Incidence and predictors of venous thromboembolism after surgery for gynecologic cancer

Xiao-Juan Wang¹, Ke-Qin Hua¹.*, Ke-Qin Hua

¹Department of Gynecology, Obstetrics and Gynecology Hospital, Fudan University, 128 Shenyang Road, 200090 Shanghai, China

*Correspondence: huakeqiaoshou@163.com (Ke-Qin Hua)

DOI: 10.31083/j.ejgo.2021.03.2240

This is an open access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

Submitted: 7 September 2020 Revised: 24 December 2020 Accepted: 28 December 2020 Published: 15 June 2021

Objective: To describe the incidence, timing, and risk factors of venous thromboembolism (VTE) after surgery for gynecological cancer and to evaluate its effects on survival.

Methods: This was a retrospective analysis from January 2008 through December 2016 at a single center. Data were recorded on surgical procedures, patient demographic characteristics, type of malignancy and VTE, and mortality outcomes within 30 days after surgery. Significant variables related to VTE were evaluated using bivariate analysis, and Logistic regression models were used to assess risk factors for VTE.

Results: The overall rate of postoperative VTE was 0.899% (36/4005) within 30 days after surgery. Of these rates, the rate in abdominal surgery was 1.66% (19/1120), and the rate in minimally invasive surgery (MIS) was 0.6% (17/2785). The median time from surgery to diagnosis was 8.5 days. In univariate analysis, VTE was statistically significantly associated with ovarian and fallopian cancer (P < 0.05), older age (P = 0.001), and blood transfusion (P < 0.001). A multivariate logistic regression model was used to adjust for variables with P < 0.2 in univariate analysis and found that except for age, the other variables continued to have a significant association with VTE.

Conclusion: The second week after surgery might be high-risk period of VTE occurring, and ovarian and fallopian tube cancer, abdominal surgery, and blood transfusion might be significant risk factors for developing VTE.

Keywords
Venous thromboembolism, Gynecologic cancer; Surgery, Pulmonary embolism; Incidence

1. Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a potentially catastrophic event associated with increased morbidity and mortality [1, 2]. However, the reported prevalence of postoperative VTE in patients with gynecological cancer varies considerably (0.5–38%) [3–7]. The accurate prevalence is unknown due to a paucity of operation-specific data and studies about risk factors in terms of gynecologic surgery.

VTE risk factors might be patient-related (including age, obesity, comorbidities), cancer-related (including tumor type, site and pathological stage), or treatment-related (including use of chemotherapy, hormonal treatment, surgery, anti-angiogenic agents) [3]. VTE is an important cause of morbidity and mortality in patients who undergo surgery for gynecologic cancer [4]. Previous studies had reported the risks and incidence of VTE in patients with gynecologic cancer, who had undergone surgery [3, 8–10]. Such studies had shown that there was a low incidence of VTE after laparoscopic surgery compared to laparotomy. However, sample size in these studies was small and limited the generalized conclusions that might be drawn from them. Furthermore, few studies have reported the risk factors and timing of clinically typical VTE [5]. When considering using extended VTE prophylaxis, accurate determination of VTE timing and risk factors was important to help direct therapy and avoid overtreatment [11].

Therefore, this study aimed to analyze the incidence of VTE in Chinese patients who underwent surgery for gynecologic cancer in our hospital and to investigate the potential predictive risk factors and interval of time for VTE to develop after surgery. Moreover, we aimed to compare the incidence of VTE after minimally invasive surgery (MIS) and after abdominal surgery. This would provide useful information for the prevention, diagnosis, and treatment of VTE in patients who accepted surgery for gynecologic cancer.

2. Materials and methods

Patients who were diagnosed with gynecological malignancies and underwent definitive surgery at a tertiary university-affiliated hospital, between January 2008, and December 2016, were included. Routes of surgery were categorized as abdominal surgery and MIS (including robotic-assisted laparoscopic, laparoscopic-assisted vaginal, and vaginal surgery). Patients diagnosed with fallopian tube or ovarian, endometrial or uterine, or cervical cancer, who were given at least one primary cancer-related surgery were identified. Patients diagnosed with endometrial cancer or uterine cancer were included if they underwent at least a hysterectomy. Patients diagnosed with cervical cancer underwent at least a hysterectomy or trachelectomy. Patients diagnosed with ovarian cancer underwent at least a salpingo-oophorectomy. Patients were followed during their hospitalization for 30 days after surgery. Patients’ demographic factors, characteristics of cancer, types of treatment, vital status, and causes of death were recorded. This study had been re-
Table 1. Clinical and demographic characteristics of patients who underwent surgery for gynecologic cancer (n = 4005).

| Variable                  | Sub-variable | Total     | No VTE | VTE | P       |
|---------------------------|--------------|-----------|--------|-----|---------|
| Age, yr                   |              |           |        |     |         |
| <50                       |              | 2235 (55.8%) | 2225 (56%) | 10 (27.8%) | 0.001*  |
| 50–59                     |              | 1205 (30.1%) | 1190 (29.9%) | 16 (44.4%) |         |
| 60–70                     |              | 463 (11.5%)  | 458 (11.5%) | 5 (13.9%) |         |
| ≥70                       |              | 102 (2.5%)   | 97 (2.4%)   | 5 (13.9%) |         |
| Site                      |              |           |        |     |         |
| uterine                   |              | 1703 (42.5%) | 1689 (42.5%) | 14 (38.9%) | <0.001* |
| ovarian and tube           |              | 130 (3.2%)   | 119 (2.9%)   | 12 (33.3%) |         |
| cervical                  |              | 2172 (54.2%) | 2162 (54.5%) | 10 (27.8%) |         |
| BMI, kg/m²                 |              |           |        |     |         |
| <20                       |              | 264 (6.6%)   | 261 (6.6%)   | 3 (8.3%) | 0.27    |
| 20–29                     |              | 2978 (74.3%) | 2949 (73.3%) | 29 (80.5%) |         |
| ≥30                       |              | 763 (19%)    | 760 (19.1%)  | 4 (11.1%) |         |
| Hypertension               |              |           |        |     |         |
| 16.8%                     |              | 672 (16.8%)   | 663 (16.7%)  | 9 (25%) | 0.185    |
| Diabetes                   |              | 175 (4.4%)   | 172 (4.3%)   | 3 (8.3%) | 0.448    |
| Respiratory morbidities    |              | 16 (0.4%)    | 15 (0.4%)    | 1 (2.8%) | 0.344    |
| Cardiac morbidities        |              | 63 (1.6%)    | 63 (1.6%)    | 0 | 0.929    |
| Anemia                     |              | 162 (4%)     | 158 (4%)     | 4 (11.1%) | 0.082    |
| Chemotherapy               |              | 97 (2.4%)    | 95 (2.4%)    | 2 (5.5%) | 0.494    |
| Operative time, hr         |              |           |        |     |         |
| <3                        |              | 1570 (39.2%) | 1560 (39.3%) | 10 (27.8%) | 0.158    |
| ≥3                        |              | 2435 (60.8%) | 2409 (60.7%) | 26 (72.2%) |         |
| Estimated blood loss, mL   |              |           |        |     |         |
| <500                      |              | 2964 (74%)   | 2941 (73.4%) | 23 (63.9%) | 0.164    |
| ≥500                      |              | 1041 (26%)   | 1028 (25.9%) | 13 (36.1%) |         |
| Blood transfusion          |              | 265 (6.6%)   | 255 (6.4%)   | 10 (27.8%) | <0.001*  |

* significant difference.

reported in accordance with the STROCSS criteria [12]. This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Obstetrics and Gynecology Hospital of Fudan University (Number: 2019-52). All patients included provided informed consent.

DVT was suspected if a difference in the circumference of either thighs or calves on one side compared to the other was equal to or larger than 2 cm. DVT was confirmed using Doppler ultrasonography. Additionally, these patients also received computed tomography (CT) of the chest. A PE was diagnosed if the patient had positive outcomes based on spiral CT, pulmonary arteriogram, or CT angiography. If autopsy was performed and a PE identified, case was recorded as PE, even though no imaging or treatment was given.

2.1 Statistical analysis

We calculated either means and standard deviations (SDs) or the medians and ranges for continuous variables as well as the frequencies (percentages) for categorical variables. Categorical and continuous variables were analyzed using x² test or Student’s t test. Logistic regression models were used to assess risk factors for VTE. A P-value less than 0.05 was considered statistically significant. SPSS software (SPSS version 16.0; SPSS Inc, Chicago, IL, USA) was used to perform the statistical analyses.

3. Results

Data for 4005 patients who underwent surgery for gynecological cancer were included and analyzed. The overall rate of postoperative VTE was 0.899% (36/4005). The rate in abdominal surgery was 1.56% (19/1220), and the rate in MIS was 0.6% (17/2785). The median time after operation to diagnosis of VTE was 8.5 days (range, 1–30 days). Of VTE events, 63.8% of patients experienced it after more than a week and 13.9% after 3 weeks. More than half of the patients were diagnosed with cervical cancer (2172 patients, 54.2%). However, a significant difference in VTE rate was observed based on cancer site (0.8% for uterine cancer, 0.5% for cervical cancer, and 8.4% for ovarian or tubal cancer). Of those with a postoperative VTE, DVT occurred in 72.2% (26/36), PE occurred in 25% (9/36), and both DVT and PE occurred in 2.8% (1/36). Four deaths were reported in the PE group for a postoperative death rate of 11.1% (4/36).

Univariate analysis of potential risk factors in women with VTE compared with that without VTE is summarized in Table 1. Statistically significant factors for VTE include ovarian and tubal cancer (P < 0.05), older age (P = 0.001), and blood transfusion (P < 0.001). There was no difference in the incidence of VTE when stratified by BMI (body mass index: P = 0.27). Other findings are as follows: hypertension (P = 0.185), diabetes (P = 0.448), respiratory morbidities (P = 0.344), cardiac morbidities (P = 0.929), anemia (P = 0.082), cholecystitis (P = 0.088), chemotherapy (P = 0.494), operative time (P = 0.158), and blood loss (P = 0.164).

We explored the incidence of VTE when stratified on the basis of the following variables (shown in the Table 2): BMI (kg/m²) (<30 vs >30), age (years) (<60 vs ≥60), operative time (hours) (<3 vs ≥3), surgical approach (MIS vs open surgery), blood loss (mL) (<500 vs ≥500), and lymphadenectomy (yes vs no). There was no difference in the risk of VTE.
and operative time (P = 0.714), operative time (P = 0.239), blood loss (P = 0.27), and lymphadenectomy (P = 0.323). However, a significant difference was seen when stratified by age (P = 0.021) and surgical approach (P = 0.002). A significant difference was also seen when stratified by blood loss associated with operative time (P < 0.001), open surgery associated with blood loss and operative time (P < 0.001); while no difference was seen when stratified by BMI associated with operative time (P = 0.703), age associated with BMI and operative time (P = 0.422), MIS associated with blood loss and operative time (P = 0.233).

Then, we used a multivariate logistic regression model to adjust for variables with P < 0.2 in univariable analysis, and found that there was no significant difference between age 50–59 years, age 60–69 years, and age 70 years or older; blood transfusion was highly significantly associated with VTE after gynecologic surgery for cancer. Other variables significant associated with VTE include hypertension, anemia, open surgery and surgical time > 3 hours (Table 3).

4. Discussion
Our study found an overall incidence of postoperative VTE of 0.87%, which was consistent with some prior studies [7, 13]. This study expanded the current literatures by supplying the largest study of risk factors for VTE specific to gynecological surgery [6, 14]. Despite this low rate, postoperative VTE was followed with serious consequences. This study demonstrated that a 30-day postoperative mortality of patients with a diagnosis of VTE was as high as 11.1%, which was higher than that reported of a 30-day mortality of 7.0% patients who underwent MIS for gynecologic cancer [7]. Perhaps, this is because in this study we included patients who underwent open abdominal surgery. It was reported that as many as 25% of PE patients experienced acute death in some scenarios [1]. In this study, 4 (44%) patients with a PE died.

Of the studied risk factors, an open abdominal approach had a significant effect on postoperative VTE. This study confirmed prior studies that have shown open surgery to be associated with more complications when compared with MIS [6, 8]. Although there had been a global trend towards decreased open abdominal surgery over the last decade, and the percentage of abdominal hysterectomies done in the United States in 2011 was 48.7% [9], our study showed that nearly a third of surgeries for gynecologic cancer were done using an open abdominal approach.

Patients with ovarian and fallopian tube cancer appeared to have a greater incidence of VTE compared to patients with uterine and cervical cancer, which has been previously reported [7, 10]. The remaining risk factors associated with VTE after surgery for gynecological cancer were older age, higher estimated blood loss, and blood transfusion, which have been reported previously [13, 15].

Early VTE (days 0–7 after surgery) is believed to be definitely associated with the surgical procedure while late VTE (days 8–90 after surgery) is assumed to reflect the period of recovery and adjuvant treatments [5]. The time intervals were studied to develop better preventive and diagnostic approaches to VTE. We found that 63.8% of VTE events occurred after more than a week and 13.9% after 3 weeks. The timing of VTE in our study was consistent with that reported in a prior study [5].

---

### Table 2. Risk of VTE stratified by age, BMI, operative time, blood loss and performing lymphadenectomy.

| Variable                        | VTE  | P    |
|--------------------------------|------|------|
| BMI kg/m² < 30                  | 30/3242 | 0.714 |
| BMI kg/m² ≥ 30                  | 6/763  |      |
| Age, yr < 60                    | 26/3429 | 0.021*|
| Age, yr ≥ 60                    | 10/576 |      |
| Operative time < 3 hr           | 13/1836 | 0.239 |
| Operative time ≥ 3 hr           | 25/2169 |      |
| Blood loss < 500 mL             | 22/2785 | 0.27  |
| Blood loss ≥ 500 mL             | 14/1220 |      |
| MIS                             | 17/2824 | 0.002*|
| Open surgery                    | 19/1181 |      |
| Lymphadenectomy                 |       |      |
| Yes                             | 28/2815 | 0.323 |
| NO                              | 8/1190  |      |
| BMI and operative time          |       |      |
| BMI < 30 and operative time < 3 hr | 8/1583  | 0.703 |
| BMI ≥ 30 and operative time > 3 hr | 5/672  |      |
| Age, BMI, and operative time    |       |      |
| < 60 yr, BMI < 30 and operative time < 3 hr | 8/1635  | 0.422 |
| > 60 yr, BMI ≥ 30 and operative time > 3 hr | 4/407  |      |
| Blood loss and operative time   |       |      |
| Blood loss < 500 mL and Operative time < 3 hr | 6/1849  | < 0.001*|
| Blood loss > 500 mL and operative time > 3 hr | 8/385  |      |
| Open surgery, Blood loss < 500 mL and Operative time < 3 hr | 2/972  | < 0.001*|
| Open surgery, Blood loss > 500 mL and Operative time > 3 hr | 7/253  |      |
| MIS, Blood loss 500 mL          | 10/1649 | 0.233 |
| MIS, Blood loss > 500 mL        | 2/87   |      |
| and operative time ≥ 3 hr       |       |      |

yr, years; hr, hours; * significant difference.

### Table 3. Multivariate regression analysis for VTE after surgery for gynecologic cancer.

| Variable                        | OR (95% CI) | P    |
|--------------------------------|-------------|------|
| Age 50–59 yr                    | reference   |      |
| Age 60–69 yr                    | 0.457 (0.137–1.397) | 0.163 |
| Age 70 yr or more               | 0.326 (0.083–1.278) | 0.108 |
| Hypertension                    | 4.252 (1.671–10.818) | 0.002*|
| Anemia                          | 14.838 (2.63–83.711) | 0.002*|
| open surgery                    | 2.53 (1.072–5.972) | 0.034*|
| operation time > 3 hr           | 4.759 (1.671–13.551) | 0.003*|
| blood loss                      | 6.732 (3.017–14.743) | 0.056 |
| blood transfusion               | 5.345 (2.115–13.506) | < 0.001*|

yr, years; hr, hours; * significant difference.
PE is the leading cause of postoperative death after surgery in this study. Of the patients studied, 11.1% (4/36) died of PE, which occurred within one week after surgery. It was reported that 3% of deaths in cancer patients were PE-related versus 1% of deaths in non-cancer patients \( (P < 0.001) \) [16]. Patients with PE are rare (5%), but their in-hospital mortality might exceed 50% [17]. Because most VTE- and PE-related deaths are unforeseen, primary prevention is the better option compared to trying to remedy such events after they occur.

There were several limitations to our study. This was a hospital-based retrospective study that was not representative of the whole country. In addition, there was a possibility that some VTE episodes that occurred more than 30-day postsurgery were missed. The use of pre-operative VTE prophylaxis was not identified. The recommendations for extended VTE prophylaxis for cancer patients in the postoperative setting are different in current practice guidelines. The European Society for Medical Oncology (ESMO) guidelines recommended thromboprophylaxis for all patients undergoing major abdominal or pelvic surgery [18], while the National Comprehensive Cancer Network (NCCN) only recommends thromboprophylaxis for patients with high risk features for VTE [19]. As such, practical application of these guidelines is still a challenge. The strengths of this study included the availability of information from a large-population that allowed us to obtain both the incidence and risk factors for VTE. Moreover, this study had shown of the interval to VTE occurrence, which emphasized the fact that more than one-half of events occurred more than one week after surgery.

5. Conclusions
This is one of the largest studies in gynecologic malignancies that focused on both risk and incidence of VTE after surgery. It highlights that more than one-half of VTE occur during the second week after surgery. Ovarian and fallopian tube cancer, abdominal surgery, and blood transfusion might were identified as risk factors for developing VTE.

Abbreviations
BMI, body mass index; DVT, deep vein thrombosis; MIS, minimally invasive surgery; PE, pulmonary embolism; VTE, venous thromboembolism.

Author contributions
XJW: Data acquisition, data analysis and interpretation, writing initial draft, and statistical analysis. KQH: Concept and design, writing critical revision, and supervision. All authors read and approved the final manuscript.

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Obstetrics and Gynecology Hospital of Fudan University (Number: 2019-52). All patients included provided informed consent.

Acknowledgment
We would like to express our gratitude to all the peer reviewers for their opinions and suggestions.

Funding
This research received no external funding.

Conflict of interest
The authors declare no conflict of interest.

References
[1] Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. American Journal of Preventive Medicine. 2010; 38: S495–S501.
[2] Rebuocas D, Costa M, Thuler L, Garces A, Aquino L, Bines J. Breast cancer-associated venous thromboembolism: a case-control study. Breast. 2016; 28: 84–88.
[3] Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. Journal of Clinical Oncology. 2009; 27: 4839–4847.
[4] Ramirez PT, Nick AM, Frumovitz M, Schmeler KM. Venous thromboembolic events in minimally invasive gynecologic surgery. Journal of Minimally Invasive Gynecology. 2013; 20: 766–769.
[5] Peedicayil A, Weaver A, Li X, Carey E, Cliby W, Mariani A. Incidence and timing of venous thromboembolism after surgery for gynecological cancer. Gynecologic Oncology. 2011; 121: 64–69.
[6] Swenson CW, Berger MB, Kamdar NS, Campbell DA, Morgan DM. Risk factors for venous thromboembolism after hysterectomy. Obstetrics & Gynecology. 2015; 125: 1139–1144.
[7] Mahdi H, Aljebori Q, Lockart D, Moulton L. Risk of venous thromboembolism following laparoscopic surgery for gynecologic malignancy. Journal of Minimally Invasive Gynecology. 2016; 23: 1057.
[8] Nieboer TE, Johnson N, Lethaby A, Lavender E, Curr E, Garry R, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database of Systematic Reviews. 2009; 3: CD003677.
[9] Mikhail E, Miladinovic B, Velanovich V, Finan MA, Hart S, Imudia AN. Association between obesity and the trends of routes of hysterectomy performed for benign indications. Obstetrics and Gynecology. 2015; 125: 912–918.
[10] Saadeh FA, Norris L, O’Toole S, Gleeson N. Venous thromboembolism in ovarian cancer: incidence, risk factors and impact on survival. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2013; 170: 214–218.
[11] Marques de Marino P, Rial Horcajo R, Garcia Granjal T, Sanchez Hervas L, Serrano Hernando FJ, Herrera Martinez MA, et al. Thromboprophylaxis in gynecologic cancer surgery: is extended prophylaxis with low molecular weight heparin justified? European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2018; 230: 90–95.
[12] Agha RA, Borrelli MR, Vella-Baldacchino M, Thavayogan R, Orgill DP. The STROCSS statement: Strengthening the Reporting of Cohort Studies in Surgery. International Journal of Surgery. 2017; 46: 198–202.
[13] Swenson CW, Berger MB, Kamdar NS, Campbell DA, Morgan DM. Risk factors for venous thromboembolism after hysterectomy. Obstetrics and Gynecology. 2015; 125: 1139–1144.
[14] Mueller MG, Pilecki MA, Catanzarite T, Jain U, Kim JYS, Kenton K. Venous thromboembolism in reconstructive pelvic surgery. American Journal of Obstetrics and Gynecology. 2015; 211: 552.e1–552.e6.
