mass index was 31.7 +/- 9.6 years. The patients who were diagnosed with VTE had a median CA125 concentration of 325.6 (245.3–2175) units/ml and a median D-dimer concentration of 678 (409–874) ng/ml on FEU (Fig. 2).

In the present study, comorbidities did not affect the rate of VTE. Interestingly, none of the 7 affected patients had any comorbidities. Most of the patients who were diagnosed with serous adenocarcinoma (71.4 %) or stage IIIc disease (57.1 %) were most likely to develop VTE (Table 2 and 3).

4. Discussion

Several studies have reported a strong, well-established relationship between ovarian cancer and VTE (Zhang et al.,2018; Ye et al., 2021; Wang and Huang, 2019). VTE was mostly detected in ovarian cancer patients either at presentation or during receiving neoadjuvant therapy. Based on the best available evidence from literature and guidelines, prophylactic anticoagulation for ovarian cancer while receiving neoadjuvant chemotherapy could reduce the risk of venous thromboembolic events (Black et al., 2024).

In the present study, 7 out of 107 ovarian cancer patients (6.5 %) were diagnosed with silent VTE, 2 patients were excluded due to presence of clinical DVT.

Table 1
Clinicopathologic characteristics.

	n = 107	%
Age/years	53.37 ± 14.14	
mean ± SD (min–max)	(11.0–73.0)	
BMI(Kg/m2)	34.11 ± 7.66	
mean ± SD(min–max)	(22.0–56.0)	
Poorly & de-differentiated adenocarcinoma	8	7.5
serous adenocarcinoma	80	74.8
Clear cell carcinoma	4	3.7
Mucinous carcinoma	4	3.7
Immature cystic teratoma. Grade III	3	2.8
Malignant mixed mullerian tumor	3	2.8
Moderate differentiated adenocarcinoma with papillary	2	1.9
Papillary sero-mucinous adenocarcinoma	3	2.8
Stage		
2b	6	5.6
3A	4	3.7
3B	15	14.0
3C	63	58.9
4A	15	14.0
4B	4	3.7

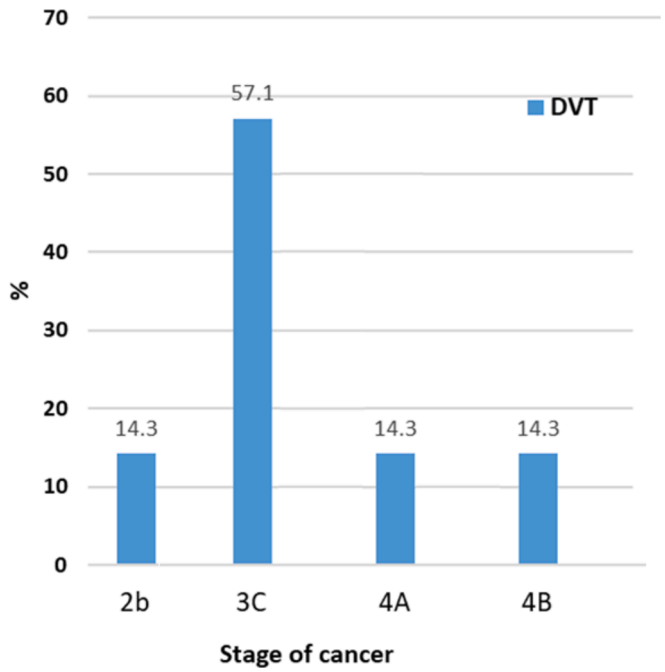

Fig. 1. Relation between tumor stage and incidence of DVT among studied cases.

In a Chinese study, Zhang *et al.* reported that age greater than 55 years, larger tumours, elevated D-dimer levels and thrombocytosis were independent risk factors for VTE (Zhang et al.,2018). Although the mean age of the 7 patients with silent VTE in our study was 56.7 years, age was not a significant factor in the incidence of VTE in patients with ovarian cancer.

According to our study, body mass index is not a predictor of the development of VTE in ovarian cancer patients, where the mean BMI of patients with VTE was 31.7 kg/m^2. L. Ye, L. Cai, Y. Fu *et al.* did not report BMI as a risk factor for VTE in patients with ovarian cancer (Ye et al., 2021). In contrast, Fotopoulou *et al.* reported a 3.2-fold increase in VTE in ovarian cancer patients who had BMIs greater than 30 kg/m^2 (Fotopoulou et al., 2021).

In the present study, we did not find an association between comorbidities such as hypertension (HTN) or diabetes mellitus (DM) and cardiovascular events or the development of VTE in ovarian cancer patients. This finding coincides with Takono *et al.*'s study, which did not report a correlation between underlying comorbidities, including HTN, hyperlipidaemia or DM, and VTE (Takano, 2018). On the other hand, X. Wang *et al.* reported that patients with HTN and DM were more susceptible to VTE, suggesting better control of their blood pressure and blood sugar levels (Wang and Huang, 2019).

Notably, the histopathological type of ovarian cancer may impact the incidence of VTE. Several studies have reported a strong association between clear cell ovarian carcinoma subtypes and VTE (Takano, 2018; Weeks et al., 2020). The possible cause is the significantly higher tissue factor (TF) expression in the clear cell ovarian carcinoma subtype than in the other histopathological subtypes, indicating an accelerated

Table 2
Relation between pathology and incidence of DVT among studied cases.

	DVT N = 7	NO DVT N = 100	test of significance#
Poorly & de-differentiated adenocarcinoma	1 (14.3)	7(7.0)	P = 0.478
serous adenocarcinoma	5 (71.4)	75 (75.0)	P = 0.833
Clear cell carcinoma	0	4(4.0)	P = 1.0
Mucinous carcinoma	0	4(4.0)	P = 1.0
Immature cystic teratoma grade III	0	3(3.0)	P = 1.0
Malignant mixed mullerian tumor	1 (14.3)	2(2.0)	P = 0.185
Moderate differentiated adenocarcinoma with papillary	0	2(2.0)	P = 1.0
Papillary sero-mucinous adenocarcinoma	0	3(3.0)	P = 1.0

#used test Fischer exact test.

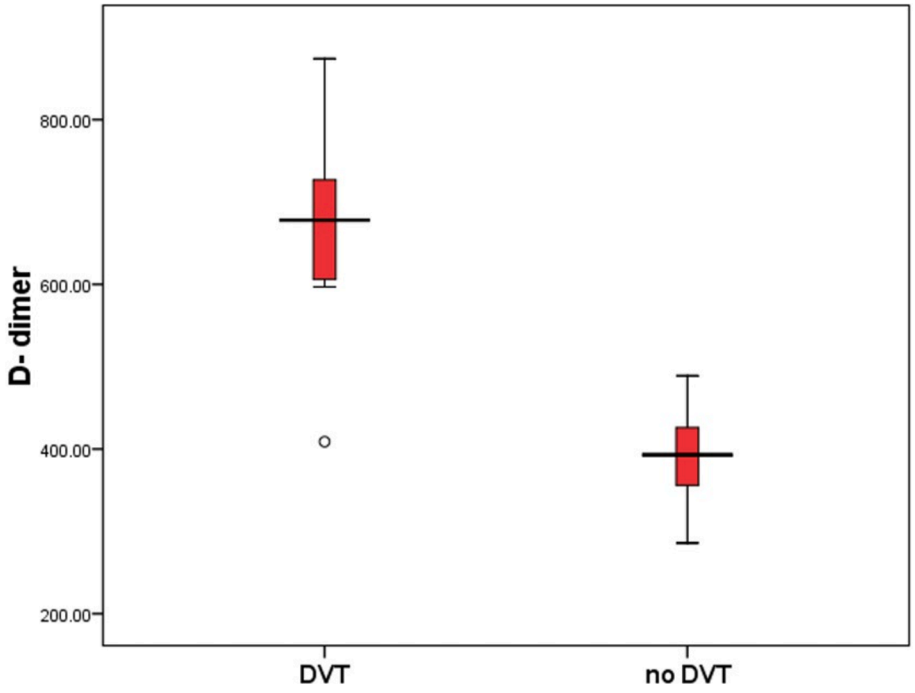

Fig. 2. Box and Whisker plot showing median interquartile range and minimum and maximum d dimer value among studied cases.

Table 3
Relation between tumor stage and incidence of DVT among studied cases.

	DVT N = 7	NO DVT N = 100	test of significance
Stage			
2b	1(14.3)	5(5.0)	P = 0.302
3A		4(4.0)	P = 1.0
	0		
3B	0	15(15.0)	P = 0.269
3C	4(57.1)	59(59.0)	P = 1.0
4A		14(14.0)	P = 0.983
	1(14.3)		
4B		3(3.0)	P = 0.240
	1(14.3)		

used test: Fischer exact test.

extrinsic coagulation pathway (Satoh, 2007; Tasaka, 2020). In our study, 5 VTE patients were diagnosed with serous adenocarcinoma (71.4 %), but it is important to highlight the small number of patients with clear cell carcinoma enrolled (only 4 patients).

Our results showed that silent VTE was more prevalent in patients with advanced FIGO stage disease, as 57.1 % of the affected patients had stage IIIc disease. This was explained in a previous study in which the risk of DVT increased with advanced disease stage due to the biological aggressiveness of the tumor (Pookcharoen et al., 2018), increased immobility of these subgroups of patients (Kim et al., 2020), and a hypercoagulable state of malignancy (Chokshi et al., 2021).

5. Conclusion

In this paper we discuss the incidence of deep venous thrombosis before interval debulking in ovarian cancer patients. Although most of ovarian cancer patients either n this study or as reported in literature presents in advanced disease stage, we found that advanced-stage cancer is more prevalent in the p atients with VTE. In such advanced stage ovarian cancer, there is significantly more patients who had VTE which might be explained by the hypothesis of hypercoagulable state of malignancy.

CRediT authorship contribution statement

Mohamed Abdelkhalek: Writing – review & editing. **Basel Refky:** Formal analysis, Conceptualization. **Mohammed Zuhdy:** Writing – review & editing. **Omar Hamdy:** Methodology, Formal analysis. **Mohamed Hamdy:** Writing – review & editing. **Khaled Gaballa:** Formal analysis, Data curation. **Amr Elalfy:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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