Risk Prediction Model of Postoperative Venous Thrombosis of Ovarian Cancer

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Research Article

Keywords: Ovarian neoplasms, Venous thromboembolism, Risk factors, Logistic models, ROC curve

Posted Date: October 29th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-949286/v1>

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Abstract

Objective

To investigate the influencing factors of venous thromboembolism (VTE) after ovarian cancer surgery, and construct its prediction model.

Methods

A total of 67 patients with ovarian cancer who developed VTE after surgery were selected from October 2008 to June 2020 in the Department of Obstetrics and Gynecology, First Hospital of Lanzhou University, and conducted a retrospective study with 100 patients without VTE after the operation who were confirmed by imaging during the same period. The clinical data of two groups of patients were analyzed and compared, and the risk prediction model was established. The ROC curve was drawn to evaluate the prediction effect of the model.

Results

Univariate analysis showed that there were statistically significant differences in age, menopausal status, hypertension, neoadjuvant chemotherapy, FIGO staging, lymph node metastasis, operation time, preoperative plasma FIB and D-dimer between the thrombosis group and the non-thrombosis group; The results of multivariate analysis showed that old age, neoadjuvant chemotherapy, late FIGO staging, high levels of plasma FIB and D-dimer before surgery are independent risk factors for VTE after ovarian cancer surgery. Construct a prediction model based on the results of multivariate regression analysis: $\text{Logit}(P) = 0.053 \times \text{age} + 0.917 \times \text{neoadjuvant chemotherapy} + 0.956 \times \text{tumor FIGO staging} + 0.398 \times \text{preoperative plasma FIB} + 0.531 \times \text{preoperative D-dimer} - 7.679$ (Neoadjuvant chemotherapy, yes=1, no=0; tumor FIGO stage $\text{I}+\text{II}=1$, $\text{III}+\text{IV}=2$; age, preoperative plasma FIB and D-dimer are actual values). The ROC curve analysis shows that the AUC value of the model is 0.773, the sensitivity is 74.6%, the specificity is 71.0%, and the total prediction accuracy rate is $(78+39)/167=0.701$.

Conclusions

Age, neoadjuvant chemotherapy, tumor FIGO staging, preoperative plasma FIB and D-dimer can be used as reliable indicators to predict the occurrence of postoperative VTE in patients with ovarian cancer. The constructed prediction model has good risk prediction ability, It has certain clinical application value.

Introduce

VTE is closely related to tumor, mainly including pulmonary embolism (PE) and deep venous thrombosis (DVT). Among gynecological malignant tumor patients, ovarian cancer patients have the highest

incidence of VTE. A retrospective study of 328 patients with ovarian cancer showed that ovarian cancer complicated with VTE was up to 39.3%^[1]. Radical resection of ovarian cancer has a large surgical scope, and surgical trauma will inevitably increase the risk of VTE again. In this paper, the related influencing factors of VTE occurrence after ovarian cancer surgery were analyzed to provide reference for the prevention of VTE occurrence and improvement of patients' quality of life.

Objects And Methods

1 Subjects and Groups In this study, 67 patients with postoperative VTE in the first Hospital of Lanzhou University (our Hospital) from October 2008 to June 2020 were selected as the thrombus group, and 100 patients with ovarian cancer without postoperative VTE were selected as the non-thrombus group.

The relevant data were retrospectively studied.

2 Inclusion and exclusion criteria

2.1 Inclusion criteria

- ☒ Surgical treatment was performed for all patients in our hospital;
- ☒ Complete clinical case data;
- ☒ Definite pathological diagnosis of ovarian cancer;
- ☒ Definite diagnosis of VTE by ultrasound or imaging department.

2.2 Exclusion criteria

- ☒ Complicated with hematological diseases;
- ☒ Taking anticoagulants or antiplatelet drugs;
- ☒ Laparoscopy was converted to laparotomy during the operation;
- ☒ With other malignant tumors;
- ☒ Patients who had been diagnosed with VTE before surgery.

3 Methods General information, preoperative laboratory examination, operation, tumor pathology and other information of patients in 2 groups were collected and recorded.

4 Statistical Methods SPSS 25.0 software was used for analysis. Normality test was performed for all quantitative data before statistics, and all data were skewness distribution, represented by median (quartile) [M (P25, P75)]. Comparison between groups was performed by Mann-Whitney U test. Qualitative data use cases (%) were compared between groups by χ^2 test. Multivariate analysis used binary Logistic

regression to construct the prediction model and draw the receiver operating characteristic (ROC) curve to evaluate the predictive value of the model. $P < 0.05$ was considered statistically significant.

Results

1 Univariate analysis of postoperative VTE for ovarian cancer

1.1 Comparison of the general clinical data of patients between the two groups In terms of age, menopausal status, hypertension and neoadjuvant chemotherapy, there were statistically significant differences between the two groups ($P < 0.05$), as shown in Table 1.

Table 1 Comparison of general clinical data between the two groups

Influence factors	Thrombus group (n=67)	Non-thrombotic group (n=100)	Z or χ^2	P
Age (years)	60.00[53.00]68.00	54.00[47.50]61.75	-3.397	0.001
BMI (kg/m ²)	21.80[20.76]24.61	22.82[20.89]24.57	-1.012	0.311
Menopausal status			5.833	0.016
No	19[28.4]	47[47.0]		
Yes	48[71.6]	53[53.0]		
Diabetes			3.689	0.055
No	57[85.1]	94[94.0]		
Yes	10[14.9]	6[6.0]		
Hypertension			4.379	0.036
No	40[59.7]	75[75.0]		
Yes	27[40.3]	25[25.0]		
Hyperlipidemia			1.030	0.310
No	56[83.6]	89[89.0]		
Yes	27[40.3]	40[40.0]		
Neoadjuvant chemotherapy			6.109	0.013
No	42[62.7]	80[80.0]		
Yes	25[37.3]	20[20.0]		
Caprini score			6.308	0.081
<5	0[0.0]	5[5.0]		
5~7	37[55.2]	65[65.0]		
8~10	28[41.8]	28[28.0]		
≥11	2[3.0]	2[2.0]		

Note: Age and BMI were represented by [M(Q)].

1.2 Preoperative laboratory examination of two groups compared plasma fibrinogen (FIB) and plasma D-dimer in 2 groups, the differences were statistically significant ($P < 0.05$), as shown in Table 2.

Table 2 Comparison of preoperative laboratory examination between the two groups[M₂₅~P₇₅]

Influence factors	Thrombus group (n=67)	Non-thrombotic group (n=100)	Z	P
PLT×10 ⁹ /L	257.00(197.00–334.00)	241.50(190.00–327.75)	-0.797	0.426
WBC×10 ⁹ /L	5.75(4.82–7.08)	5.63(4.37–7.15)	-0.668	0.504
HGBg/L	122.00(108.00–135.00)	127.00(115.00–138.75)	-1.914	0.056
PTs	11.70(10.80–12.70)	11.50(10.80–11.98)	-1.235	0.217
APTTs	30.60(28.00–33.20)	32.40(29.40–34.87)	-1.535	0.125
FIBg/L	4.14(3.25–5.00)	3.49(3.00–4.30)	-2.842	0.004
D-D(ug/mL)	1.50(0.80–2.27)	0.85(0.48–1.35)	-3.647	<0.001
CA125U/mL	192.13(64.90–463.40)	141.30(24.68–657.48)	-0.741	0.459
HE4pmol/L	167.50(98.60–369.70)	133.40(68.88–382.93)	-1.837	0.066

1.3 Comparison of surgical conditions between the two groups Comparison of surgical duration between the two groups was statistically significant ($P < 0.05$), as shown in Table 3.

Table 3 Comparison of surgical conditions between the two groups

Influence factors	Thrombus group (n=67)	Non-thrombotic group (n=100)	Z or χ^2	P
Operation time (min)	290(240–330)	250(210–300)	-1.985	0.047
Intraoperative blood loss (ml)	350(200–500)	300(200–400)	0.047	0.074
Operation method			1.376	0.241
The cavity mirror	32(47.8)	57(57.0)		
open	35(52.2)	43(43.0)		
Intraoperative/postoperative blood transfusion			0.525	0.469
No	61(91.0)	94(94.0)		
Yes	6(9.0)	6(6.0)		
Postoperative preventive measures			0.632	0.729
No	17(25.4)	22(22.0)		
Machinery/medicine	20(29.8)	27(27.0)		
Mechanical + medicine	30(44.8)	51(51.0)		

Note: The operative time and intraoperative blood loss were represented by [M (P25, P75)].

1.4 Comparison of postoperative tumor pathology between the two groups FIGO stage and lymph node metastasis of the two groups were statistically significant ($P < 0.05$), as shown in Table 4.

Table 4 Comparison of postoperative tumor pathology between the two groups

Influence factors	Thrombus group (n=67)	Non-thrombotic group (n=100)	Z or χ^2	P
Tumor diameter (cm)	10.00±8.00~12.50	10.05±7.00~12.92	-0.150	0.881
Tumor FIGO staging			8.202	0.004
I + II	15~22.4	44~44.0		
III + IV	52~77.6	56~56.0		
Tumor tissue typing			0.175	0.676
Serous	49~73.1	76~76.0		
The serous	18~26.9	24~24.0		
Degree of tumor differentiation			2.727	0.256
Low level	14~20.9	13~13.0		
In the level	18~26.9	23~23.0		
High level	35~52.2	64~64.0		
Lymph node metastasis			4.580	0.032
No	36~53.7	70~70.0		
Yes	31~46.3	30~30.0		

Note: Tumor diameter was expressed by [M (P25, P75)]

2 Multifactor analysis of postoperative VTE for ovarian cancer The meaningful indicators in the univariate analysis were included in the multifactor analysis. Logistic regression analysis showed that age, neoadjuvant chemotherapy, TUMOR FIGO stage, preoperative FIB and D-dimer were independent risk factors for the occurrence of postoperative VTE for ovarian cancer, as shown in Table 5.

Table 5 Lgistic regression analysis of VTE occurrence after ovarian cancer surgery

Influence factors	Assignment	β	SE	Wald χ^2	<i>P</i>	<i>OR</i>	95% <i>CI</i>
age	The actual value	0.053	0.025	4.288	0.038	1.054	1.003~1.108
Menopausal status	0= no, 1= yes	0.025	0.519	0.002	0.962	1.025	0.371~2.832
hypertension	0= no, 1= yes	0.323	0.409	0.626	0.429	1.383	0.620~3.079
Neoadjuvant chemotherapy	0= no, 1= yes	0.917	0.412	4.960	0.026	2.502	1.116~5.607
Tumor FIGO staging	1 = $\text{I} + \text{II}$, 2 = $\text{III} + \text{IV}$	0.956	0.441	4.700	0.030	2.602	1.096~6.178
Lymph node metastasis	0= no, 1= yes	0.085	0.412	0.043	0.836	1.089	0.486~2.441
The operation time	The actual value	0.003	0.002	2.171	0.141	1.003	0.999~1.008
FIB	The actual value	0.398	0.162	6.057	0.014	1.489	1.084~2.044
D - dimer	The actual value	0.531	0.184	8.338	0.004	1.700	1.186~2.437
constant		-7.679	1.807	18.054	<0.001		

3 Construction of prediction Model (Logit Model) and ROC Curve Analysis The prediction model of postoperative venous thrombosis of ovarian cancer was constructed according to the results of binary Logistic analysis: $\text{Logit}(P) = 0.053 \times \text{Age} + 0.917 \times \text{Neoadjuvant chemotherapy} + 0.956 \times \text{Tumor FIGO stage} + 0.398 \times \text{Plasma fibrinogen} + 0.531 \times \text{D-dimer} - 7.679$ (neoadjuvant chemotherapy, yes =1, no =0; Tumor FIGO stage $\text{I} + \text{II} = 1$, $\text{III} + \text{IV} = 2$; Age, plasma fibrinogen and D-dimer are actual values). Hosmer-lemeshow test was used to analyze the fitting degree of the model, $P = 0.436$, greater than 0.05, indicating that the model had a good fitting degree and could be used to predict the occurrence of VTE after ovarian cancer surgery. The ROC curve was drawn based on the results of multi-factor analysis. The results showed that the AUC value of the model was 0.773, 95%CI: 0.707 ~ 0.844, and the maximum Yoden index was 0.456. At this time, the sensitivity and specificity of the model were 74.6% and 71.0%. The total prediction accuracy was $(78+39) / 167 = 0.701$. shown in Figure 1 and Table 6.

Table 6 Comparison between model prediction results and actual results

The actual results	Total	Predicted value	
		In VTE	Without VTE
In VTE	67	39	28
Without VTE	100	22	78

Discussion

Tumor is closely related to thrombosis; malignant tumor will exacerbate thrombosis and cause cancer-associated thrombosis (CAT); conversely, thrombosis will accelerate the progression of malignant tumor. It is called thrombosis-associated cancer (TAC) [2]. The incidence of postoperative VTE is higher in gynecological patients due to the possible use of hormones, special surgical site and other reasons. In previous studies, perioperative VTE occurred in 38% of patients with gynecologic cancer, much higher than in patients with benign gynecologic surgery (14%) [3]. The incidence of VTE in ovarian cancer patients is the highest among gynecological tumors due to advanced age, multiple internal and surgical complications, late stage of diagnosis, pelvic compression by tumor and large amount of ascites, large surgical range, and long treatment course [4]. Literature has reported that up to 60% of VTE occurs in elderly patients over 70 years old [5]. A retrospective study on the incidence of preoperative VTE in 387 patients with primary ovarian cancer found that the incidence of preoperative VTE and PE were 13.4% and 9.3%, respectively. The risk of preoperative VTE in patients aged ≥ 60 years was significantly higher than that in patients aged < 60 years [5], which was basically consistent with the results of this study. The reason may be related to the decrease of physical activity and venous pump failure in most elderly patients, and the increase of coagulation promoting factors, such as factor X and factor XII , homocysteine and fibrinogen with age [5-6]. In addition, in addition to the type and stage of cancer itself, the biggest risk factor for VTE is the presence of two or more potential chronic comorbidities, which are commonly diabetes, hypertension, chronic kidney disease, heart failure and lung disease [7]. Therefore, elderly, obese, hypertensive and diabetic patients should increase physical activity, eat a light diet, control BMI and actively control blood pressure and glucose levels.

Neoadjuvant chemotherapy is of great significance in the treatment of ovarian cancer. However, studies have shown that chemotherapy increases the risk of thrombosis in patients with malignant tumor by 6-7 times [8], which may be related to the direct damage of chemotherapy drugs to endothelial cells, the reduction of endogenous anticoagulants, the increase in the number of pro-coagulant proteins and the enhancement of their activity. In addition, chemotherapy can activate platelets, and may also lead to cell apoptosis and cytokine release, thereby enhancing the expression of tissue factors, resulting in the highly active form of monocyte/macrophage tissue factors, which are considered as physiological initiator of coagulation [2]. Ovarian cancer lesion resection and lymph node dissection cause severe trauma to human tissues, resulting in vascular endothelial injury and coagulation factor X leakage, resulting in cytokine

release and activation of exogenous coagulation pathway^[9]. The long operation time and postoperative bed rest lead to a long time of immobility of the limbs, the decline of the lower limb muscle pump function, slow blood flow and even stagnation, and then lead to thrombosis. In the literature, more than 100 minutes of operation time was associated with an increased risk of DVT (OR=1.30, 95%CI: 1.12-2.21) and PE (OR=1.25, 95%CI: 1.11-2.43), each additional 10 minutes after 100 minutes increased the risk of DVT by 7%, while the risk of PE increased by 5%^[10]. In addition, most studies have pointed out that the recovery of minimally invasive surgery is faster, the patients move to the ground earlier, and some risk factors for THE formation of VTE are avoided, thus the risk of VTE is lower than that of open surgery. However, some other scholars believe that the risk of thrombosis is increased due to the long time of minimally invasive gynecological surgery, the pressure of lower limb veins subjected to pneumoperitoneum, blocked blood return, and the increased operation time caused by laparoscopy or robotic surgery^[11]. In fact as long as patients surgery, and surgery related factors on the impact of thrombosis occurs cannot be avoided, but you can try to reduce risks in other way, such as operation skills, choose a suitable operation method, etc., at the same time improve the high-risk group recognition, to ensure more reasonable and normative thromboembolism prophylaxis.

According to previous studies, tumor pathology may affect the occurrence of venous thrombosis. Duska et al.^[12] showed that patients with advanced ovarian cancer were more likely to develop VTE than those with early ovarian cancer (P=0.004). On the one hand, tumor stage is late, huge tumor piece and a large number of ascites oppress pelvic vein, affect the blood circulation of pelvic cavity and lower limb, affect blood flow rate thereby, increase blood viscosity; On the other hand, with the progression of malignant tumors, the serum levels of pro-clotting factor D-dimer, fibrinopeptide A and von Willebrand factor (vWF) increase, and the risk of DVT naturally increases significantly^[13]. In ovarian cancer organization classification, epithelial carcinoma, most studies have found that is derived from epithelial tissue tumors often expressed higher levels of tissue factor, and release the micro vesicles (MVs) to the circulatory system, through the combined with endothelial cell activation or directly activate other cells, such as platelet trigger VTE^[14], more illustrates the ovarian cancer patients with VTE risk. In epithelial ovarian cancer, the risk of VTE in patients with clear cell carcinoma is 2.5 times higher than that in other epithelial ovarian cancer subtypes^[12]. However, routine VTE screening for all women with pelvic masses is impractical and increases the patient's cost burden. Therefore, it is necessary to combine other effective factors to predict whether they are at high risk of thrombosis clinically. For example, the study notes that Platelet, hemoglobin, white blood cell, D-dimer, prothrombin fragment and coagulation factor γ can be used to predict the risk of ovarian cancer VTE^[3], among which D-dimer is the most widely used. However, since most cancer patients have a high level of D-dimer, it is generally believed that the risk of VTE should be warned if the index is greater than 0.5 $\mu\text{g/mL}$, and VTE cannot be diagnosed^[9]. Higher d-dimer level before treatment is associated with poor prognosis in ovarian cancer patients with VTE, and may be used as a useful prognostic biomarker^[15].

High-risk patients are identified by using internationally recognized thrombotic risk assessment scales, such as Caprini assessment scale and Padua assessment scale. If patients are found to be at risk of VTE

after comprehensive assessment, preventive measures should be actively taken, mainly mechanical prevention and drug anticoagulant prevention. Mechanical prophylaxis does not increase the risk of bleeding and can be used continuously during hospitalization^[16]. Low molecular weight Heparin (LMWH) has a long half-life, high bioavailability, and higher anti-xa activity. Meta-analysis results showed that LMWH can effectively prevent DVT in patients with gynecological malignant tumor (RR=0.16, 95%CI:0.05 ~ 0.47)^[17]; it has also been proved to significantly reduce the risk of recurrent VTE (RR=0.58, 95%CI: 0.43-0.77), and is a reliable method for preventing postoperative venous thromboembolism^[18]. However, patients with cancer VTE are still at high risk of recurrent VTE and anticoagulation-related bleeding despite appropriate treatment^[19].

Therefore, for patients undergoing cancer surgery, VTE prophylaxis with the highest prophylactic dose of LMWH is recommended once a day, starting at the earliest 12 hours before surgery and lasting at least 7-10 days^[20]. In 2019, Chinese Society of Clinical Oncology (CSCO) formulated The Chinese Expert Guidelines for the Prevention and Treatment of Tumor-Related Venous Thromboembolism (2019 Version) in combination with relevant foreign guidelines and the current situation of tumor-related VTE in China. To provide reference for the clinical prevention and treatment of tumor-associated thrombosis^[21]. In this study, 167 patients with 123 cases (73.4%) were using drugs or (and) mechanical means to prevent blood clots, were the first day after surgery, showed the woman clinical doctors to patients at risk of VTE has a certain predictability, but even taking precautions, there are still part of VTE, suggests high-risk patients prevent degree is not enough, Low-risk patients may receive unnecessary overprevention, so a more rational and specific plan for VTE prevention is needed.

In conclusion, the occurrence of VTE after ovarian cancer surgery is the result of multiple factors. Advanced age, neoadjuvant chemotherapy, late tumor FIGO stage, high preoperative FIB and D-dimer are independent risk factors for the occurrence of VTE after ovarian cancer surgery. For high-risk patients, timely monitoring of relevant indicators combined with imaging monitoring can reduce the incidence of VTE to a certain extent, and help clinicians better grasp the patient's condition, so as to formulate corresponding intervention plans.

Declarations

Funding Information

Science and Technology Project of Gansu Province, No.20JR5RA361

Ethical Approval

The study has received ethical approval.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Figures

Figure 1

ROC curve analysis of the combined variable PRE and related factors