

Analysis of Related Factors of Venous Thromboembolism in Patients with Ovarian Cancer

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Abstract: *Objective:* To analyze the related factors of venous thromboembolism in patients with ovarian cancer. *Methods:* A total of 86 patients with ovarian cancer complicated with VTE who were treated in a hospital from January 2021 to December 2022 were selected. The medical records of the patients were collected. The revised Caprini risk assessment scale (version 2013) was used to evaluate the risk level of VTE in patients with ovarian cancer, and the risk factors of VTE in patients with ovarian cancer were analyzed. *Results:* According to the revised Caprini risk assessment scale, 86 patients were scored, including 23 cases (26.74%) of high risk and 62 cases (72.09%) of extremely high risk. Among 86 patients, 77 cases (89.53%) were epithelial cancer, 75 cases (87.21%) were poorly differentiated cancer, 71 cases (82.56%) were International Federation of Gynecology and Obstetrics (FIGO) stage III-IV, and 28 cases (32.56%) were complicated with ascites. Thrombosis occurred before neoadjuvant chemotherapy in 9 cases (10.47%), during neoadjuvant chemotherapy in 5 cases (5.81%), before surgery in 21 cases (24.42%), during surgery in 1 case (jugular vein thrombosis), and after surgery in 50 cases (58.14%). VTE occurred in 26 patients (30.26%) with central venous catheter implantation and 22 patients (25.58%) with lymph node metastasis. *Conclusions:* According to the modified Caprini risk assessment scale, high risk and very high risk ovarian cancer patients are at high risk of VTE. The modified Caprini risk assessment scale is helpful for clinical early identification of patients with high risk of VTE. Tumor histological type, tumor grade, tumor staging and surgical treatment are related to the occurrence of VTE in patients with ovarian cancer.

Keywords: Ovarian Cancer, Venous Thromboembolism, Risk Factors, Tumor Histological Type, Tumor Grade, Tumor Staging

1. Introduction

Ovarian cancer is the third most common gynecological malignant tumor in the world, and its mortality ranks the first among gynecological malignant tumors [1]. In 2020, there were more than 310,000 new cases of ovarian cancer and about 207,000 deaths worldwide, with about 52,000 new cases and 22,000 deaths in China, which seriously threaten the life and health of women [2, 3]. At present, the main treatment for ovarian cancer is surgery and chemotherapy. However, extensive pelvic and upper abdominal surgery increases the incidence of postoperative complications, which affects the survival rate [4]. Venous thromboembolism (VTE) refers to

the abnormal formation of blood clots in the veins, resulting in partial or total blockage of blood vessels. VTE, including deep vein thrombosis (DVT) and pulmonary thromboembolism (PE), is a common complication of malignant tumors, with an incidence rate of 4%-20%, and is also an important cause of increased risk of morbidity and mortality in cancer patients [5, 6]. The total incidence of VTE after gynecological surgery in China is 0.02%-2.26%, while the incidence of VTE after gynecological malignant tumor surgery is 2.90%-19.87%. The risk of VTE in patients with gynecological malignant tumors is about 14 times higher than that in patients with gynecological benign diseases [7]. Studies have reported [8] that the proportion of gynecological malignancies in patients

with thrombosis is about 26.8%, among which ovarian epithelial cancer accounts for 13.0%, cervical cancer accounts for 9.8%, and uterine body cancer accounts for 4.0%. Among the three major gynecological malignant tumors, patients with ovarian cancer have the highest incidence of VTE [9], which is related to various risk factors such as advanced age, reduced physical activity, hypercoagulable state, tumor compression, large range of tumor cell reduction, and chemotherapy in patients with ovarian cancer [10]. Since the occurrence of VTE will have a serious adverse effect on the quality of life and prognosis of patients with ovarian cancer, this study analyzed the related factors of VTE risk in patients with ovarian cancer, in order to guide clinicians to better prevent VTE and provide reference for evaluating the disease.

2. Material and Methods

2.1. General Information

The medical records of ovarian cancer patients treated in our hospital from January 2021 to December 2022 were collected. Inclusion criteria:

- (1) Primary ovarian cancer confirmed by pathological examination;
- (2) DVT was diagnosed by color Doppler ultrasound; Pulmonary thromboembolism was diagnosed by pulmonary angiography.
- (3) Complete medical records. Exclusion criteria: 1) History of other pelvic malignant tumors in the past 5 years; 2) previous history of thrombosis or vascular disease; 3) use of drugs affecting coagulation function; 4) major trauma or surgical history within 3 months. The volume of peritoneal effusion collected in this study was the data recorded during the operation, and the volume of peritoneal effusion ≥ 200 ml seen during the operation was considered as the presence of peritoneal effusion.

2.2. Observation Indexes and Evaluation Methods

Caprini risk assessment scale is a risk assessment system for thrombosis, which is mainly used in risk assessment of surgical patients [11]. Lou Yinghua et al. [12] found through case-control study that Caprini risk assessment model can better predict the risk of postoperative DVT in patients undergoing gynecological malignant tumor surgery, and corresponding preventive measures can be taken according to the score and risk degree. The scale contains 40 risk factors such as age, body mass index, surgery, and history of VTE. According to the impact of each risk factor, the score is assigned to 1-5 points, and the patients are divided into four groups according to the total score: low-risk (0-1 points), medium-risk (2 points), high-risk (3-4 points), and extremely high-risk (≥ 5 points) [8]. In this study, the clinical data of 86 patients were retrospectively collected through the hospital's electronic medical record management system. The clinical data included age, volume of ascites, tumor type, tumor grade, International Federation of Gynecology and Obstetrics (FIGO)

tumor staging, central venous catheterization, neoadjuvant chemotherapy, blood transfusion therapy, lymph node metastasis and the occurrence of VTE were analyzed.

3. Results

3.1. Caprini Risk Assessment Scale Score

According to the revised Caprini risk assessment scale, the risk of VTE of 86 patients was counted and divided into low risk, medium risk, high risk and very high risk. There were 1 case of moderate risk, 23 cases of high risk and 62 cases of very high risk.

Table 1. Results of the Caprini risk assessment for 86 patients with ovarian cancer.

Grades	Example (n)	Percentage (%)
Low risk (0-1 score)	0	0
Moderate risk (2 points)	1	1.16
High risk (3-4 points)	23	26.74
Extremely high risk (≥ 5 points)	62	72.09

3.2. Patients with VTE

A total of 86 patients with ovarian cancer complicated with venous thromboembolism were enrolled in this study. The age ranged from 40 to 83 years, with an average age of 62.66 ± 10.53 years. Among the 86 patients, 75 cases were diagnosed as simple DVT, 1 case was diagnosed as simple PE, 10 cases were complicated with DVT and PE, and 8 cases were secondary PE after DVT. Among the patients with DVT, 26 cases were bilateral lower extremity veins, 29 cases were left lower extremity veins, 25 cases were right lower extremity veins, 2 cases occurred in the neck and 1 case occurred in the pelvis. There were 75 cases of lower extremity muscular vein thrombosis, 5 cases of peroneal vein thrombosis, 2 cases of jugular vein thrombosis, and 1 case of pelvic vein thrombosis.

Table 2. General information of VTE in 86 patients with ovarian cancer.

Indicators	Example (n)	Percentage (%)
Age (years)		
≤ 40	1	1.16
41~60	35	40.70
61~74	37	43.02
≥ 75	13	15.12
Types of Thrombus		
DVT	75	87.21
PE	1	1.16
DVT+PE	10	11.63
Site of thrombus		
Left lower limb	29	33.72
Right lower limb	25	29.07
Both lower limbs	26	30.23
Other	3	3.49

3.3. Risk Factors

3.3.1. Histological Type and Tumor Stage

Among the 86 patients, 77 cases were epithelial carcinoma, including 69 cases of serous carcinoma, 5 cases of clear cell carcinoma and 3 cases of mucinous cystadenocarcinoma.

There were 9 cases of non-epithelial carcinoma, 3 cases of granular cell tumor, 1 case of malignant teratoma, 1 case of dysgerminoma, and 4 cases of mixed tumors. There were 75 cases of poorly differentiated carcinoma and 11 cases of moderately differentiated carcinoma. 15 cases were FIGO stage I-II; 71 cases were stage III-IV.

3.3.2. Volume of Ascites and Timing of Thrombosis

Among the 86 patients, 28 patients were complicated with ascites, including 17 patients with ascites volume >1000ml. Among the 86 patients, thrombosis occurred before neoadjuvant chemotherapy in 9 cases, during neoadjuvant chemotherapy in 5 cases, before surgery in 21 cases, during surgery in 1 case (jugular vein thrombosis), and after surgery in 50 cases, of which 30 cases were found within 1 day after surgery, 17 cases were found within 2-7 days after surgery, and 3 cases occurred during chemotherapy.

3.3.3. Other Factors

Other risk factors for thrombosis include central venous catheter, neoadjuvant chemotherapy, and lymph node metastasis. Among the 86 patients, there were 51 patients with central venous catheter, of which 26 patients developed VTE during catheter, accounting for 30.23%, and 2 patients with jugular vein thrombosis were patients with central venous catheter. Among the 25 patients who received neoadjuvant chemotherapy, 5 patients developed VTE during treatment. Lymph node metastasis occurred in 22 patients.

Table 3. Analysis of risk factors for VTE in 86 patients with ovarian cancer.

Indicators	Example (n)	Percentage (%)
Tumor type		
Epithelial carcinoma	77	89.53
Non-epithelial carcinoma	9	10.47
Grade of tumor		
Poorly differentiated	75	87.21
Moderately high differentiation	11	12.79
Tumor staging		
I + II	15	17.44
III + IV	71	82.56
Volume of ascites		
Yes	28	32.56
No	58	67.44
Timing of blood clots		
Before neoadjuvant chemotherapy	9	10.47
During neoadjuvant chemotherapy	5	5.81
Before surgery	21	24.42
During the operation	1	1.16
After surgery	50	58.14
Insert a central venous catheter		
Yes	26	30.23
No	60	69.77
Receiving neoadjuvant chemotherapy		
Yes	25	29.07
No	61	70.93
Lymphatic metastasis		
Yes	22	25.58
No	64	74.42

4. Discussion

Cancer is closely related to venous thrombosis, and the risk

of VTE in cancer patients is significantly higher than that in normal people. After the occurrence of thrombosis, malignant tumors will also migrate, metastasize and spread, leading to poor prognosis of patients [13]. Studies [14] have shown that the mechanism of VTE in patients with malignant tumors involves cytokines, tissue factors, inflammatory response, cancer procoagulants and vascular wall damage, which is a process with the participation of multiple factors. In addition, ovarian cancer patients are difficult to be detected in the early stage, and most of them are in the middle and late stages when they are found. Due to the compression effect of large pelvic tumors and massive ascites on pelvic veins, venous blood stasis will be aggravated and venous return will be blocked [15]. In addition, under the influence of factors such as limb immobilization, venous catheterization, radiotherapy and chemotherapy during surgical treatment, the risk of VTE in patients is greatly increased [16]. The formation of thrombosis will block the venous lumen and block the return of deep veins, resulting in various degrees of dysfunction. Improper treatment can easily lead to pulmonary embolism and cerebral embolism, which endangers the life safety of patients [17]. Therefore, it is of great value to evaluate the risk of thrombosis in patients with ovarian cancer for improving the survival rate and quality of life of patients.

4.1. Multivariate Assessment

caprini risk assessment scale was used for multivariate evaluation, and the results showed that 85 patients were at high risk and extremely high risk, accounting for 98.84%, indicating that the scale had a good predictive value for early clinical identification of VTE risk patients. The contents of age 61-74 years old, malignant tumor, central venous catheterization, planned laparoscopic surgery, planned open surgery appeared most frequently in the two sub-items, while the contents of stroke (< 1 month), elective joint replacement, hip or pelvic or lower limb fracture, acute spinal cord injury (< 1 month) did not appear in the five sub-items. Therefore, we believe that the content of item 2 should be focused on and evaluated in the future, and the content of item 5 should be omitted. In view of the lack of a unified reference scheme for the risk assessment and prevention of VTE in gynecological patients in China, it is necessary to develop a specialized VTE score table according to the disease characteristics of gynecological cancer patients.

4.2. Histological Type, Grade, and Tumor Stage

Previous studies [18] have pointed out that the risk of thrombosis in patients with malignant tumors is related to the pathological type of tumors, and gynecological tumors (cervical cancer, ovarian cancer, etc.), gastric cancer, pancreatic cancer, esophageal cancer, and lung cancer are high-risk tumors for thrombotic diseases. In this study, 77 patients were epithelial ovarian cancer, accounting for 89.53%, indicating that the occurrence of VTE is closely related to the type of tumor, partly because epithelial cancer

is the pathological type with the highest incidence of ovarian cancer. It is also possible that there are differences in tumor types specific venous thrombosis pathways, leading to different coagulation status of malignant tumors from different sources, which has a great impact on thrombosis [13].

Among the 86 patients, 75 cases (87.21%) were poorly differentiated cancer, indicating that the lower the degree of tissue differentiation of ovarian cancer patients, the higher the risk of VTE. Li Aoming et al. [19] showed that the risk of VTE in patients with poorly differentiated gynecological malignant tumors was 8 times higher than that in patients with moderately and well differentiated tumors, which was similar to our results. In this study, there were 71 patients with FIGO stage iii-iv, accounting for 82.56%, indicating that clinical stage was significantly related to the occurrence of VTE. Gan Ling et al. [20] found in a study of 165 cases of gynecological malignant tumors that tumor stage was an independent risk factor for the occurrence of postoperative DVT in the lower extremities. Lv Shenglan [21] found that the risk of VTE in patients with stage III and IV surgery was 1.97 times higher than that in patients with stage I and II surgery, suggesting that the more advanced the tumor stage, the more likely to have thrombosis. The main reason is that with the increase of ovarian malignant tumor stage, the level of plasma D-dimer gradually increases, and the high blood coagulation leads to the formation of thrombosis [22, 23].

4.3. Volume of Peritoneal Effusion and Timing of Thrombosis

A Japanese single-center retrospective study [24] identified massive ascites as an independent risk factor for venous thromboembolism in patients with ovarian cancer before treatment. The main reason may be blood concentration caused by intravascular dehydration and direct compression of ascites on veins, leading to thrombosis. In the data collected in this study, only 17 of 28 patients had ascites volume >1000ml, indicating that massive ascites is not sensitive to the risk of VTE in patients with ovarian cancer. The reason may be that most patients with advanced ovarian malignant tumors have received 2-4 cycles of neoadjuvant chemotherapy before surgery, and the ascites volume has been significantly reduced or disappeared at the time of surgery. Therefore, it is still necessary to increase the sample size to further study the correlation between the volume of ascites at the first diagnosis, the volume of ascites at the time of surgery and thrombosis.

Surgery is the main treatment for patients with ovarian cancer, and it is also a risk factor for VTE in patients with gynecological tumors [25]. Some studies [26, 27] have shown that the diagnosis and treatment methods such as surgery, chemotherapy and anti-angiogenesis targeted therapy are closely related to the formation of VTE. In this study, among 86 patients with VTE, 50 cases occurred after surgery, accounting for 58.14%, and 29 cases were detected by routine lower extremity ultrasound Doppler examination one day after surgery, which was close to the study results of Tang Qin et al.

[28]. This may be due to factors such as a large amount of procoagulant substances entering the blood circulation caused by surgical trauma, and prolonged immobilization of the patient's limbs caused by the extension of the operation time, etc., which significantly slowed down the blood flow velocity of the patient's lower extremity veins and thus increased the risk of thrombosis [29, 30]. This study also found that the most common site of VTE is the lower extremity, and the incidence of VTE in the left lower extremity is higher than that in the right lower extremity. This may be because the left common iliac vein is below the left common iliac artery, and the compression of the artery affects the venous blood return, so the left lower limb is more prone to DVT than the right lower limb [19].

4.4. Other Factors

Among the 86 patients, only 5 patients developed VTE during neoadjuvant chemotherapy, suggesting that there was no correlation between neoadjuvant chemotherapy and VTE. Although central venous catheter is widely used in the treatment of patients with malignant tumors, only 26 patients with central venous catheter developed VTE during catheterization in this study, indicating that central venous catheter insertion is not a sensitive factor for VTE in ovarian cancer patients. Chen Ying et al. [31] found through multivariate regression analysis that lymph node metastasis was an independent risk factor for DVT after gynecological malignant tumor surgery, and the risk of venous thrombosis in patients with lymph node metastasis was 2.654 times that in patients without lymph node metastasis, which may be due to the higher content of procoagulant substances in patients with lymph node metastasis, resulting in patients with prone to thrombosis. In this study, only 22 patients had lymphatic metastasis, which may be caused by the lack of lymph node dissection in some patients and the inability to obtain relevant data. Therefore, whether lymph node metastasis affects the risk of VTE still needs to be further studied with more accurate and larger sample size.

5. Conclusions

In conclusion, Caprini score (version 2013) has a good predictive value for patients at high risk of VTE, and can accurately and comprehensively assess the risk of VTE in patients. Tumor type, poor tissue differentiation, advanced clinical stage and surgical treatment are related to the occurrence of VTE in ovarian cancer patients. The volume of ascites, central venous catheter placement, neoadjuvant chemotherapy and lymph node metastasis are not sensitive to VTE in ovarian cancer patients. In clinical practice, we should strengthen VTE risk screening, enhance the identification of patients with high risk of VTE, and take hierarchical management according to the predicted risk stratification, which can reduce the incidence of VTE. However, there are still not comprehensive limitations in this study, the number of patients is relatively small, and it is still necessary to increase the sample size for further verification.

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