Clinical and Applied Thrombosis/Hemostasis
Volume 28: 1-8

DOI: 10.1177/10760296221095558
journals.sagepub.com/home/cat
SAGE

# Development and Validation of a Nomogram to Predict the Probability of Venous Thromboembolism in Patients with Epithelial Ovarian Cancer

**Yuhan Wang, MS[1], Haijian Zhou, MS[1], Guanglei Zhong, MS[1], Zhaojie Fu, MS[1], Yu Peng, MS[1], and Tingting Yao, PhD[1,2]**

## Abstract

**Objective:** To identify predictive factors and develop a nomogram to predict the probability of venous thromboembolism for epithelial ovarian cancer patients. **Methods:** Our study cohort was composed of 208 EOC patients who had received initial treatment in Sun Yat-sen Memorial Hospital from January 2016 to March 2020. Clinicopathological variables predictive of VTE were identified using univariate logistic analysis. A multivariate logistic regression model was used to select the predictive factors used for nomogram. The accuracy of nomogram was evaluated by the Concordance index (C-index), the area under the receiver–operator characteristic (ROC) curve, area under concentration-time curve (AUC) and the calibration curve. **Results:** Advancing age (hazard ratio [HR], 1.042; 95% confidence interval [CI], 1.000-1.085; $P = .048$), higher D-dimer level (HR, 1.144; 95%CI, 1.020-1.283; $P = .022$), lower PR immunohistochemical positive rate (HR, 0.186; 95%CI, 0.034-1.065; $P = .059$) and higher Ki67 immunohistochemical positive rate (HR, 4.502; 95%CI, 1.637-12.380; $P = .004$) were found to be independent risk factors for VTE, and were used to construct the nomogram. The C-index for VTE prediction of the nomogram was 0.75. **Conclusions:** We constructed and validated a nomogram able to quantify the risk of VTE for EOC patients, which can be applied in recognizing EOC patients with high risk of VTE.

## Keywords

venous thromboembolism, epithelial ovarian cancer, predictive model, predictive factor, nomogram

Date received: 23 January 2022; revised: 8 March 2022; accepted: 1 April 2022.

## Introduction

Venous thromboembolism (VTE), which mainly consists of deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common comorbidity among patients with gynecological malignancies. Multiple studies have shown that cancer patients who develop VTE have higher mortality and lower quality of life.[1-3] Patients with ovarian cancer are particularly prone to thrombosis due to activation of the in vivo coagulation system, previous studies reported that up to 20% of women with ovarian cancer suffer from VTE.[4-6]

The ninth American College of Chest Physicians evidence-based clinical practice guidelines recommended a routine assessment to identify patients at high risk of VTE.[7] Two classical risk assessment models including the Caprini and Rogers scores are currently available. However, as most gynecological cancer patients are in the high-risk group, the value of these scoring systems in ovarian cancer patients is limited.[8,9] Therefore, it is necessary to establish an accurate VTE risk assessment tool for ovarian cancer patients.

[1] Department of Gynecological Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China
[2] Key Laboratory of malignant tumor gene regulation and target therapy of Guangdong Higher Education Institutes, Sun Yat-sen University, Guangzhou, China

**Corresponding Author:**
Department of Gynecological Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, 107 Yan Jiang West Road, Guangzhou 510120, People's Republic of China.
Email: yaotting@mail.sysu.edu.cn

Nomogram is a predictive model, which can simplify the statistical predictive model into a simple graphical representation that generates a numerical probability of a clinical event.[10] Nomogram is tailored to the profile of an individual patient, which helps to provide personalized treatment for patients. To date, there have been no studies using nomogram as a predictive model of VTE for epithelial ovarian cancer (EOC) patients. This study aims to develop a nomogram to predict the probability of VTE for women with EOC.

## Patients and Methods

### Patient Selection

We conducted a retrospective analysis of patients with EOC who had received initial treatment in Sun Yat-sen Memorial Hospital from January 2016 to March 2020. The inclusion criteria were as follows: (a) histologic diagnosis confirmed EOC; (b) patients receiving initial treatment in our hospital. Patients who meet any of the following criteria will be excluded from the study: (a) age younger than 18 years; (b) non-EOC diagnosis according to pathological examination; (c) secondary ovarian cancer or associated with other primary tumors; (d) survival time less than six months; (e) had missing clinical data.

### Data Collection

For each patient, the following parameters were abstracted: (a) patient clinical demographics including age at cancer diagnosis, gravidity, body mass index (BMI), menopausal status, the number of comorbid conditions coexisting in the patient, hospital day and treatment strategy; (b) laboratory test results obtained at the time of initial cancer diagnosis including D-dimer, international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT), serum albumin, hyperlipemia, platelet count, cancer antigen 125 (CA-125), carbohydrate antigen 199 (CA-199), carcinoembryonic antigen (CEA) and Human epididymis protein 4 (HE4); (c) tumor size obtained from preoperative imaging findings (computed tomography, magnetic resonance imaging, or sonography); (d) pathology information including histologic subtype, Federation International of Gynecology and Obstetrics (FIGO) stage and immunohistochemical (IHC); (e) detailed information for symptomatic VTE including the type of VTE and interval between the initial diagnosis and VTE.

### Definitions

Comorbid conditions including hypertension, coronary artery disease or vascular disease, cardiac conduction disorder or atrial fibrillation, prior stroke or transient ischemic attack, systemic autoimmune disease and diabetes mellitus. A separate variable was created according to the number of comorbid conditions coexisting in a patient. Hyperlipidemia is defined as an increase in plasma levels of cholesterol and (or) triglycerides. The method used at our medical center to determine D-dimer is turbidimetric inhibition immuno assay, and the reference range for normal values is 0-0.55 mg/L FEU.

### Follow Up

All patients without thrombosis were followed up for at least 6 months from the time of initial diagnosis of ovarian cancer to the last chemotherapy treatment. Symptomatic and documented VTE is the endpoint. We did not do routine VTE screening for patients, color Echo-Doppler, computerized tomography, magnetic resonance imaging and angiography were only used in suspicious patients with symptoms to discover symptomatic VTE. The follow-up duration was measured from the date of initial diagnosis to the date of discovery of VTE, death or last follow-up.

### Statistical Analysis

Variables that showed statistically significant in the univariate logistic regression were subsequently included in the multivariate logistic regression model to identify significant factors through backward: logisticregression (LR) selection. All reported P values are two-sided, and factors with P values less than 0.05 were considered significant.

After identifying significant factors related to the occurrence of VTE through multivariate analyses using SPSS software (version 25.0), a nomogram for predicting the VTE probability was constructed using the R software (version 4.0.0). The accuracy of nomogram was evaluated by the Concordance index (C-index), the area under the receiver–operator characteristic (ROC) curve (AUC) and calibration curve which was analyzed by plotting predicted nomogram and the actual VTE rate of patients.

## Results

### Patient Characteristics

According to the criteria above, 208 EOC patients who received primary debulking surgery in Sun Yat-sen Memorial Hospital from January 2016 to March 2020 were included in this study. The patient clinicopathologic characteristics are shown in Table 1. 119 (67.2%) of the non-VTE patients and 21 (67.7%) VTE patients in this study had blood lipid examination at the time of initial diagnosis of ovarian cancer, among which 15 (8.5%) non-VTE patients and 5 (16.1%) VTE patients was discovered with hyperlipidemia. None of the patients in this study had a smoking habit, so the relationship between smoking and VTE was not known in the study. The median follow-up time for the entire cohort was 746 (2-1680) days, and VTE was found in 31 patients (14.9%), including 30 cases of DVT of lower extremity and 1 case of thrombosis in jugular vein catheterization. The median time to VTE was 158 days.

### Development and Validation of the Nomogram Model

Univariate logistic analyses (Table 2) revealed that age ($P = .010$), postmenopause ($P = .015$), comorbid conditions

**Table 1.** Clinicopathologic Characteristics of Patients with Epithelial Ovarian Cancer.

| Variable | Overall cohort (n = 208) | VTEcohort (n = 31) |
|---|---|---|
| Age [years; median (range)] | 52.6 (23-83) | 57.3 (34-83) |
| Postmenopause [cases (%)] | | |
| No | 90 (43.3%) | 7 (22.6%) |
| Yes | 118 (56.7%) | 24 (77.4%) |
| BMI [$kg/m^2$; median (IQR)] | 22.5 (20.5-24.1) | 22.2 (19.9-25.6) |
| Gravidity [times; median (range)] | 3 (0-10) | 3 (1-6) |
| Comorbid conditions [cases (%)] | | |
| 0 | 152 (73.1%) | 19 (61.3%) |
| 1 | 44 (21.2%) | 7 (22.6%) |
| 2 | 9 (4.3%) | 3 (9.7%) |
| 3 | 3 (1.4%) | 2 (6.5%) |
| Hospital day [days; median (range)] | 37 (8-116) | 41 (11-98) |
| Primary debulking surgery [cases (%)] | | |
| Yes | 156 (75%) | 22 (71%) |
| No | 52 (25%) | 9 (29%) |
| D-dimer [mg/L FEU; median (IQR)] | 3.1 (1.0-3.9) | 4.5 (1.9-6.2) |
| International normalized ratio [INR; median (IQR)] | 1.06 (0.98-1.09) | 1.09 (1.01-1.09) |
| PT [s; median (IQR)] | 12.1 (11.3-12.6) | 12.1 (11.7-12.6) |
| APTT [s; median (IQR)] | 25.8 (23.0-28.0) | 25.3 (22.6-28.1) |
| Albumin [g/L; median (IQR)] | 37.6 (34.2-41.9) | 38.0 (34.5-43.0) |
| Platelet count [$\times 10^9$/L; median (IQR)] | 335.1 (256.0-395.8) | 320.1 (214.0-380.0) |
| CA125 [U/mL; median (IQR)] | 1342.7 (151.0-1329.8) | 1525.5 (239.0-1669.0) |
| CA199 [U/mL; median (IQR)] | 622.7 (6.1-40.2) | 3876.6 (8.4-86.5) |
| CEA [ng/mL; median (IQR)] | 64 (0.9-2.9) | 402.7 (1.4-4.8) |
| HE4 [pmol/L; median (IQR)] | 627.8 (152.0-704.5) | 793.3 (196.6-835.6) |
| Tumor size [mm; median (IQR)] | 101.2 (65.0-124.5) | 113.9 (66.0-150.0) |
| Histology [cases (%)] | | |
| Serous | 144 (69.2%) | 21 (67.7%) |
| Mucinous | 14 (6.7%) | 1 (3.2%) |
| Endometroid | 19 (9.1%) | 5 (16.1%) |
| Clear cell | 26 (12.5%) | 4 (12.9%) |
| Others | 5 (2.4%) | 0 |
| FIGO stage [cases (%)] | | |
| I | 43 (20.7%) | 7 (22.6%) |
| II | 17 (8.2%) | 1 (3.2%) |
| III | 112 (53.8%) | 15 (48.4%) |
| IV | 36 (17.3%) | 8 (25.8%) |
| ER immunohistochemical positive rate [%; median (IQR)] | 66% (46%-1) | 59% (30%-90%) |
| PR immunohistochemical positive rate [%; median (IQR)] | 27% (0%-50%) | 15% (0%-25%) |
| P53 immunohistochemical positive rate [%; median (IQR)] | 68% (43%-95%) | 64% (3%-96%) |
| Ki67 immunohistochemical positive rate [%; median (IQR)] | 51% (30%-70%) | 61% (50%-70%) |
| Prophylactic anticoagulation [cases (%)] | 142 (68.3%) | 18 (58.1%) |
| VTE [cases (%)] | | |
| No | 177 (85.1%) | - |
| Yes | 31 (14.9%) | - |
| Follow-up [days; median (range)] | 746 (2-1680) | 157 (1-1200) |

($P = .035$), D-dimer level ($P = .007$), PR (progesterone receptor) IHC positive rate ($P = .019$) and Ki67 IHC positive rate ($P = .014$) were predictive factors for VTE. In multivariate logistic analysis, four variables were regarded as independent predictors for VTE, including advancing age (hazard ratio [HR], 1.042; 95% confidence interval [CI], 1.000-1.085; $P = .048$), higher D-dimer level (HR, 1.144; 95%CI, 1.020-1.283; $P = .022$), lower IHC positive rate (HR, 0.186; 95%CI, 0.034-1.065; $P = .059$) and higher Ki67 IHC positive rate (HR, 4.502; 95%CI, 1.637-12.380; $P = .004$).

The prognostic nomogram that in combination of all independent predictive factors is shown in Figure 1. The c-index for this VTE predicted nomogram was 0.75 (95%CI, 0.6659-0.834) and the ROC curve of the nomogram was shown in Figure 2. Establish acalibration curve, which showed both actual probability of VTE and the predicted probability of VTE (Figure 3). The 45° gray line represents an ideal prediction, and the dotted curve represents the predictive performance of the nomogram. The two lines overlap closely, indicating that the nomogram accurately estimated the probability of VTE in this patient cohort.

**Table 2.** Logistic Regression Analyses of Venous Thromboembolism.

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| Variable | HR (95% CI) | P value | HR (95% CI) | P value |
| Age | 1.052 (1.012-1.093) | 0.010 | 1.042 (1.000-1.085) | 0.048 |
| Postmenopause | 3.027 (1.240-7.388) | 0.015 | | 0.619 |
| BMI | | 0.660 | | |
| Gravidity | | 0.593 | | |
| Comorbid conditions | | | | |
| 0 | | 0.077 | | 0.282 |
| 1 | 1.324 (0.517-3.390) | 0.558 | | 0.417 |
| 2 | 3.500 (0.807-15.18) | 0.094 | | 0.102 |
| 3 | 14.00 (1.210-161.9) | 0.035 | | 0.356 |
| Hospital day | | 0.135 | | |
| Primary debulking surgery | | 0.575 | | |
| D-dimer | 1.152 (1.039-1.279) | 0.007 | 1.144 (1.020-1.283) | 0.022 |
| INR | | 0.249 | | |
| PT | | 0.978 | | |
| APTT | | 0.578 | | |
| Albumin | | 0.682 | | |
| Platelet count | | 0.462 | | |
| CA125 | | 0.630 | | |
| CA199 | | 0.139 | | |
| CEA | | 0.153 | | |
| HE4 | | 0.249 | | |
| Tumor size | | 0.144 | | |
| Histology | | | | |
| Serous | | 0.658 | | |
| Mucinous | | 0.454 | | |
| Endometroid | | 0.197 | | |
| Clear cell | | 0.915 | | |
| Others | | 0.999 | | |
| FIGO stage | | | | |
| I | | 0.438 | | |
| II | | 0.307 | | |
| III | | 0.645 | | |
| IV | | 0.504 | | |
| ER immunohistochemical positive rate | | 0.217 | | |
| PR immunohistochemical positive rate | 0.135 (0.026-0.715) | 0.019 | 0.189 (0.034-1.065) | 0.059 |
| P53 immunohistochemical positive rate | | 0.545 | | |
| Ki67 immunohistochemical positive rate | 8.997 (1.564-51.74) | 0.014 | 11.48 (1.676-75.66) | 0.013 |
| Prophylactic anticoagulation | | 0.189 | | |

## Discussion

Patients with malignant tumor were reported to have a 7-fold increased risk of VTE.[11] The prognosis of cancer patients who develop VTE is very poor. In addition to metastasis, thromboembolism events are the main cause of death in cancer patients.[12] EOC patients are particularly prone to VTE, due to activation of the in vivo coagulation system, and the occurrence of VTE has adverse effects on the survival of patients with ovarian cancer. A 2019 study pointed out that the 1-year cumulative incidence of VTE in EOC patients was 20.8% with a low incidence of 3.8% at the time of diagnosis,[13] which means most VTE in ovarian cancer can be prevented. Therefore, if patients diagnosed with EOC who are at high risk for VTE can be treated with preventive anticoagulant therapy to reduce the incidence of thrombosis, the survival of patients with ovarian cancer may be significantly improved. Several clinical prediction models for VTE in the oncological patients exist,[14,15] but there is no accurate model specially for ovarian cancer patients. Therefore, an accurate VTE risk prediction model suitable for ovarian cancer patients is urgently needed.

In this study, we developed a nomogram model, based on clinicopathological characteristics of our study cohort composed of 208 EOC patients, to predict the possibility of VTE. The nomogram accurately predicted the VTE probability with a c-index of 0.75. The AUC for the prediction of VTE was 0.75, which also suggested that the nomogram achieved a good predictive efficacy. This study showed that our nomogram might be effective and practical for clinicians and would allow to better estimate the probability of VTE in EOC patients.

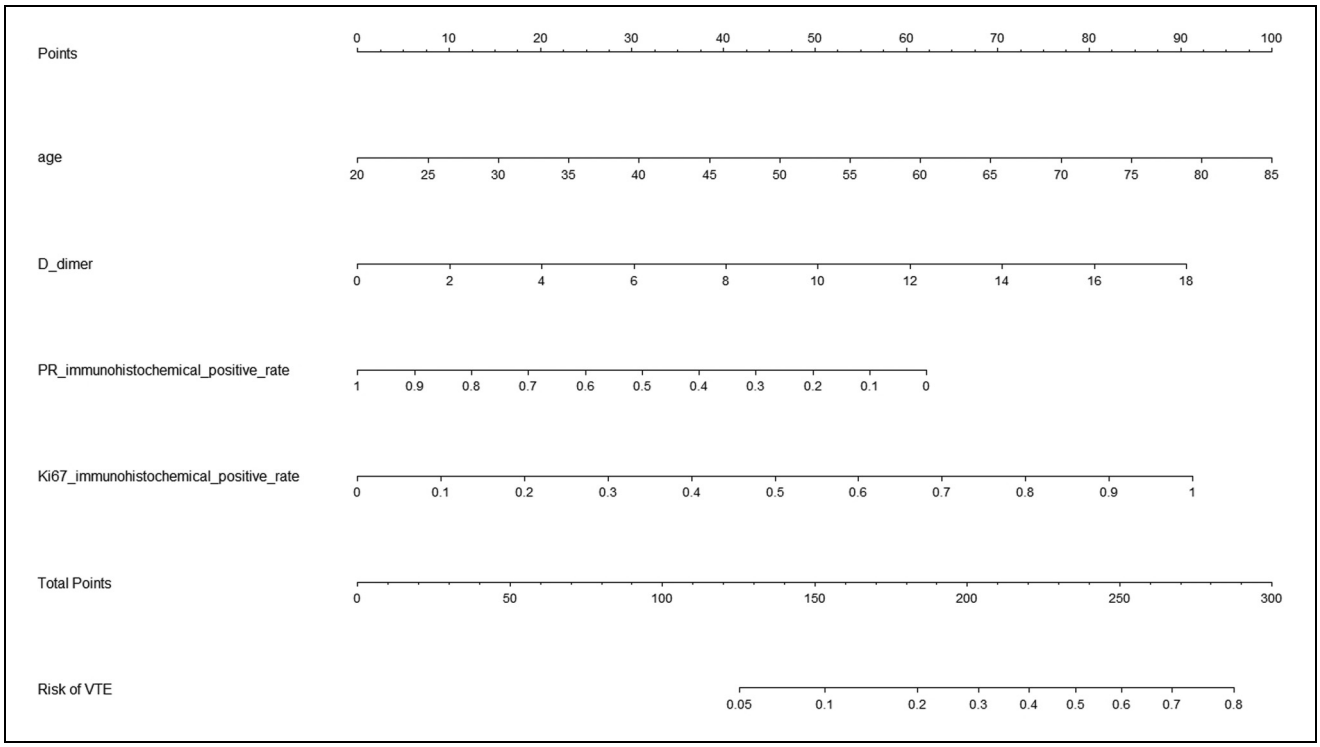


**Figure 1.** Nomogram for predicting venous thromboembolism probability in patients with epithelial ovarian cancer.

We conducted multivariate logistic regression analysis in SPSS software (version 25.0), identify significant factors through backward: LR selection and defined factors whit P values less than 0.05 as significant. In the process of analysis, we found that the P value of PR IHC positive rate was 0.059 but it was still included in the final model. PR IHC positive rate was excluded from the model when we used forward: LR selection method, but the AUC changed to 0.732, so we keep this factor in the model.

Our study showed that advancing age, higher D-dimer level, lower PR IHC positive rate and higher Ki67 IHC positive rate were risk factors for VTE. Many studies came to the conclusion that D-dimer level is a predictor for VTE, and some studies have attempted to establish a cut-off value to differentiate patients with a high risk of VTE. Kawaguchi R, et al came to the conclusion that the suitable cut-off value of D-dimer for detecting VTE in EOC patients appears to be 1.5 μg/mL, with a 61.1% specificity and 100% sensitivity.[16] Ebina Y, et al reported a suitable D-dimer cut-off value of 10.9 mg/mL, with 92.9% specificity and 52.0% sensitivity.[17] Meanwhile, a 2017 study came to the conclusion that different D-dimer cut-off values should be set for different age groups.[18] A recognized and accurate cut-off value of D-dimer is not available at present. In this study, D-dimer was also considered as an independent predictor of VTE, and D-dimer in this nomogram is a continuous variable, which may be more conducive to the individualized estimation of the incidence of VTE in patients than setting a cut-off value.

Immunohistochemistry (IHC) is increasingly used in the diagnosis and treatment of tumors, and ER (estrogen receptor), PR, Ki67 and P53 are commonly used IHC markers in ovarian cancer. The tumor expression of ER is highly expressed in many epithelial ovarian cancers and may be a potential target for endocrine therapy.[19] The PR was shown to be associated with improved overall survival in patients with ovarian cancer.[20,22] Ki67 is a well-known proliferation marker that is highly expressed in malignant cells but almost undetectable in normal cells.[23] The presence of p53 immunoreactivity is correspond to the expression of missense mutation of the P53 gene, which may be one of the causes of tumor formation.[24] Many ovarian cancer patients have abnormal levels of hemostatic serum markers, leading to an activation of the coagulation system, which makes patients more prone to VTE and promotes tumor progression.[25] Schüler-Toprak S, et, al. performed IHC analyses of 171 ovarian cancer patients and found that the expression of PR and Ki-67 was significantly correlated with the progression-free survival.[26] In this study, we innovatively incorporated the results of immunohistochemistry into the thrombosis risk prediction, and finally PR and Ki67 were included in the prediction model as risk factors of VTE, among which the presence of PR immunoreactivity was a protective factor of VTE and the presence of Ki67 immunoreactivity was a risk factor of VTE. Further studies are needed to determine the association between PR, Ki67 and VTE and tumor progression.

The aggressive subtype clear cell carcinoma (CCC) was proven to be a risk factor in many studies,[3,4] while in this study histology did not show significance. We thought the main reason of this result was that the study population of our study is relatively small. CCC is a rare pathologic type, only 26 patients in this study was diagnosed with ovarian CCC, this may have prevented the effect of CCC on VTE from showing up in this patient cohort. Some studies considered advanced stage as a predictor of VTE,[3,27,28]

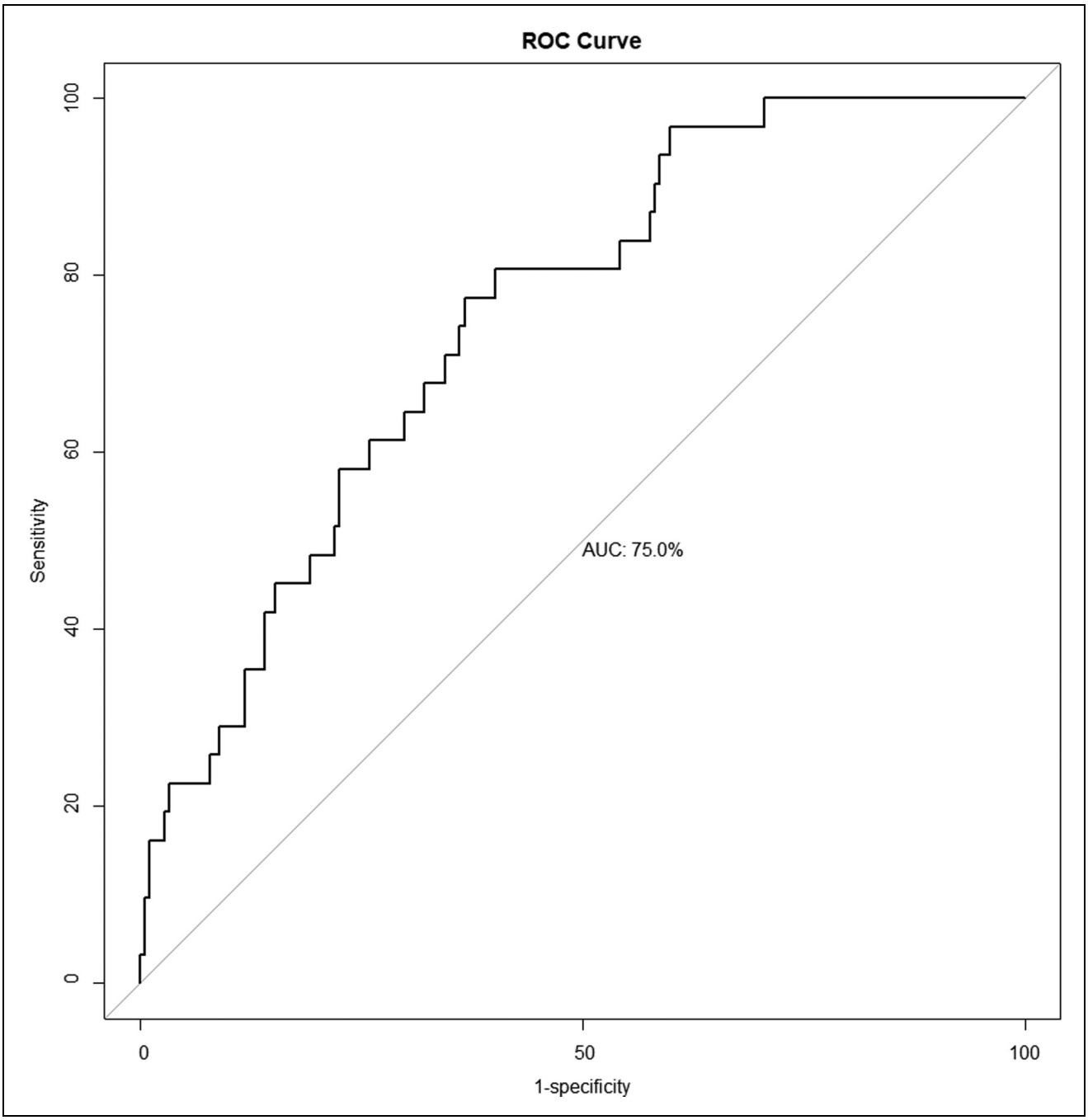


**Figure 2.** ROC curves of the nomogram.

while stage was not included in the final model in this study, which is consistent with a 2019 study.[13] This may be due to the relatively small sample size of our study and the fact that 37.2% of stage I patients in this study were of clear cell type. These two factors may have a mixed effect on the result.

Since only 140 (67.3%) of the patients in this study had blood lipid examination at the time of initial diagnosis of ovarian cancer, so hyperlipidemia was not included in the model and was analyzed using Chi-square test. The result showed that $\chi^2 = 1.83$ and $P = .176$, hyperlipidemia was not a significance predictor for VTE.

In this study, 142 (68.3%) patients received prophylactic anticoagulant therapy after surgery. Contrary to our expectation, prophylactic anticoagulation was not an independent predictor of VTE in this study. One possible explanation is that according to the American College of Chest Physicians (ACCP)-9 guidelines,[7] the duration of prophylactic anticoagulant therapy for high-VTE-risk patients undergoing abdominal or pelvic surgery for malignant tumors should be four weeks, while the duration of prophylactic anticoagulant therapy for patients in our study ranges from 3 to 10 days, insufficient treatment time may cause inaccurate results.

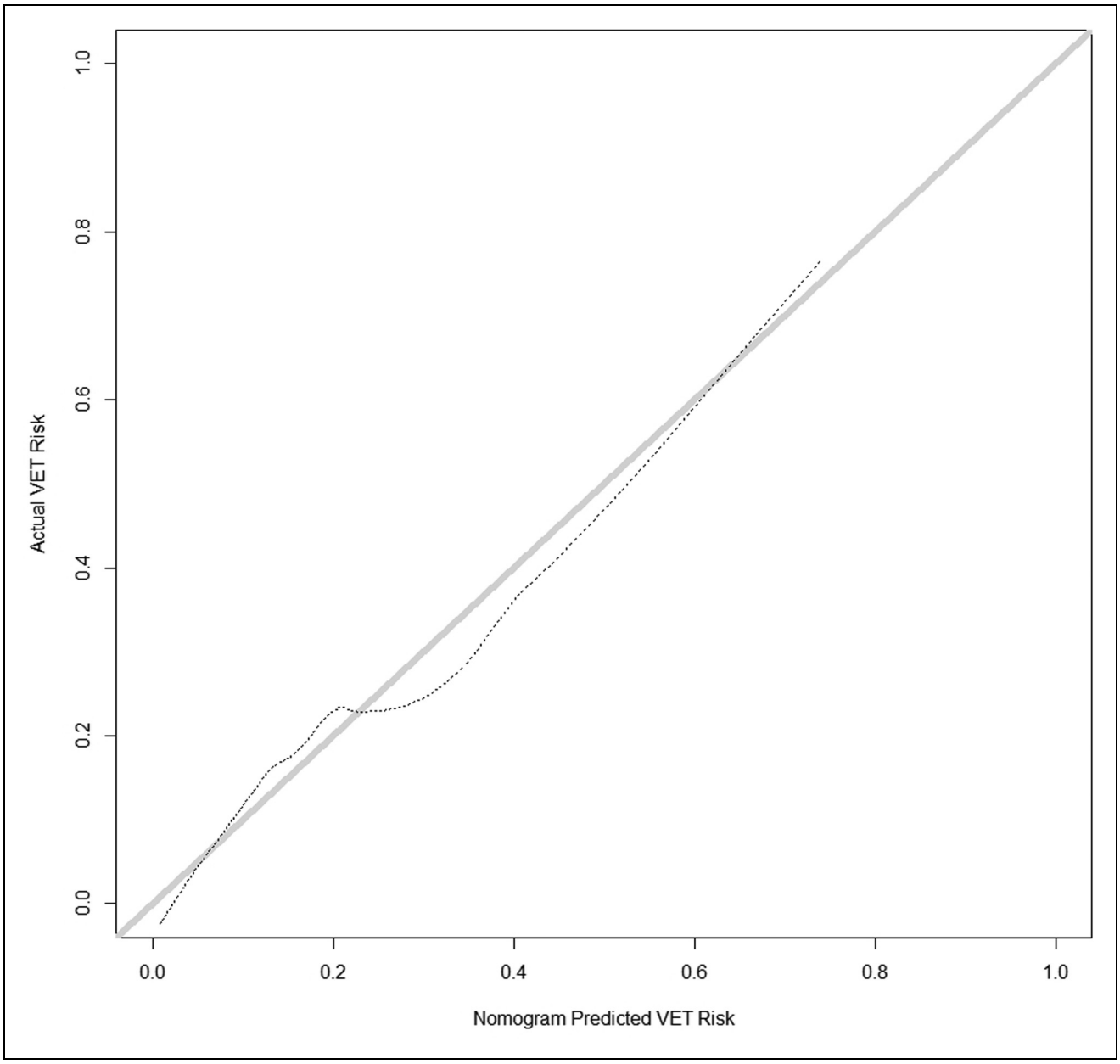


**Figure 3.** Calibration curve of the nomogram. (The gray line represents the actual VTE probability, while the dotted line represents the probability of the VTE predicted by nomogram.)

This study still has several limitations due to its retrospective nature and small sample size. Besides, as this study has a single-center cohort, selection bias was inevitable which may influence the result. Finally, though AUC and calibration curve showed that the nomogram has a high accuracy, it still needs external validation to evaluate its prediction ability. A multicenter validation with larger sample size is needed to obtain high level clinical application evidence.

## Conclusion

We recommend a routine assessment to identify EOC patients who are at high risk of VTE, using preventive anticoagulant therapy to improve the overall survival and quality of life of EOC patients. This study developed a predictive nomogram for VTE probability in EOC patients. Highly consistent calibration curve, high C-index and AUC indicate good discrimination and differentiation of the nomogram.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work

was supported by the Csco-Pilot Cancer Research Fund, Natural Science Foundation of Guangdong Province, (grant number Y-2019AZMS-0393, 2021A1515010267).

## ORCID iD

Tingting Yao https://orcid.org/0000-0002-0231-6047

## References


1. Gary T, Belaj K, Steidl K, et al. Asymptomatic deep vein thrombosis and superficial vein thrombosis in ambulatory cancer patients: impact on short-term survival. *Br J Cancer*. 2012;107(8):1244-1248. doi:10.1038/bjc.2012.401
2. Jacobson G, Lammli J, Zamba G, Hua L, Goodheart MJ. Thromboembolic events in patients with cervical carcinoma: incidence and effect on survival. *Gynecol Oncol*. 2009;113(2):240-244. doi:10.1016/j.ygyno.2009.01.021
3. Abu Saadeh F, Norris L, O'Toole S, Gleeson N. Venous thromboembolism in ovarian cancer: incidence, risk factors and impact on survival. *Eur J Obstet Gynecol Reprod Biol*. 2013;170(1):214-218. doi:10.1016/j.ejogrb.2013.06.004
4. Rodriguez AO, Wun T, Chew H, Zhou H, Harvey D, White RH. Venous thromboembolism in ovarian cancer. *Gynecol Oncol*. 2007;105(3):784-790. doi:10.1016/j.ygyno.2007.02.024
5. Tateo S, Mereu L, Salamano S, et al. Ovarian cancer and venous thromboembolic risk. *Gynecol Oncol*. 2005;99(1):119-125. doi:10.1016/j.ygyno.2005.05.009
6. Black D, Iasonos A, Ahmed H, Chi DS, Barakat RR, Abu-Rustum NR. Effect of perioperative venous thromboembolism on survival in ovarian, primary peritoneal, and fallopian tube cancer. *Gynecol Oncol*. 2007;107(1):66-70. doi:10.1016/j.ygyno.2007.05.040
7. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: american College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e227S-e277S. doi:10.1378/chest.11-2297
8. Stroud W, Whitworth JM, Miklic M, et al. Validation of a venous thromboembolism risk assessment model in gynecologic oncology. *Gynecol Oncol*. 2014;134(1):160-163. doi:10.1016/j.ygyno.2014.04.051
9. Barber EL, Clarke-Pearson DL. The limited utility of currently available venous thromboembolism risk assessment tools in gynecological oncology patients. *Am J Obstet Gynecol*. 2016;215(4):445.e1-445.e9. doi:10.1016/j.ajog.2016.04.034
10. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol*. 2008;26(8):1364-1370. doi:10.1200/JCO.2007.12.9791
11. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA*. 2005;293(6):715-722. doi:10.1001/jama.293.6.715
12. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost*. 2007;5(3):632-634. doi:10.1111/j.1538-7836.2007.02374.x
13. Kahr HS, Christiansen OB, Grove A, et al. Venous thromboembolism in epithelial ovarian cancer. A prospective cohort study. *Thromb Res*. 2019(9);181:112-119. doi:10.1016/j.thromres.2019.07.027
14. Angelini D, Khorana AA. Risk assessment scores for cancer-associated venous thromboembolic disease. *Semin Thromb Hemost*. 2017;43(5):469-478. doi:10.1055/s-0036-1597281
15. Pabinger I, van Es N, Heinze G, et al. A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts. *Lancet Haematol*. 2018;5(7):e289-e298. doi:10.1016/S2352-3026(18)30063-2
16. Kawaguchi R, Furukawa N, Kobayashi H. Cut-off value of D-dimer for prediction of deep venous thrombosis before treatment in ovarian cancer. *J Gynecol Oncol*. 2012;23(2):98-102. doi:10.3802/jgo.2012.23.2.98
17. Ebina Y, Uchiyama M, Imafuku H, Suzuki K, Miyahara Y, Yamada H. Risk factors for deep venous thrombosis in women with ovarian cancer. *Medicine (Baltimore)*. 2018;97(23):e11009. doi:10.1097/MD.0000000000011009
18. Prochaska JH, Frank B, Nagler M, et al. Age-related diagnostic value of D-dimer testing and the role of inflammation in patients with suspected deep vein thrombosis. *Sci Rep*. 2017;7(1):4591. doi:10.1038/s41598-017-04843-x
19. Langdon SP, Gourley C, Gabra H, Stanley B. Endocrine therapy in epithelial ovarian cancer. *Expert Rev Anticancer Ther*. 2017;17(2):109-117. doi:10.1080/14737140.2017.1272414
20. Sieh W, Kobel M, Longacre TA, et al. Hormone-receptor expression and ovarian cancer survival: an Ovarian Tumor Tissue Analysis consortium study. *Lancet Oncol*. 2013;14(9):853-862. doi:10.1016/S1470-2045(13)70253-5
21. Luo H, Li S, Zhao M, Sheng B, Zhu H, Zhu X. Prognostic value of progesterone receptor expression in ovarian cancer: a meta-analysis. *Oncotarget*. 2017;8(22):36845-36856. doi:10.18632/oncotarget.15982
22. Le Page C, Rahimi K, Mes-Masson AM, Kobel M. Prognostic value of progesterone receptor expression in tubo-ovarian high-grade serous carcinoma of the COEUR cohort. *Histopathology*. 2019;74(4):663-666. doi:10.1111/his.13784
23. Yang C, Zhang J, Ding M, et al. Ki67 targeted strategies for cancer therapy. *Clin Transl Oncol*. 2018;20(5):570-575. doi:10.1007/s12094-017-1774-3
24. Battifora H. p53 immunohistochemistry: a word of caution. *Hum Pathol*. 1994;25(5):435-437. doi:10.1016/0046-8177(94)90113-9
25. Swier N, Versteeg HH. Reciprocal links between venous thromboembolism, coagulation factors and ovarian cancer progression. *Thromb Res*. 2017(2);150:8-18. doi:10.1016/j.thromres.2016.12.002
26. Schuler-Toprak S, Weber F, Skrzypczak M, Ortmann O, Treeck O. Estrogen receptor beta is associated with expression of cancer associated genes and survival in ovarian cancer. *BMC Cancer*. 2018;18(1):981. doi:10.1186/s12885-018-4898-0
27. Gerotziafas GT, Taher A, Abdel-Razeq H, et al. A Predictive Score for Thrombosis Associated with Breast, Colorectal, Lung, or Ovarian Cancer: the Prospective COMPASS-Cancer-Associated Thrombosis Study. *Oncologist*. 2017;22(10):1222-1231. doi:10.1634/theoncologist.2016-0414
28. Trugilho IA, Renni MJP, Medeiros GC, Thuler LCS, Bergmann A. Incidence and factors associated with venous thromboembolism in women with gynecologic cancer. *Thromb Res*. 2020;185(1):49-54. doi:10.1016/j.thromres.2019.11.009