Risk Factors For Perioperative Venous Thromboembolism in Patients With Gynecological Malignancies

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Abstract

Introduction Venous thromboembolism (VTE), is a frequent postoperative complication of gynecologic malignancies during perioperative period. Although a number of risk factors for perioperative VTE with gynecological malignancies have been reported, the findings are diverse or even contradictory. In addition, most of the existing studies were retrospective case-control studies with small sample sizes. This study was a prospectively matched case-control study and aimed to specifically explore the risk factors related to surgery for perioperative VTE in gynecologic malignancies.

Material and methods Overall, 734 patients with gynecologic malignancies were enrolled in this study. 54 patients who developed VTE were included as the case group. A total of 270 non-VTE patients matched in a ratio of 1:5 as a control group with the matched principle of the same ethnicity and similar date of surgery (difference ± 3 days). The demographic characteristics, clinical data, laboratory tests, surgical data, and data related to the occurrence of VTE were collected during the follow-up period. Conditional logistic regression models were used for univariate and multifactorial analyses. Factors related to surgical treatment, especially those could be intervened and prevented, were used as target factors, which were gradually corrected by demographic data, clinical data, laboratory tests and other factors related to surgery, and sensitivity analysis was performed.

Results: The results of univariate analysis showed that age, place of residence, occupation, high-fat diet, menopause, comorbid chronic diseases, duration of upper extremity indwelling needle retention, disease diagnosis, sleep during hospitalization, admission albumin, surgical approach, duration of intensive care unit (ICU) admission, start of anticoagulant use, time to resume postoperative anal evacuation, duration of bed rest, duration of drinking abstinence, difference between postoperative and admission Caprini scores, duration of abdominal drainage tube retention, and intraoperative bleeding were risk factors for VTE in patients with perioperative gynecologic malignancies ($P < 0.05$). Stepwise corrected multifactorial conditional logistic regression analysis showed that admission albumin < 46.40 g/L and large difference between postoperative and admission Caprini scores were risk factors for the development of VTE in patients with gynecologic malignancies in the perioperative period, and the risk of VTE in patients with admission serum albumin < 46.40 g/L was 4.885 times higher than that in patients with admission serum albumin ≥ 46.40 g/L; The larger difference between postoperative and admission Caprini scores, the higher the risk of VTE, and a 1-point increase in the difference between postoperative and admission Caprini scores was associated with a 2.174-fold increase in the risk of VTE (95% CI: 1.255 to 3.766, $P = 0.006$).

Conclusions: The main risk factors for perioperative VTE in gynecologic malignancies are serum albumin lower than 46.40 g/L and large difference between postoperative and admission Caprini scores. More attention should be paid to the dynamic changes of serum albumin and Caprini scores of patients in the perioperative period and those factors should be targeted to intervene in order to reduce the perioperative VTE.

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) is a common complication in patients with gynecologic malignancies, with an incidence ranging from 3–25%. The incidence of VTE is even higher in patients undergoing surgery for gynecological malignancy^[1]. It has been reported that the incidence of postoperative DVT in patients with gynecological malignancies was 12–33%^[2] and that of perioperative DVT was 19.6–38%^[3]. VTE is the most common cause of death in patients with cancer after surgery within 30 days^[4].

There were many studies on the risk factors of perioperative VTE in patients with gynecological malignancies, however, the findings of existing studies are diverse or even contradictory^[5–7]. M Sakon found that female gender, operation site, age > 60 years, and operation time were four risk factors found to be significant^[5]. Qing Tian have pointed out that Age > 50 years, hypertension, D-dimer > 0.5 mg/L, duration of surgery ≥ 60 min, intraoperative pneumoperitoneum pressure ≥ 15 mmHg, duration of days in bed > 3 days were the independent risk factors for DVT in patients undergone gynecological laparoscopic surgery^[6]. In our previous meta-analysis study^[7], we found that the risk factors for perioperative VTE in patients with gynecological malignancy may include advanced age, BMI > 26 kg/m², increased platelet count, elevated D-dimer level, long duration of surgery, long time in bed after surgery, long-term hospital stay, large amount of intraoperative blood loss, tumor differentiation (GREAD3), tumor staging (stage IV), and operative approach (laparotomy). Other studies have found that surgery is the main pathogenic factor of perioperative VTE^[8], including intraoperative posture, intraoperative peripheral vascular injury^[9], intraoperative hypothermia^[10] and preoperative enema, diet prohibition time, postoperative recovery time of anal exhaust, etc. Consequently, surgical factors are the most important and most likely to be intervened factors for the occurrence of perioperative VTE. However, most of these studies were retrospective case-control studies with small sample sizes^[11, 12]. Therefore, there may be retrospective bias in the process of extracting patient medical records such as case selection bias, information bias and so on^[13].

As such, in this study, we conducted a matched case-control study to prospectively collect perioperative surgery-related factors without knowing the patients' VTE outcomes, especially focusing on surgery-related factors and strictly adhering to inclusion and exclusion criteria. To control for

bias in the case-control study design as much as possible, we also used a stepwise corrected multifactorial conditional logistic regression analysis with multiple models to gradually correct the confounding factors. To further validate the stability of the results, we performed the sensitivity analyses. So that to explore the risk factors related to surgery for perioperative VTE in gynecologic malignancies and provide a basis for the prevention and clinical intervention, and provide a scientific basis for further construction of risk assessment models of perioperative VTE in gynecologic malignancies.

Materials And Methods

Study design

This was a prospectively matched case-control study. Between December 2019 and February 2021, patients with gynecologic malignancies who were admitted to a tertiary women's and children's specialized hospital in Chengdu, Sichuan Province, undergoing surgical treatment were recruited for this study. We excluded subjects meeting one of the following criteria: (1) Combination of other primary malignant tumors (other than gynecologic malignancies) ; (2) Confirmed preoperative DVT by the vascular ultrasound ; (3) using anticoagulant drug within 1 week before surgery. Patients who developed VTE in the perioperative period were included as the case group, according to the matched principle of the same ethnicity and similar date of surgery (difference ± 3 days), we selected five patients from this cohort to each case in a ratio of 1:5 as a control group.

Data collection

The demographic characteristics, clinical data, laboratory tests, surgery related data, and data related to the occurrence of VTE were collected during the follow-up period. The following data were collected for analysis: age, marriage, work type, Body Mass Index (BMI), education, living environment, diagnosis, tumor types/stages, lymph node metastasis, radiotherapy, chemotherapy, chronic disease, history of VTE, menopause, varicose veins, leg edema, duration of upper limb indwelling needle retention, disease diagnosis, whether to stay in the intensive care unit (ICU), duration of ICU admission, blood type, coagulation function and blood biochemistry, surgical approach, duration of bed rest, blood transfusion, prophylactic thrombosis-specific compression stockings, intermittent pneumatic therapy, prophylactic anticoagulation, start of anticoagulant use, postoperative Caprini score, admission Caprini score, difference between postoperative and admission Caprini scores, duration of abdominal drainage tube retention, VTE type, site, DVT discovery time, PTE occurrence time, etc.

Diagnoses were objectively confirmed by color Doppler ultrasound for DVT and a ventilation-perfusion scan or computed tomography pulmonary angiography scan for PTE.

Ethical Approval

Written informed consent was obtained from each participant, and the study was approved by the Ethics Committee of West China Second University Hospital, Sichuan University. All authors had full access to all the data in this study.

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 software. Continuous data were presented as mean $\pm$ standard deviation and median (interquartile range, IQR) for non-normally distributed data. Categorical variable was presented as number (percentage), risk ratio and 95% confidence interval (CI). A P-value of 0.05 was considered statistically significant.

Conditional logistic regression models were used for univariate and multifactorial analyses. Surgery related data, especially those could be intervened and prevented, were used as target factors, which were gradually corrected with demographic data, clinical data, laboratory tests and other factors related to surgery, and sensitivity analysis was performed.

Results

We enrolled 734 patients in this study. During the follow-up period, 54 patients who developed VTE were included as the case group. And according to the matched principle of the same ethnicity and similar date of surgery (difference ± 3 days), a total of 270 non-VTE patients matched in a ratio of 1:5 as a control group.

The age ranged from 15~81 years with a mean age of 50.46 ± 11.09 years. The case group (55.98 ± 9.45 years) was much older than the control group (49.36 ± 11.08 years). The admission BMI ranged from $16.94 \sim 40.27$ kg/m² with a mean of 23.39 ± 3.24 kg/m². The mean admission BMI of the case group (23.55 ± 2.83 kg/m²) was similar to that of the control group (23.35 ± 3.33 kg/m²). The characteristics of perioperative VTE in case group are shown in Table 1.

The characteristics of perioperative VTE in case group:

Table 1. *The characteristics of the 54 perioperative VTE in patients with gynecologic malignancies*

Items	Data in Detail
Age	2 patients were at 34 and 40 years of age, 52 patients with VTE were over 40 years of age, 36 patients were between 41~60 years of age, 16 patients were above 60.
Sits of VTE	38 (70.3%) patients with DVT, 9 (16.7%) patients with PTE, and 7 (13.0%) patients with DVT+PTE. all DVT occurred in the lower limbs: 13 cases (28.9%) of left lower extremity DVT, 15 cases (33.3%) of right lower extremity DVT, and 17 cases (37.8%) of double lower extremity DVT.
Time of VTE	51 patients were examined for VTE on postoperative days 2 to 8, 3 cases on postoperative days 9, 10, and 12, respectively. 16 cases of PTE occurred within the seventh postoperative day, and 62.5% (10/16) of these PTEs occurred on the second and third postoperative days.

Abbreviation: DVT, deep vein thrombosis; PTE, pulmonary thromboembolism.

Comparison of General demographic data Related to Perioperative DVT

The General demographic data included age, BMI, work type, place of residence, sleep status during hospitalization, High-fat diet; Except BMI, there were significant differences between the VTE and non-VTE groups in the above-mentioned parameters ($P < 0.05$) as shown in Table 2.

Table 2. Comparison of General demographic data Related to Perioperative VTE

Variables	VTE(n=54)	Non-VTE(n=270)	Crude OR(95%CI)	P-value
Age (yrs.)				0.006
≤40	2 (3.7)	49 (18.1)	1.000	-
41~60	36 (66.7)	182 (67.4)	4.706 (1.110~19.959)	0.036
≥61	16 (29.6)	39 (14.4)	10.334 (2.217~48.177)	0.003
BMI(kg/m ²)				0.518
<18.5	15(5.6)	3(5.6)	1.000	-
18.5~24.99	189(70.0)	34(63.0)	0.883(0.243~3.215)	0.850
25~29.99	56(20.7)	16(29.6)	1.389(0.362~5.325)	0.632
≥30	10 (3.7)	1(1.9)	0.511(0.047~5.543)	0.581
Work Type				
mental labour	23 (42.6)	169 (62.6)		
physical labour	31 (57.4)	101 (37.4)	1.000	-
			2.234 (1.239~4.026)	0.008
Place of Residence				
rural area	27 (50.0)	89 (33.0)		-
City	27 (50.0)	181 (67.0)	1.000	0.019
			0.489 (0.269~0.890)	
Sleep status during hospitalization				
normal				
abnormal	36 (66.7)	132 (48.9)		-
	18 (33.3)	138 (51.1)	1.000	0.011
			0.416 (0.212~0.818)	
High-fat diet				
No	49 (90.7)	209 (77.4)		
Yes	5 (9.3)	61 (22.6)	1.000	-
			0.367 (0.142~0.945)	0.038

Clinical Data Analyses

As shown in Table 3, comparison of clinical data related to perioperative VTE were made between the 2 groups, including menopause, chronic disease, duration of upper limb indwelling needle retention (h), disease diagnosis. All the parameters were different between the VTE and non-VTE groups (P < 0.05).

Table 3. Comparison of Clinical Data Related to Perioperative VTE

Variables	VTE(n=54)	Non-VTE(n=270)	Crude OR(95%CI)	P-value
menopause				
No	13 (24.1)	145(53.7)		-
Yes	41 (75.9)	125(46.3)	1.000 3.608 (1.840~7.073)	< 0.001
With chronic disease				
No	37 (68.5)	235 (87.0)		-
Yes	17 (31.5)	35 (13.0)	1.000 3.061 (1.554~6.031)	0.001
duration of upper limb indwelling needle retention (h)	171(121-258)	143(108-188)	1.995 (1.071~3.717)	0.030
Disease diagnosis	22 (40.7)	130 (48.1)	-	0.037
cervical cancer	7 (13.0)	69 (25.6)	1.000	-
endometrial cancer	18 (33.3)	57 (21.1)	0.601 (0.240~1.506)	0.277
ovarian cancer	5 (9.3)	12 (4.4)	1.888 (0.927~3.844)	0.080
carcinoma of vulva	2 (3.7)	2 (0.7)	2.411 (0.781~7.441)	0.126
carcinoma of fallopian tube	22 (40.7)	130 (48.1)	5.148 (0.694~38.208)	0.109

laboratory tests analyses

As shown in Table 4, laboratory tests were compared between the VTE and the non-VTE groups. The admission serum albumin(Alb) level was found to be significantly different between the 2 groups (P =.005), while there were no differences in any of the other parameters (all P > 0.05).

Table 4 Comparison of laboratory tests analyses Related to Perioperative DVT

Variables	VTE(n=54)	Non-VTE(n=270)	Crude OR(95%CI)	P-value
PLT $\times 10^9/L$	201.70 $\pm$ 71.55	182.13 $\pm$ 68.63	1.004 (1.000~1.008)	0.059
PT $\times s$	11.00 $\pm$ 0.79	11.23 $\pm$ 0.96	0.782 (0.574~1.066)	0.120
APTT $\times s$	26.08 $\pm$ 2.27	26.38 $\pm$ 2.53	0.955 (0.856~1.065)	0.405
TT $\times s$	17.39 $\pm$ 1.10	18.04 $\pm$ 9.52	0.917 (0.672~1.252)	0.587
FIB $\times g/L$	338.26 $\pm$ 103.74	321.11 $\pm$ 93.98	1.002 (0.999~1.005)	0.231
admission Alb $\times g/L$	44.62 $\pm$ 2.80	46.28 $\pm$ 3.79	0.902 (0.839~0.970)	0.005

Surgery related factors

The operative data included anal evacuation time(h),duration of bed rest(h),surgical approach,prophylactic thrombosis-specific compression stockings,intermittent pneumatic therapy,prophylactic anticoagulation,start of anticoagulant use(h),blood transfusion,postoperative Caprini score,Caprini score post-admission,admission Caprini score,duration of ICU admission(h),duration of abdominal drainage tube retention; Anal evacuation time(h),duration of bed rest(h),surgical approach, prophylactic thrombosis-specific compression stockings,start of anticoagulant use(h),postoperative Caprini score,difference between postoperative and admission Caprini scores,duration of ICU admission(h),duration of abdominal drainage tube retention were different between the VTE and non-VTE groups ($P<0.05$), while no significant differences were found between the VTE and non-VTE groups in the other parameters, including intermittent pneumatic therapy,prophylactic anticoagulation,blood transfusion,admission Caprini score, (all $P>0.05$) as shown in Table 5.

Table 5. Comparison of surgery factors Related to Perioperative DVT

Variables	VTE(n=54)	Non-VTE(n=270)	Crude OR(95%CI)	P-value
Anal evacuation time(h)	67(48-91)	50(33-68)	1.020 (1.011~1.030)	< 0.001
Duration of bed rest(h)	82(48-121)	61(42-86)	1.012 (1.005~1.018)	< 0.001
Surgical approach				
Laparoscope	20 (37.0)	147 (54.4)	1.000	-
Laparotomy	34 (63.0)	123 (45.6)	1.962 (1.090~3.530)	0.025
Intermittent pneumatic therapy				
No	10 (18.5)	43 (15.9)	1.000	-
Yes	44 (81.5)	227 (84.1)	0.815 (0.362~1.832)	0.620
Prophylactic anticoagulation				
No	5 (9.3)	21 (7.8)	1.000	-
Yes	49 (90.7)	249 (92.2)	0.835 (0.309~2.253)	0.722
Start of anticoagulant use(h)				
<20	29 (53.7)	104 (38.5)	1.000	-
≥20	25 (46.3)	166 (61.5)	0.542 (0.300~0.978)	0.042
Blood transfusion				
No	43 (79.6)	225 (83.3)	1.000	-
Yes	11 (20.4)	45(16.7)	1.288 (0.610~2.723)	0.507
Postoperative Caprini score	6(5-8)	5(5-6)	1.578 (1.301~1.915)	< 0.001
Caprini score _{post-admission}	2(2-4)	2(2-5)	2.053 (1.523~2.768)	< 0.001
Admission Caprini score	4(3-5)	3(3-4)	1.167 (0.959~1.421)	0.123
Duration of ICU admission(h)	18(0-50)	18(0-24)	1.009 (1.002~1.016)	0.015
Duration of abdominal drainage tube retention	93(56-145)	73(44-111)	1.004 (1.000~1.008)	0.045

Logistic Regression Analyses

The results of univariate analysis showed that age, place of residence, work type, high-fat diet, menopause, comorbid chronic diseases, duration of upper extremity indwelling needle retention, disease diagnosis, sleep during hospitalization, admission albumin, surgical approach, duration of ICU admission, start of anticoagulant use, time to resume postoperative anal evacuation, duration of bed rest, difference between postoperative and admission Caprini score, duration of abdominal drainage tube retention may be the risk factors for VTE in patients with perioperative gynecologic malignancies ($P<0.05$). But,the main purpose of our study was focusing on exploring the risk factors related to surgery for perioperative VTE in gynecologic malignancies. especially the reversible or preventable factors. Therefore, the following 11 objective factors were finally determined as target factors, including sleep during hospitalization, admission albumin, surgical approach, duration of ICU admission, the forbidden drink time,start of anticoagulant use, time to resume postoperative anal evacuation, duration of bed rest, difference

between postoperative and admission Caprini scores, duration of abdominal drainage tube retention and intraoperative blood loss. These above target factors were gradually corrected with demographic data, clinical data, laboratory tests and surgery related factors. Laboratory test results showed no statistical significance except for the serum albumin level, so no correction was required. Therefore, the final corrected data include age, place of residence, work type, high-fat diet,menopause, chronic disease, duration of upper limb indwelling needle, disease diagnosis.

As shown in Table 6, Stepwise corrected multifactorial conditional logistic regression analysis results showed that admission albumin<46.40 g/L and large difference between postoperative and admission Caprini score were risk factors for the development of VTE in patients with gynecologic malignancies in the perioperative period, and the risk of VTE in patients with admission serum albumin<46.40 g/L was 4.885 times higher than that in patients with admission serum albumin≥46.40 g/L. The larger difference between postoperative and admission Caprini score, the higher the risk of VTE, and a 1-point increase in the difference between postoperative and admission Caprini scores was associated with a 2.174-fold increase in the risk of VTE (95% CI: 1.255 to 3.766, P= 0.006).

Table 6 . Stepwise corrected multifactorial conditional logistic regression analysis for perioperative VTE

	Demographic data corrected (MODE 1)		Clinical+ Demographic data corrected (MODE 2)		Clinical+ Demographic+ Surgery related data corrected MODE 3		Multivariate Logistic Regression (MODE 4)	
Variable	Adjust OR(95%CI) value	P-	Adjust OR(95%CI) value	P-	AdjustOR(95%CI) value	P-	AdjustOR(95%CI) P-value	
Sleep status during hospitalization								
normal	1.000				1.000			
abnormal	0.435(0.212~0.891)	0.023	1.000 0.318(0.135~0.747)	0.009	0.301(0.125~0.728)	0.008	1.000 0.427(0.153~ 1.196)	0.106
admission Alb (g/L)								
≥46.40	1.000	-		-		-	1.000	-
<46.4	3.061 (1.530~6.125)	0.002	1.000 3.908 (1.759~8.683)	0.001	1.000 3.865 (1.701~8.781)	0.001	4.885 (1.651~ 14.451)	0.004
Anal evacuation time(h)		0.001		0.008		0.037		0.112
	1.018 (1.008~1.028)		1.015 (1.004~1.026)		1.014 (1.001~1.028)		1.016 (0.996~1.037)	
Duration of bed rest(h)	-	0.012	-	0.045	-	0.095		
	1.000	-	1.000	-	1.000	-		
≤44	1.735	0.267	1.608	0.391	1.739	0.338		
45-63	0.656~4.584	0.810	0.544~4.755)	0.471	0.560~5.399	0.379		
64-91	0.880	0.008	0.649	0.072	0.571	0.198		
> 91	0.310~2.498		0.200~2.104		0.163~1.993			
	3.430 1.376~8.551		2.600 0.919~7.356		2.262 0.653~7.843			
Start of anticoagulant use(h)								
<20	1.000	-						
≥20	0.660 (0.353~1.235)	0.194						
Duration of ICU admission h	1.007 (1.001~1.014)	0.029	1.005 (0.997~1.013)	0.199				
The forbidden drink time(h)								
<24	1.000	-						
≥24	1.726 (0.912~3.264)	0.093						
Surgical approach								
Laparoscope	1.000	-						
		0.067						

Laparotomy	1.811 (0.959~3.418)							
Caprini score _{post-admission}	2.165 (1.527~3.071)	< 0.001	2.094 (1.443~3.040)	< 0.001	2.087 (1.405~3.101)	< 0.001	2.174 (1.2553.766)	0.006
Duration of abdominal drainage tube retention	1.003 (0.999~1.007)	0.158						
intraoperative blood loss(ml)								
<200	1.000	-	1.000	-	1.000	-		
≥200	3.174 (1.475~6.831)	0.003	2.401(1.062~5.324)	0.035	2.006 (0.7955.059)	0.140		

Sensitivity Analyses

All factors with statistical significance ($P < 0.05$) in the univariate analysis results and Caprini score value at admission were included in multivariate conditional logistic regression for analysis. Four factors including albumin in hospital, Caprini score_{post-admission}, sleep status during hospitalization and Anal evacuation time were removed one by one for sensitivity analysis. All the results are stable as shown in Supplementary Table1.

Discussion

VTE is a frequent complication of gynecologic malignancies during perioperative period. Reviews of the literature report the incidence of VTE in patients with gynecologic malignancies from 3% to 25%^[14,15]. Given the high frequency of VTE and associated morbidity and mortality, ascertaining predictive factors might be warranted to identify the high risk patients who may potentially benefit from closer surveillance or pharmacological thromboprophylaxis.

In our study, a total of 54 patients developed VTE. Age stratification was performed according to Caprini rating scale^[16], and it was found that 3.7% of the patients were ≤ 40 years old, 29.6% were ≥ 61 years old, and most of the patients (66.7%) were aged between 41 and 60 years old. Univariate analysis showed that age was a risk factor for perioperative VTE in gynecological malignancies, and the older the age, the higher the risk of VTE. Compared with patients aged ≤ 40 years, the risk of VTE was significantly increased in patients older than 40 years, and the risk of VTE was significantly higher in patients aged ≥ 61 years than in patients aged 41-60 years. This may be related to age-related endothelial dysfunction and platelet function changes^[17], especially in elderly patients with tumors^[18,19]. According to the results of this study and our previous studies, patients over 40 years, especially over 60 years, are at higher risk of VTE. Therefore, it is necessary to strengthen the dynamic assessment of the risk of perioperative VTE in these people and to take preventive measures in advance to reduce the incidence of VTE.

In our study, DVT accounted for 70.3%, PTE accounted for 16.7%, and DVT+PTE accounted for 13.0%, among which DVT occurred all in lower limbs: 28.9% DVT in left lower limbs, 33.3% DVT in right lower limbs, and 37.8% DVT in both lower limbs. This is consistent with the results of Nordstom et al.^[20], indicating that DVT of lower extremities is more likely to happen after surgery for gynecological malignancies. Previous studies have shown that the proportion of DVT in the left lower extremity is higher than that in the right extremity due to the anatomical characteristics of local veins^[21,22]. However, no significant difference was found in the incidence of VTE between the left and right lower limbs. This may be related to the simultaneous influence of various factors that may lead to changes in vascular wall, platelet and hemodynamics^[23].

In the 54 cases of VTE, 94.4% of the patients occurred VTE in 2 ~ 8 days after surgery, while PTE occurred within 7 days after surgery, of which 62.5% occurred in 2 and 3 days after surgery. This is consistent with the results of existing relevant studies. Multiple studies have shown that perioperative VTE in patients with gynecological malignant tumors mostly occurs within 10 days after surgery^[24,25]. Peedicayil et al.^[26] also found that 75% of VTE in gynecological cancer patients occurred within 1 week after surgery. The occurrence time of postoperative VTE may be related to many factors, including the operation time, operation approach and duration of bed rest, etc. In our study, color Doppler ultrasound was arranged immediately when patients were with numbness, swelling, pain and changes in skin temperature and skin color of lower limbs. Other patients who were asymptomatic were examined only at admission or before discharge. Therefore, in this study, only the time when patients were detected with VTE could be known, the actual occurrence time of VTE maybe earlier than the inspection time. More large sample and multi-center studies are needed to provide evidence for the effective prevention of perioperative VTE in gynecological malignancies.

The results showed that the large difference between postoperation and admission Caprini scores was a risk factor for perioperative VTE in gynecological malignancies. The larger the difference, the higher the risk. Every point increased in the difference between Caprini score after operation and that at admission, the risk of postoperative VTE increased by 2.174 times (95%CI: 1.255 to 3.766). Therefore, it is very important to evaluate dynamic Caprini score timely and accurately in perioperative period. Caprini risk assessment model, as a widely used VTE risk assessment model in the world, has been extensively verified in different populations, including patients with cancer^[27]. Studies have shown that the occurrence of VTE can be effectively reduced by taking targeted preventive measures after evaluating the risk of VTE in postoperative patients with gynecological tumors according to Caprini score^[28], however, the application of Caprini risk assessment model in patients with gynecological malignant tumors still needs to be supplemented and improved^[29].

The results of this study showed that there was no statistical difference in Caprini score between the case group and the control group at admission ($P=0.123$), and it was unscientific to evaluate the risk of perioperative VTE in patients with gynecological malignancies only by Caprini score once at admission. In addition to the traumatic stress response of the operation itself, which increases the risk of VTE in patients^[30], the injury of vascular endothelium and the influence of surgical trauma on the coagulation system of the body promote the elements of VTE formation. Therefore, the evaluation of perioperative VTE should take into account the surgical approach, surgical duration, and other potential risk factors caused by surgery^[31, 32]. The risk of VTE is also changing in the perioperative period. It is reliable to evaluate the risk of VTE based on the difference value of Caprini score before and after surgery. In clinical practice, Caprini score should be evaluated dynamically and timely and more attention should be paid to the size and causes of the score difference, so as to take targeted measures to eliminate reversible risk factors and reduce the impact of irreversible risk factors as far as possible.

We found that serum albumin level was an influential factor for perioperative VTE in gynecological malignancies, and high albumin was a protective factor. The risk of VTE in patients with serum albumin $<46.40\text{g/L}$ was 4.885 times higher than that in patients with serum albumin $\geq 46.40\text{g/L}$ ($P=0.004$). This is similar to the conclusion of previous studies. Studies on malignant VTE in digestive system showed that the risk of VTE increased when albumin $<30\text{g/L}$ ($\text{OR}=2.980$, $P=0.002$)^[33]. A Meta-analysis results also showed that albumin $<30\text{g/L}$ was a risk factor for VTE in lung cancer ($\text{OR}=4.01$, $P<0.001$)^[34]. Studies on related factors of VTE in malignant solid tumors showed that high albumin was a protective factor ($\text{OR}=0.863$, $P<0.05$), and it was suggested that patients with malignant solid tumors with VTE should maintain albumin above 35.505 (g/L) ^[35]. At present, there are few studies on the relationship between albumin and VTE, and the mechanism of action between VTE and albumin is still unclear^[36]. It may be related to the physiological effects of serum albumin, including the protection of vascular endothelial integrity^[37, 38], the maintenance of the body's plasma colloid osmotic pressure, and the regulation of coagulation^[39, 40]. When serum albumin concentration is high, it promotes the above physiological effects and is not conducive to the formation of thrombosis. The results of this study and previous studies all suggest that low protein is a risk factor for VTE, so more attention should be paid to albumin and dynamic monitoring should be taken during perioperative period.

This study tried to control the effects of confounding factors by prospective data collection, matching cases, and stepwise correction regression. However, there were still some deficiencies: (1) Laboratory examination: this study is a real world study, clinical examination of some indicators, such as genetic thrombi, has not been carried out, which may affect the results of the study. (2) Sample: Due to the limitations of time, manpower and material resources, this study was only carried out in the gynecological ward of one third-grade Grade A specialized hospital for women and children in Sichuan Province. The sample size was small, and the hospital grade and patient population were limited, so bias was inevitable in the research results. Therefore, the representativeness and generalization of the research results need to be improved by further research.

Conclusion

VTE in patients with gynecologic malignancies is affected by many factors, but the main risk factors for perioperative VTE are serum albumin lower than 46.40 g/L and large difference between postoperative and admission Caprini scores. Therefore, medical staff should pay more attention to the dynamic changes of serum albumin and Caprini scores of patients in the perioperative period, so as to identify the high-risk factors of VTE timely and actively take effective measures.

Patients with the following characteristics are at high risk of perioperative VTE: patients who are menopausal, serum albumin less than 46.40 g/L at admission, with a difference between postoperative and admission Caprini scores greater than 3; patients with a difference between postoperative and admission Caprini scores less than 3 but admission Caprini scores greater than 5. Patients at high risk of perioperative VTE can be screened quickly and easily by the above association rules, and then the possibility of VTE can be actively and dynamically assessed and individualized preventive measures can be taken.

Prevention of perioperative VTE in patients with gynecologic malignancies is crucial. Risk factors for VTE should be dynamically assessed based on basic patient data, clinical data, and treatment progress, and individualized preventive measures should be actively taken for the presence/potential or emerging high-risk factors to reduce the occurrence of postoperative VTE.

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Authors' contributions:

Yi Yang: Writing the article

Se-Ge Ma: Data Collection and analysis

Yan Huang: Research concept and design, final approval of article

Jun Zhu: Critical revision of the article

Ethics approval: The study was approved by the Ethics Committee of West China Second University Hospital, Sichuan University.

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Disclosure

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