Am J Cancer Res 2026;16(4):1393-1414
www.ajcr.us /ISSN:2156-6976/ajcr0171479

Original Article

Multidimensional impact of venous thromboembolism on survival outcomes in ovarian cancer patients: deconstructing competing risks between thrombosis-related and tumor-related mortality

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Received January 14, 2026; Accepted March 25, 2026; Epub April 15, 2026; Published April 30, 2026

Abstract: Ovarian cancer carries one of the highest risks of venous thromboembolism (VTE) among gynecological malignancies, yet the independent contribution of VTE to cause-specific mortality remains insufficiently characterized. This retrospective study included 550 primary epithelial ovarian cancer patients who underwent surgery between January 2015 and December 2022 (VTE group, n=68; non-VTE group, n=482), with a median follow-up of 50 months. Fine-Gray competing-risk models and Cox proportional hazards regression were applied to evaluate mortality outcomes. VTE incidence was 12.4%. Elevated D-dimer (odds ratio [OR]=5.398, P<0.001), elevated platelet count (OR=1.007, P=0.005), and operative time ≥240 min (OR=2.255, P=0.033) were identified as independent risk factors for VTE occurrence, while elevated hemoglobin (OR=0.962, P=0.002) and CA125>500 U/mL (OR=0.335, P=0.008) were associated with reduced risk. VTE independently worsened overall survival (HR=2.533, P<0.001). Competing-risk analysis revealed that VTE significantly increased both tumor-related death (SHR=1.624, P=0.014) and VTE-related death (SHR=4.086, P<0.001). At 60 months, cumulative tumor-related mortality was 54.9% versus 34.5%, and VTE-related mortality was 14.7% versus 3.5% in VTE versus non-VTE groups, respectively. Subgroup analyses demonstrated consistent adverse effects of VTE across most clinical subgroups, with a trend toward stronger VTE-related mortality impact in patients with lower tumor burden (CA125≤500 U/mL, P interaction=0.070). Among VTE patients, guideline-adherent anticoagulation significantly reduced VTE-related mortality (P<0.001) but did not significantly affect tumor-related death (P=0.681). These findings demonstrate that VTE imposes a dual mortality burden in ovarian cancer, and the competing-risk framework more accurately delineates this impact than conventional survival analysis. Early VTE recognition and guideline-adherent anticoagulation should be prioritized within the comprehensive management of ovarian cancer.

Keywords: Ovarian cancer, venous thromboembolism, competing risk, Fine-Gray model, cumulative incidence function, anticoagulation therapy

Introduction

The most lethal gynecological malignancy is ovarian cancer. GLOBOCAN 2022 estimates about 325000 new cases and 207000 deaths worldwide in that year. Ovarian cancer is the eighth most common and the fourth deadliest cancer for women [1]. As early symptoms are often vague and effective screening methods unfeasible, approximately 70% will have advanced disease at diagnosis. According to a study, the five-year survival rate is 30-50% [2]. Despite the continuing changes to the surgical technique and the introduction of platinum-based chemotherapy regimens, as well as the addition of targeted agents (e.g., PARP inhibitors) to first-line and maintenance therapy, overall survival for advanced ovarian cancer is not satisfactory [3].

Venous thromboembolism (VTE) is a frequent complication of cancer and can be fatal. As

early as 19th century, Trousseau highlighted the strong association between malignancy and thrombosis which is now referred to as Trousseau syndrome [4]. The cancer-related VTE's mechanisms are intricate, involving the tissue factor expression by tumor cells, procoagulant microparticle release, platelet activation, coagulation cascade's activation, and inflammation-induced endothelial dysfunction [5]. Epidemiological findings reveal a 4-7 fold increased risk for VTE among cancer patients compared to the general population. VTE is the second most common cause for dying in hospital in cancer patients after disease progression [6].

Ovarian cancer is the due one of the highest risks of VTE. A systematic review and meta-analysis reported an overall VTE incidence of about 9% in ovarian cancer patients on chemotherapy [7]. For patients receiving neoadjuvant chemotherapy (NACT), the risk of VTE increases even further; several systematic reviews and a multicenter cohort study have reported rates of 10%-13% [8-10]. The risk of venous thrombosis and pulmonary embolism rapidly increases in the presence of various factors such as enhanced disease stage, ascites, compression by pelvic mass of vessels, extensive surgery, prolonged operative times and platinum-based chemotherapy [11]. The presence of VTE not only significantly increases the risk of mortality but may also delay antitumor treatment, reduce patients' quality of life, and increase healthcare costs [12].

Past research analyzing the prognosis of VTE in ovarian cancer has limitations. The study most often used overall survival as a single endpoint without distinguishing between tumour-related deaths and VTE-related deaths, which makes it impossible to estimate the contribution of each component to the overall result. Traditional Kaplan-Meier analysis and Cox proportional hazards approaches treat competing events as censored. When multiple outcomes study the same patient, it violates the independent censoring assumption and may lead to a systematic bias in cummulative incidence estimates [13]. Competing-risk methods represent more accurately the probabilities of different outcomes. The Fine-Gray subdistribution hazard model offers direct estimates of the effect of exposure variables on the cumulative incidence of a specific event. In addition, there is a lack of data available on the influence of guideline-adherent anticoagulation on cause-specific mortality in ovarian cancer patients with VTE.

In this context, we conducted our analysis of competing-risk with death from tumor and VTE as the two main outcomes. We evaluated the independent impact of VTE on different mortality endpoints, heterogeneity across clinical subgroups, and the prognostic effect of anticoagulation adherence in VTE. The aim of this project is to provide VTE prevention, early detection, and standardised management evidence to optimize the overall treatment of ovarian cancer.

Materials and methods

Sample size calculation

The aim of this study was to determine the effect of venous thromboembolism on survival in ovarian cancer patients through a retrospective cohort study. The total events were ensured sufficient through the event-count method of estimating the sample size for Cox proportional hazards models. Because competing-risk models typically require sample sizes that are no smaller than those for conventional survival analysis, the actual sample and event counts attained in this study satisfied the statistical power requirements for such an analysis. Based on findings from Penfound et al. [12], who reported a VTE incidence of approximately 9.44% and significantly elevated mortality risk among VTE patients (HR≈2.5), we calculated the required number of events using the Schoenfeld formula: $d = (Z\alpha/2 + Z\beta)^2/[P1 \times P2 \times (\ln HR)^2]$, where $Z\alpha/2=1.96$ (two-sided $\alpha=0.05$), $Z\beta=0.84$ (power 1-β=80%), P1=0.12 (proportion in VTE group), P2=0.88 (proportion in non-VTE group), and HR=2.5. The minimum number of death events required was 89. With an overall mortality rate of approximately 45%, the needed sample size was N=89/0.45≈198 patients. To account for the need to differentiate causes of death and perform subgroup analyses in competing-risk analysis, the sample size was increased. The sample size requirements were met, as shown in **Figure 1**, with 550 patients enrolled in this study with 243 deaths.

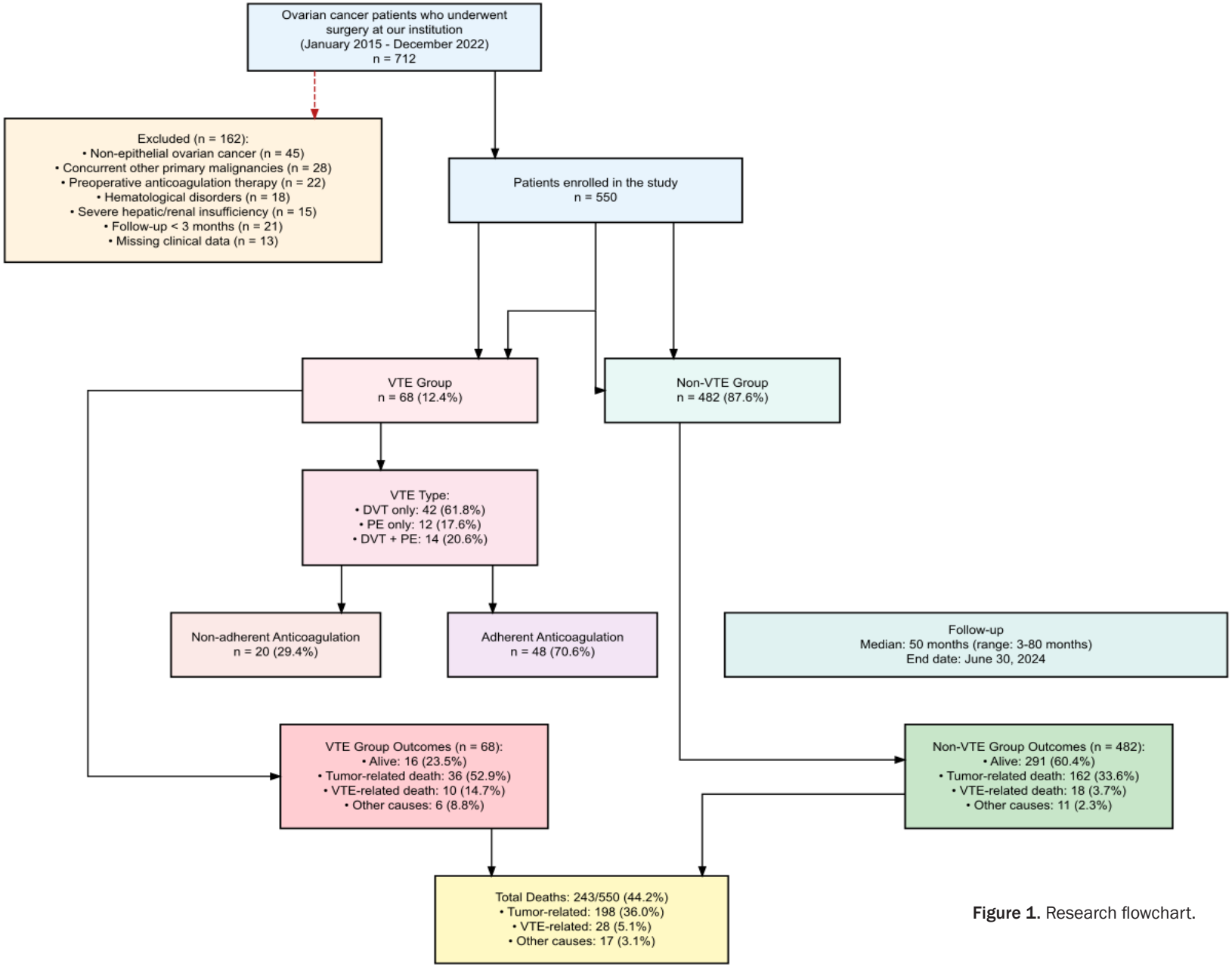

Figure 1. Research flowchart.

Patient selection

A total of 550 patients with ovarian cancer, who underwent surgery at the Northwest Women's and Children's Hospital and Norinco General Hospital between January 2015 and December 2022, were studied using retrospective data to analyse clinical data. This study was approved by the Ethics Committee of Northwest Women's and Children's Hospital. The requirement for informed consent was waived owing to the retrospective nature of the study. Inclusion criteria included: (1) Pathologically confirmed primary epithelial ovarian cancer [14]; (2) Underwent primary or interval cytoreductive surgery; (3) Complete clinicopathological data; and (4) Complete follow-up data. The exclusion criteria were: 1) concurrent illnesses of other malignant tumors, 2) anticoagulant therapy before the procedure (except when prophylactic), 3) hematologic disorders affecting coagulation function, 4) severe liver or kidney insufficiency, 5) follow up <3 months, 6) lack of a sufficient amount of clinical data.

Clinical data collection

General patient characteristics collected included age, body mass index (BMI), comorbidities (hypertension, diabetes, coronary heart disease), and prior VTE history. Data on the tumor included the International Federation of Gynecology and Obstetrics (FIGO) stage [15], histological type (high-grade serous carcinoma versus the rest), cytoreductive surgery status (optimal cytoreduction defined as ≤1 cm of residual disease), serum Cancer Antigen 125 (CA125) and perioperative parameters (operating time and intraoperative blood loss).

Treatment-related data included chemotherapy regimen (paclitaxel plus carboplatin versus other regimens), whether patients received neoadjuvant chemotherapy, and whether they received poly ADP-ribose polymerase (PARP) inhibitor maintenance therapy.

VTE-related data included VTE occurrence, VTE type (deep vein thrombosis [DVT], pulmonary embolism [PE], or DVT combined with PE), timing of VTE (perioperative versus non-perioperative), and anticoagulation treatment details. Guideline-adherent anticoagulation was defined as completing at least 3 months of standard-dose anticoagulation per guideline recommendations. Non-adherent anticoagulation referred to incomplete treatment courses or insufficient dosing for various reasons.

Preoperative coagulation and hematological parameters collected included D-dimer, fibrinogen, platelet count, prothrombin time (PT), hemoglobin, and albumin.

Laboratory testing

All laboratory parameters were measured from fasting venous blood samples collected within one week before surgery. D-dimer was measured by immunoturbidimetry (Shanghai Enzyme-linked Biotechnology Co., Ltd., lot number: ML-E12345). Fibrinogen was measured by the clotting method (Shanghai Enzyme-linked Biotechnology Co., Ltd., lot number: ML-E12346). Prothrombin time was measured by the clotting method using a Sysmex CS-5100 automated coagulation analyzer (Sysmex Corporation, Japan). Platelet count and hemoglobin were measured using a Sysmex XN-9000 automated hematology analyzer (Sysmex Corporation, Japan). Albumin was measured by the bromocresol green method using a Hitachi 7600 automated biochemical analyzer (Hitachi, Japan). CA125 was measured by electrochemiluminescence immunoassay using a Roche Cobas e801 system (Roche, Switzerland).

VTE diagnostic criteria

VTE in this study was defined as deep vein thrombosis (DVT) and/or pulmonary embolism (PE); superficial vein thrombosis was not included. VTE diagnosis was based on a symptom-driven approach, whereby imaging examinations were performed in patients presenting with clinical symptoms suggestive of VTE (e.g., lower extremity swelling, pain, dyspnea, or chest pain), rather than routine screening in asymptomatic patients. DVT was diagnosed by lower extremity venous color Doppler ultrasonography, characterized by solid hypoechoic or anechoic filling within the deep venous system (including femoral, popliteal, and tibial veins), incompressibility under probe pressure, and color flow signal defects. PE was diagnosed by computed tomography pulmonary angiography (CTPA), characterized by filling defects within the main pulmonary artery or its branches [16, 17].

Anticoagulation treatment protocol

For ovarian cancer patients diagnosed with VTE, anticoagulation therapy was administered according to international guidelines for cancer-associated thrombosis (ITAC 2022, ASCO 2023). The treatment protocol consisted of three phases: (1) Initial phase (first 5-10 days): Low-molecular-weight heparin (LMWH) was administered at therapeutic doses (e.g., enoxaparin 1 mg/kg twice daily or 1.5 mg/kg once daily; dalteparin 200 IU/kg once daily). For patients with stable disease, low bleeding risk, and no significant drug-drug interactions, direct oral anticoagulants (DOACs) such as rivaroxaban (15 mg twice daily for the first 21 days) or apixaban (10 mg twice daily for the first 7 days) were considered as alternatives.

(2) Long-term phase (up to 6 months): LMWHs (e.g. dalteparin 150 IU/kg once daily after the first month) or DOACs (rivaroxaban 20 mg once daily; apixaban 5 mg twice daily) were continued. Selection of LMWH or DOACs was individualized based on bleeding risk, renal function, possible drug-drug interactions with anticancer therapies and patient choice.

(3) Extended phase (greater than 6 months): In case of active cancer/ongoing chemotherapy prolonged anticoagulation was continued with periodic reassessment of risk-versus-benefit situation. Anticoagulation was considered guideline adherent if at least 3 months of therapeutic-dose anticoagulation was delivered. Non-adherent anticoagulation was defined as its premature discontinuation or use of subtherapeutic doses because of high bleeding risk, poor compliance, disease progression or costs. According to ISTH, the dose in patients with thrombocytopenia ($<50\times10^9$/L) and patients with renal impairment (creatinine clearance <30 mL/min) was adjusted.

Outcome measures

Primary outcomes: Death caused by tumor progression, recurrence, malignant bowel obstruction or cachexia. A death caused due to any of a fatal PE, acute MI, or a cerebral embolism.

Secondary outcomes: Overall survival (OS) is the time from surgery to death from any cause or last follow-up. The occurrence of VTE is defined as the time from surgery to the first confirmed diagnosis of VTE.

Follow-up

Patient survival information was collected through outpatient visits, inpatient medical record review, and telephone follow-up. Follow-up ended on June 30, 2024, with a median follow-up of 50 months (range: 3-80 months). Follow-up data contained details on survival status, death date and cause of death. Cause of death was determined through a standardized adjudication process. Primary information sources included inpatient medical records, death certificates, imaging and laboratory reports, and family-reported information obtained via telephone follow-up. All available clinical information was reviewed independently by two attending gynecologic oncologists who were blinded to each other's assessments. Causes of death were classified into three categories according to pre-specified definitions: (1) tumor-related death, defined as death attributable to tumor progression, recurrence, malignant bowel obstruction, or cancer-related cachexia; (2) VTE-related death, defined as death attributable to fatal pulmonary embolism, acute myocardial infarction secondary to thromboembolism, or cerebral embolism confirmed by clinical, imaging, or autopsy findings; and (3) other-cause death, defined as death from causes unrelated to tumor or thromboembolism, including cardiovascular events (heart failure, sudden cardiac death), septic shock, gastrointestinal bleeding, or accidental death. In cases of disagreement between the two reviewers, a third senior gynecologic oncologist was consulted, and consensus was reached through discussion. The inter-rater agreement for cause-of-death classification was assessed using Cohen's kappa coefficient (κ=0.83), indicating strong agreement.

Statistical analysis

Statistical analyses were performed using R version 4.5.1 and SPSS version 27.0. Normally distributed continuous variables are presented as mean ± standard deviation (SD), and between-group comparisons were performed using independent-samples t-tests. Non-normally distributed continuous variables are presented as median (interquartile range) [M (Q1, Q3)] with between-group comparisons using

Mann-Whitney U tests. Categorical variables are expressed as count (percentage) [n (%)] along with between-group comparisons via chi-square tests or Fisher's exact test. Receiver operating characteristic (ROC) curves were used to evaluate the predictive value of continuous variables for VTE. Areas under the curve (AUC) were calculated for continuous variables and optimal cut-off values were obtained. Collinearity among candidate variables was assessed prior to each multivariate model using two complementary approaches: Spearman rank correlation analysis, with $|r|>0.6$ defined as strong collinearity; and variance inflation factor (VIF) calculation, with VIF>5 defined as the threshold for problematic collinearity. When collinearity was detected between two variables, the variable with greater clinical relevance or superior predictive performance was retained and the other excluded. Univariate and multivariate logistic regression analyses were used to identify risk factors for VTE, and the results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). The factors affecting the Overall Survival (OS) of patients were analyzed using Univariate and multivariate Cox proportional hazards regression, and expressed as hazard ratios (HR) and 95% confidence intervals (CI). The impact of VTE in the Fine-Gray competing-risk model was assessed according to different types of mortality. In particular, tumour-related death and VTE-related death were the primary endpoints while other-cause death was a competing event. Cumulative incidence function (CIF) curves were created, and daff of cumulative incidence between groups was compared using Gray test. Multivariate analyzes Fine-Gray regression results of overall cumulative mortality are expressed in Shr subdistribution hazard ratio for complication and 95% CI. The subgroup analyses by FIGO stage, histological type, cytoreductive surgery status, age, CA125 level, and chemotherapy regimen interrogated the heterogeneity of VTE's effect on death outcomes, with P interactions calculated. A two-tailed *P*-value of less than 0.05 was considered statistically significant.

Results

Baseline patient characteristics

This study enrolled 550 ovarian cancer patients, including 68 in the VTE group (12.4%) and 482 in the non-VTE group (87.6%). The overall median follow-up was 50 months (range: 3-80 months; IQR: 34-60 months). The VTE group had a significantly shorter median follow-up of 34 months (range: 3-65 months; IQR: 17-54 months) compared with 51 months (range: 3-80 months; IQR: 37-62 months) in the non-VTE group (Mann-Whitney U test, W= 10459.5, P<0.001), consistent with the higher mortality burden in VTE patients. Of the 550 enrolled patients, 12 (2.2%) were lost to follow-up after their last recorded contact, including 2 (2.9%) in the VTE group and 10 (2.1%) in the non-VTE group, with a median time to last contact of 41 months (range: 7-65 months; IQR: 12-53 months). The loss-to-follow-up rate was low and balanced between groups (Fisher's exact test, P=0.721). These patients were censored at the date of their last known contact in all survival analyses. Significant differences existed between groups regarding surgical and coagulation-related parameters. The VTE group had a higher proportion of patients with operative time ≥240 min (P=0.005) and intraoperative blood loss ≥1000 ml (P=0.029). For coagulation and hematological parameters, the VTE group showed significantly higher D-dimer (P< 0.001), fibrinogen (P<0.001), platelet count (P< 0.001), and prothrombin time (P=0.042), while hemoglobin (P<0.001) and albumin (P=0.015) were significantly lower. No significant differences were observed between groups for age, BMI, FIGO stage, histological type, cytoreductive surgery status, chemotherapy regimen, neoadjuvant chemotherapy, PARP inhibitor maintenance therapy, hypertension, diabetes, coronary heart disease, prior VTE history, or CA125 level (all P>0.05) (**Table 1**; **Figure 2**).

Risk factor analysis for VTE in ovarian cancer patients

To identify independent risk factors for VTE in ovarian cancer patients, we first performed correlation analysis among variables with significant baseline differences. Results showed strong correlations (r>0.6) between D-dimer and fibrinogen (r=0.645), D-dimer and FIGO stage (r=0.661), and operative time and intraoperative blood loss (r=0.668) (**Figure 3**). Collinearity screening identified three strongly correlated variable pairs: D-dimer and fibrinogen (r=0.645, VIF=1.336 and 1.134 respectively), D-dimer and FIGO stage (r=0.661), and operative time and intraoperative blood loss (r=0.668). Accordingly, fibrinogen was excluded in favour of D-dimer (AUC=0.823 vs 0.810);

Table 1. Comparison of baseline characteristics between VTE and non-VTE groups in ovarian cancer patients

Variable	Total	VTE group (n=68)	Non-VTE group (n=482)	χ^2/t	*P* value
Age group				1.800	0.180
<65 years	382 (69.45%)	52 (76.47%)	330 (68.46%)		
≥65 years	168 (30.55%)	16 (23.53%)	152 (31.54%)		
BMI group				0.206	0.650
<28 kg/m^2	440 (80.00%)	53 (77.94%)	387 (80.29%)		
≥28 kg/m^2	110 (20.00%)	15 (22.06%)	95 (19.71%)		
FIGO stage				6.254	0.100
Stage I	157 (28.55%)	12 (17.65%)	145 (30.08%)		
Stage II	65 (11.82%)	7 (10.29%)	58 (12.03%)		
Stage III	196 (35.64%)	32 (47.06%)	164 (34.02%)		
Stage IV	132 (24.00%)	17 (25.00%)	115 (23.86%)		
Histological type				0.178	0.673
High-grade serous carcinoma	376 (68.36%)	48 (70.59%)	328 (68.05%)		
Others	174 (31.64%)	20 (29.41%)	154 (31.95%)		
Cytoreductive surgery				0.848	0.357
Optimal (R0/R1)	359 (65.27%)	41 (60.29%)	318 (65.98%)		
Suboptimal (R2)	191 (34.73%)	27 (39.71%)	164 (34.02%)		
Operative time				7.932	0.005
<240 min	290 (52.73%)	25 (36.76%)	265 (54.98%)		
≥240 min	260 (47.27%)	43 (63.24%)	217 (45.02%)		
Intraoperative blood loss				4.738	0.029
<1000 ml	393 (71.45%)	41 (60.29%)	352 (73.03%)		
≥1000 ml	157 (28.55%)	27 (39.71%)	130 (26.97%)		
Chemotherapy regimen				0.228	0.633
TC regimen	458 (83.27%)	58 (85.29%)	400 (82.99%)		
Others	92 (16.73%)	10 (14.71%)	82 (17.01%)		
Neoadjuvant chemotherapy				0.393	0.531
Yes	129 (23.45%)	18 (26.47%)	111 (23.03%)		
No	421 (76.55%)	50 (73.53%)	371 (76.97%)		
PARP inhibitor maintenance				0.074	0.785
Yes	186 (33.82%)	22 (32.35%)	164 (34.02%)		
No	364 (66.18%)	46 (67.65%)	318 (65.98%)		
Hypertension				0.557	0.455
Yes	126 (22.91%)	18 (26.47%)	108 (22.41%)		
No	424 (77.09%)	50 (73.53%)	374 (77.59%)		
Diabetes				2.122	0.145
Yes	81 (14.73%)	14 (20.59%)	67 (13.90%)		
No	469 (85.27%)	54 (79.41%)	415 (86.10%)		
Coronary heart disease				0.043	0.837
Yes	45 (8.18%)	6 (8.82%)	39 (8.09%)		
No	505 (91.82%)	62 (91.18%)	443 (91.91%)		
Prior VTE history				0.266	0.606
Yes	22 (4.00%)	4 (5.88%)	18 (3.73%)		
No	528 (96.00%)	64 (94.12%)	464 (96.27%)		
CA125				3.399	0.065
≤500 U/ml	284 (51.64%)	28 (41.18%)	256 (53.11%)		
>500 U/ml	266 (48.36%)	40 (58.82%)	226 (46.89%)		
D-dimer (mg/L)	1.27 [0.67, 1.83]	3.18 [1.84, 4.22]	1.18 [0.61, 1.62]	8.632	<0.001
Fibrinogen (g/L)	3.31 [2.71, 3.95]	4.53 [3.75, 5.38]	3.22 [2.59, 3.78]	8.279	<0.001
Platelet count (×10^9/L)	272.90 [224.72, 330.98]	329.15 [261.85, 370.30]	268.05 [218.82, 319.50]	5.152	<0.001
Prothrombin time (s)	11.63±1.09	11.88±1.20	11.59±1.07	-2.041	0.042
Hemoglobin (g/L)	112.30 [101.75, 123.38]	102.75 [91.92, 117.23]	113.15 [103.00, 123.92]	4.078	<0.001
Albumin (g/L)	36.40±4.97	35.03±5.55	36.60±4.86	2.446	0.015

Note: VTE, Venous Thromboembolism; BMI, Body Mass Index; FIGO, International Federation of Gynecology and Obstetrics; HGSC, High-Grade Serous Carcinoma; TC, Paclitaxel plus Carboplatin; PARP, Poly ADP-Ribose Polymerase; CA125, Cancer Antigen 125.

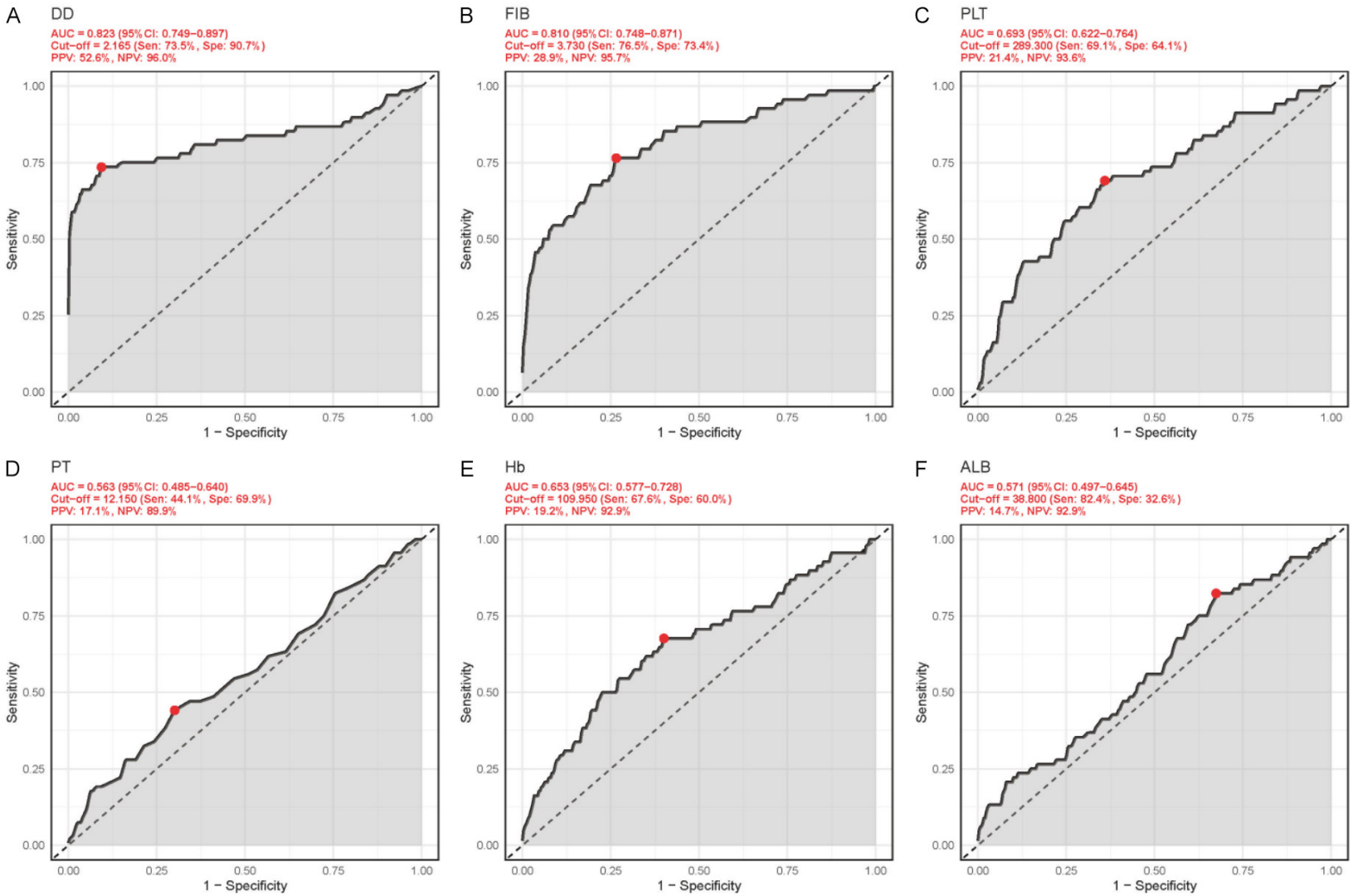

Figure 2. ROC curves of coagulation and hematological parameters for predicting VTE in ovarian cancer patients. A. D-dimer; B. Fibrinogen; C. Platelet count; D. Prothrombin time; E. Hemoglobin; F. Albumin. Note: ROC, Receiver Operating Characteristic; AUC, Area Under the Curve; VTE, Venous Thromboembolism; DD, D-dimer; FIB, Fibrinogen; PLT, Platelet; PT, Prothrombin Time; Hb, Hemoglobin; ALB, Albumin.

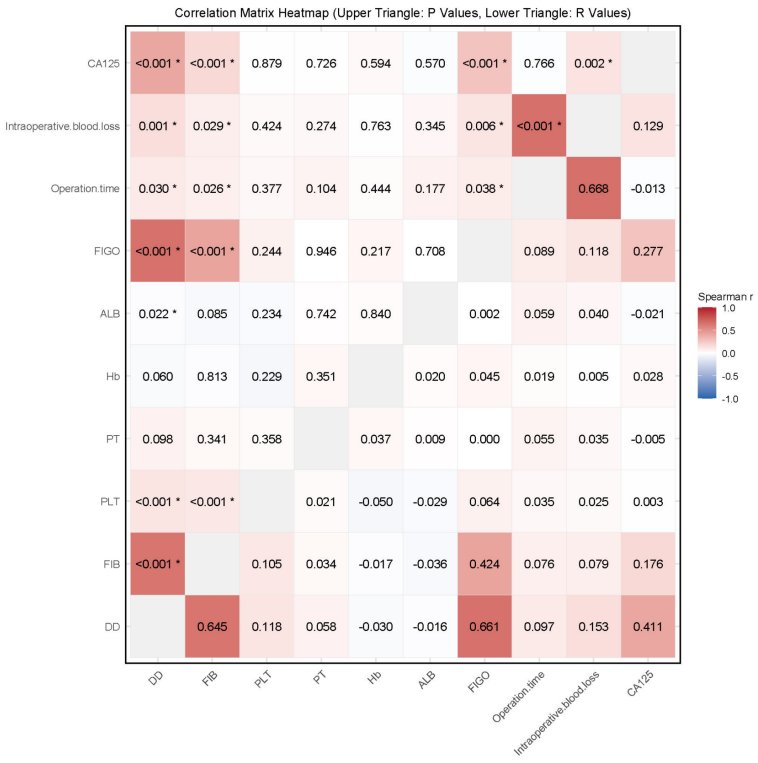

Figure 3. Correlation analysis of differential variables. Note: DD, D-dimer; FIB, Fibrinogen; PLT, Platelet; PT, Prothrombin Time; Hb, Hemoglobin; ALB, Albumin; FIGO, International Federation of Gynecology and Obstetrics; CA125, Cancer Antigen 125.

FIGO stage was excluded as it is not a preoperative coagulation-related variable; and intraoperative blood loss was excluded in favour of operative time, which is clinically more actionable and assessable preoperatively. All retained variables had VIF<5 (**Table 2**), confirming acceptable collinearity in the final model.

Univariate logistic regression showed that D-dimer (P<0.001), platelet count (P<0.001), prothrombin time (P=0.043), hemoglobin (P< 0.001), albumin (P=0.015), and operative time (P=0.006) were significantly associated with VTE occurrence, while CA125 approached significance (P=0.067).

Variables with P<0.1 in univariate analysis were entered into multivariate logistic regression. Results showed that elevated D-dimer (OR=5.398, 95% CI: 3.669-8.414, P<0.001), elevated platelet count (OR=1.007, 95% CI: 1.002-1.011, P=0.005), and operative time ≥240 min (OR=2.255, 95% CI: 1.085-4.871, P=0.033) were independent risk factors for VTE in ovarian cancer patients. Elevated hemoglobin (OR=0.962, 95% CI: 0.939-0.985, P=0.002) and CA125> 500 U/ml (OR=0.335, 95% CI: 0.145-0.741, P=0.008) were independently associated with reduced VTE risk. Prothrombin time (P=0.181) and albumin (P=0.262) were not significant in multivariate analysis (**Table 3**).

Cause of death analysis between VTE and non-VTE groups

Among 550 ovarian cancer patients, 243 died: 52 in the VTE group and 191 in the non-VTE group. When classified by cause, tumor-related death was the leading cause, followed by non-tumor-related death. The distribution of death causes differed significantly between groups. The VTE group had a significantly higher proportion of non-tumor-related deaths and a lower proportion of tumor-related deaths compared with the non-VTE group (P=0.009). Among non-tumor-related deaths, thrombosis-related deaths were significantly more common in the VTE group (P=0.049), with fatal pulmonary embolism as the predominant cause. No significant differences existed between groups for cardiovascular death (P=0.355) or other-cause death (P=0.262) (**Table 4**).

Analysis of factors affecting overall survival in ovarian cancer patients

To identify independent prognostic factors for OS in ovarian cancer patients, we first performed Spearman correlation analysis among variables with P<0.1 in univariate Cox regression (**Figure 4**). Collinearity screening showed strong correlation between D-dimer and FIGO stage (r=0.661, exceeding the |r|>0.6 threshold), and strong correlation between operative time and intraoperative blood loss (r=0.668). D-dimer was therefore excluded from multivariate Cox regression, with VTE (core exposure

Table 2. Variable assignments and collinearity diagnostics for logistic regression

Variable	Assignment	Description	VIF
FIGO stage	I-II=0, III-IV=1	Early vs Advanced	2.565
Operative time	<240 min =0, ≥240 min =1	Based on clinical experience	1.550
Intraoperative blood loss	<1000 ml =0, ≥1000 ml =1	Based on clinical experience	1.037
CA125	≤500 U/ml =0, >500 U/ml =1	Commonly used cutoff in literature	1.030
D-dimer	Continuous	-	1.134
Fibrinogen	Continuous	-	1.336
Platelet count	Continuous	-	1.640
Prothrombin time	Continuous	-	1.672
Hemoglobin	Continuous	-	1.734
Albumin	Continuous	-	1.543

Note: VIF, Variance Inflation Factor; FIGO, International Federation of Gynecology and Obstetrics; CA125, Cancer Antigen 125.

Table 3. Logistic regression analysis of independent risk factors for VTE

Variable	Univariate			Multivariate		
	OR	*P* value	95% CI	OR	*P* value	95% CI
D-dimer	4.839	<0.001	3.432-6.822	5.398	<0.001	3.669-8.414
Platelet count	1.009	<0.001	1.006-1.013	1.007	0.005	1.002-1.011
Prothrombin time	1.274	0.043	1.008-1.610	1.248	0.181	0.904-1.735
Hemoglobin	0.963	<0.001	0.946-0.980	0.962	0.002	0.939-0.985
Albumin	0.938	0.015	0.891-0.988	0.960	0.262	0.893-1.030
Operative time ≥240 min	2.100	0.006	1.243-3.549	2.255	0.033	1.085-4.871
CA125>500 U/ml	1.618	0.067	0.967-2.708	0.335	0.008	0.145-0.741

Note: OR, odds ratio; CI, confidence interval; VTE, venous thromboembolism; CA125, cancer antigen 125.

Table 4. Comparison of causes of death between VTE and non-VTE groups in ovarian cancer patients

Variable	Total (n=243)	VTE group (n=52)	Non-VTE group (n=191)	χ^2	*P* value
Cause of death				6.826	0.009
Tumor-related death	198 (81.48%)	36 (69.23%)	162 (84.82%)		
Tumor progression/recurrence	168 (69.14%)	30 (57.69%)	138 (72.25%)		
Malignant bowel obstruction	18 (7.41%)	4 (7.69%)	14 (7.33%)		
Cachexia	12 (4.94%)	2 (3.85%)	10 (5.24%)		
Non-tumor-related death	45 (18.52%)	16 (30.77%)	29 (15.18%)	6.826	0.009
Thrombosis-related death	28 (11.52%)	10 (19.23%)	18 (9.42%)	3.856	0.049
Fatal pulmonary embolism	18 (7.41%)	8 (15.38%)	10 (5.24%)		
Acute myocardial infarction	6 (2.47%)	1 (1.92%)	5 (2.62%)		
Cerebral embolism	4 (1.65%)	1 (1.92%)	3 (1.57%)		
Cardiovascular death	9 (3.70%)	3 (5.77%)	6 (3.14%)	0.856	0.355
Heart failure	5 (2.06%)	2 (3.85%)	3 (1.57%)		
Sudden cardiac death	4 (1.65%)	1 (1.92%)	3 (1.57%)		
Other causes	8 (3.29%)	3 (5.77%)	5 (2.62%)	1.256	0.262
Septic shock	4 (1.65%)	2 (3.85%)	2 (1.05%)		
Gastrointestinal bleeding	2 (0.82%)	1 (1.92%)	1 (0.52%)		
Accident	2 (0.82%)	0 (0.00%)	2 (1.05%)		

Note: VTE, Venous Thromboembolism; PE, Pulmonary Embolism; MI, Myocardial Infarction.

variable) and FIGO stage (most important prognostic staging system) retained. Intraoperative blood loss was excluded in favour of operative time due to both strong collinearity (r=0.668)

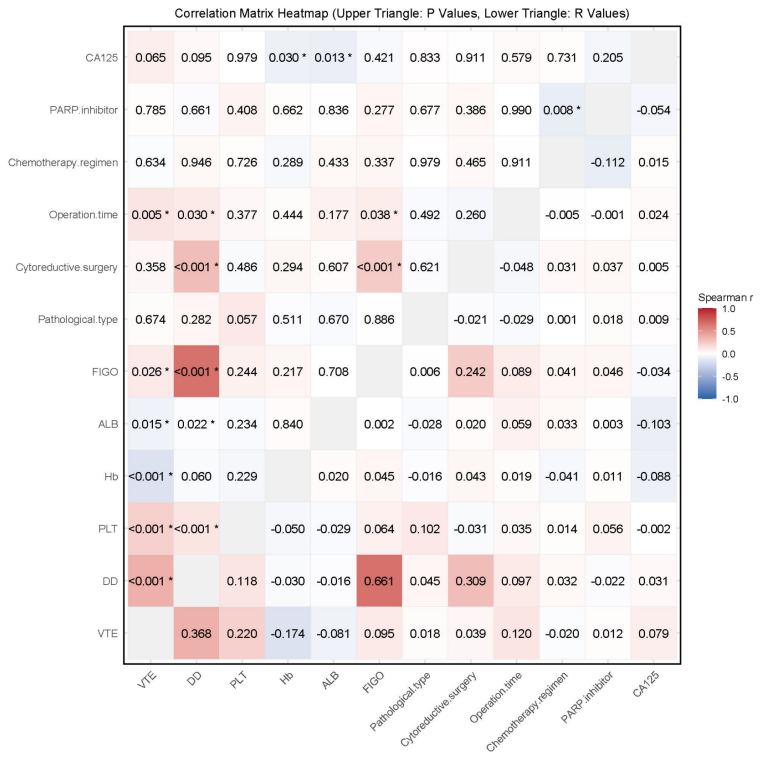

Figure 4. Heatmap of Spearman correlation analysis for predictive variables associated with overall survival. Note: Upper triangle shows *P* values; Lower triangle shows Spearman correlation coefficients (r). *P<0.05. D-dimer was excluded from multivariate analysis due to strong correlation with FIGO stage (r=0.661) and moderate correlation with VTE (r=0.368).

and the fact that intraoperative blood loss is an intraoperative outcome rather than a preoperatively predictable prognostic factor. Spearman correlation coefficients among all remaining variables were <0.4 and VIF values were all <5, confirming acceptable collinearity for simultaneous model inclusion.

Univariate Cox regression showed that VTE (P<0.001), D-dimer (P<0.001), platelet count (P=0.041), FIGO stage (P<0.001), histological type (P=0.004), cytoreductive surgery status (P<0.001), intraoperative blood loss (P< 0.001), PARP inhibitor maintenance therapy (P=0.012), and CA125 (P=0.002) were significantly associated with OS. Chemotherapy regimen (P=0.089) and hemoglobin (P=0.074) approached significance. Age (P=0.597), BMI (P=0.867), operative time (P=0.368), neoadjuvant chemotherapy (P=0.934), hypertension (P=0.651), diabetes (P=0.537), coronary heart disease (P=0.692), prior VTE history (P= 0.449), prothrombin time (P=0.420), and albumin (P=0.809) showed no significant associations with OS.

Variables with P<0.1 in univariate analysis (excluding D-dimer and intraoperative blood loss) were entered into multivariate Cox regression. Results showed that VTE (HR=2.533, 95% CI: 1.794-3.576, P<0.001), FIGO stage III-IV (HR=1.668, 95% CI: 1.259-2.210, P<0.001), high-grade serous carcinoma (HR=1.546, 95% CI: 1.159-2.062, P=0.003), suboptimal cytoreduction (HR=1.789, 95% CI: 1.379-2.322, P<0.001), TC chemotherapy regimen (HR= 1.452, 95% CI: 1.051-2.007, P=0.024), absence of PARP inhibitor maintenance therapy (HR=1.545, 95% CI: 1.164-2.050, P=0.003), and CA125> 500 U/ml (HR=1.361, 95% CI: 1.049-1.765, P=0.020) were independent risk factors for OS. Platelet count (P=0.656) and hemoglobin (P=0.486) were not significant in multivariate analysis (**Table 5**).

Competing-risk analysis of VTE's impact on mortality outcomes in ovarian cancer patients

We used the Fine-Gray competing-risk model to analyze VTE's impact on different mortality outcomes in ovarian cancer patients. With tumor-related and VTE-related death as primary endpoints and other-cause death as a competing event, we plotted CIF curves. Results showed that the VTE group had significantly higher cumulative incidence of tumor-related death than the non-VTE group (Gray's test χ^2=11.747, P<0.001). At 60 months, cumulative incidence of tumor-related death was 54.9% in the VTE group versus 34.5% in the non-VTE group, an absolute difference of 20.4%. Similarly, cumulative incidence of VTE-related death was significantly higher in the VTE group (Gray's test χ^2=14.472, P<0.001). At 60 months, cumulative incidence of VTE-related death was 14.7% in the VTE group versus only 3.5% in the non-VTE group, an absolute difference of 11.2%. These results indicate that VTE not only significantly increases VTE-related

Table 5. Univariate and multivariate Cox regression analysis of factors affecting overall survival in ovarian cancer patients

Variable	Univariate Cox			Multivariate Cox		
	β	*P* value	HR (95% CI)	β	*P* value	HR (95% CI)
VTE (Yes vs No)	1.040	<0.001	2.829 (2.078-3.852)	0.929	<0.001	2.533 (1.794-3.576)
Age (<65 vs ≥65 years)	0.072	0.597	1.075 (0.822-1.406)	-	-	-
BMI (<28 vs ≥28 kg/m^2)	-0.027	0.867	0.973 (0.708-1.338)	-	-	-
FIGO stage (III-IV vs I-II)	0.660	<0.001	1.935 (1.470-2.547)	0.512	<0.001	1.668 (1.259-2.210)
Histological type (HGSC vs Others)	0.415	0.004	1.514 (1.138-2.015)	0.436	0.003	1.546 (1.159-2.062)
Cytoreduction (Suboptimal vs Optimal)	0.659	<0.001	1.934 (1.498-2.496)	0.582	<0.001	1.789 (1.379-2.322)
Operative time (<240 vs ≥240 min)	0.116	0.368	1.122 (0.873-1.443)	-	-	-
Blood loss (<1000 vs ≥1000 ml)	-0.980	<0.001	0.375 (0.264-0.533)	-	-	-
Chemotherapy (TC vs Others)	0.272	0.089	1.312 (0.959-1.795)	0.373	0.024	1.452 (1.051-2.007)
Neoadjuvant chemotherapy (Yes vs No)	0.013	0.934	1.013 (0.751-1.365)	-	-	-
PARP inhibitor (No vs Yes)	0.355	0.012	1.426 (1.082-1.879)	0.435	0.003	1.545 (1.164-2.050)
Hypertension (Yes vs No)	0.068	0.651	1.071 (0.797-1.438)	-	-	-
Diabetes (Yes vs No)	-0.113	0.537	0.893 (0.624-1.278)	-	-	-
Coronary heart disease (Yes vs No)	0.088	0.692	1.093 (0.705-1.694)	-	-	-
Prior VTE history (Yes vs No)	0.234	0.449	1.263 (0.690-2.313)	-	-	-
CA125 (>500 vs ≤500 U/ml)	0.405	0.002	1.499 (1.163-1.932)	0.308	0.020	1.361 (1.049-1.765)
D-dimer (mg/L)	0.235	<0.001	1.265 (1.149-1.394)	-	-	-
Platelet count (×10^9/L)	0.002	0.041	1.002 (1.000-1.003)	<0.001	0.656	1.000 (0.999-1.002)
Prothrombin time (s)	0.047	0.420	1.048 (0.935-1.175)	-	-	-
Hemoglobin (g/L)	-0.008	0.074	0.992 (0.984-1.001)	-0.003	0.486	0.997 (0.989-1.005)
Albumin (g/L)	-0.003	0.809	0.997 (0.972-1.023)	-	-	-

Note: HR, Hazard Ratio; CI, Confidence Interval; OS, Overall Survival; VTE, Venous Thromboembolism; BMI, Body Mass Index; FIGO, International Federation of Gynecology and Obstetrics; HGSC, High-Grade Serous Carcinoma; TC, Paclitaxel plus Carboplatin; PARP, Poly ADP-Ribose Polymerase; CA125, Cancer Antigen 125. D-dimer was excluded from multivariate analysis due to collinearity with FIGO stage and VTE.

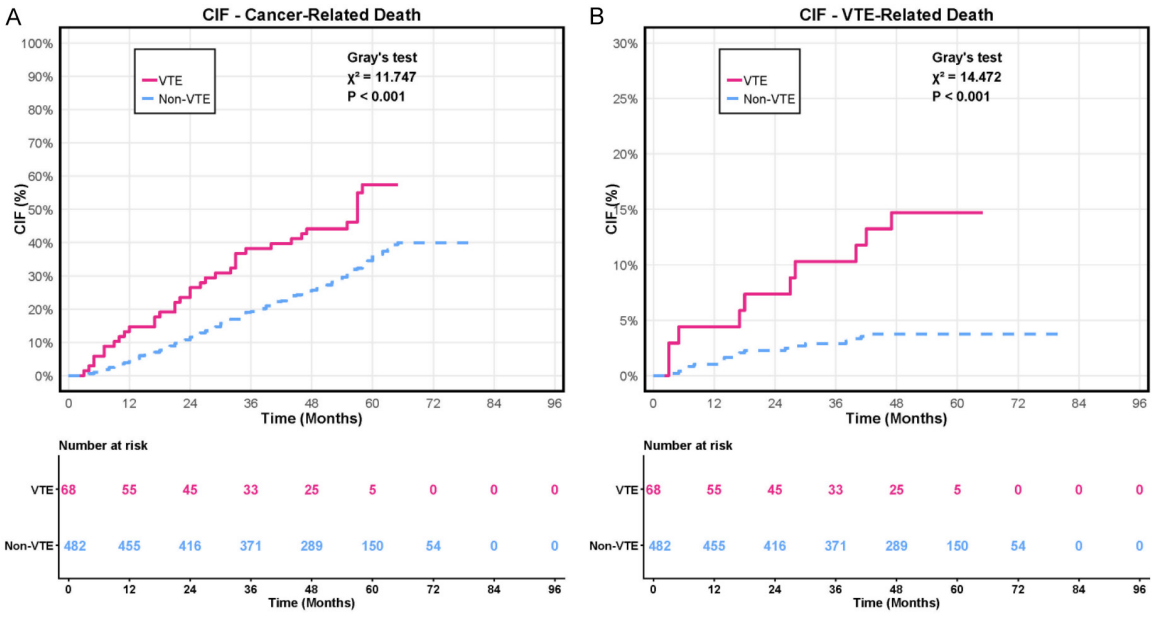

Figure 5. Cumulative incidence function curves of death outcomes in VTE and non-VTE groups. A. Cumulative incidence of cancer-related death; B. Cumulative incidence of VTE-related death. Note: Other causes of death were treated as competing events. Gray's test was used to compare cumulative incidence between groups. CIF, Cumulative Incidence Function; VTE, Venous Thromboembolism.

mortality risk but is also closely associated with elevated tumor-related mortality risk (**Figure 5**).

Competing-risk regression analysis of VTE's impact on tumor-related death

We used the Fine-Gray competing-risk model to analyze VTE's impact on tumor-related death in ovarian cancer patients, with VTE-related death and other-cause death as competing events. Univariate Fine-Gray regression showed that VTE (P<0.001), FIGO stage III-IV (P<0.001), high-grade serous carcinoma (P=0.027), suboptimal cytoreduction (P<0.001), intraoperative blood loss ≥1000 ml (P<0.001), CA125> 500 U/ml (P=0.003), D-dimer (P=0.009), and fibrinogen (P=0.014) were significantly associated with tumor-related mortality risk. Age (P=0.912), BMI (P=0.825), operative time (P= 0.650), chemotherapy regimen (P=0.138), neoadjuvant chemotherapy (P=0.761), PARP inhibitor maintenance therapy (P=0.174), hypertension (P=0.321), diabetes (P=0.884), coronary heart disease (P=0.811), prior VTE history (P=0.272), platelet count (P=0.111), prothrombin time (P=0.828), hemoglobin (P=0.216), and albumin (P=0.471) showed no significant associations.

Variables with P<0.1 in univariate analysis were entered into multivariate Fine-Gray competing-risk modeling. Three variable pairs exceeded the pre-specified collinearity threshold of |r|> 0.6: D-dimer and FIGO stage (r=0.661), fibrinogen and D-dimer (r=0.645), and intraoperative blood loss and operative time (r=0.668). Accordingly, D-dimer, fibrinogen, and intraoperative blood loss were excluded from multivariate modeling, with FIGO stage, D-dimer (retained over fibrinogen based on superior AUC), and operative time as the respective retained variables. VIF values for all retained variables were <5. Multivariate analysis showed that VTE (SHR=1.624, 95% CI: 1.104-2.388, P=0.014), FIGO stage III-IV (SHR=1.590, 95% CI: 1.177-2.150, P=0.003), high-grade serous carcinoma (SHR=1.463, 95% CI: 1.069-2.001, P=0.017), suboptimal cytoreduction (SHR=1.605, 95% CI: 1.199-2.147, P=0.001), and CA125>500 U/ml (SHR=1.502, 95% CI: 1.124-2.007, P=0.006) were independent risk factors for tumor-related death in ovarian cancer patients (**Table 6**).

Competing-risk regression analysis of VTE's impact on VTE-related death

We used the Fine-Gray competing-risk model to analyze VTE's impact on VTE-related death in ovarian cancer patients, with tumor-related death and other-cause death as competing events. Univariate Fine-Gray regression showed that VTE (P<0.001), D-dimer (P=0.053), fibrinogen (P=0.029), and absence of PARP inhibitor maintenance therapy (P=0.066) were associated with VTE-related mortality risk. Age (P=0.289), BMI (P=0.848), FIGO stage (P=0.196), histological type (P=0.229), cytoreductive surgery status (P=0.333), operative time (P=0.758), intraoperative blood loss (P= 0.213), chemotherapy regimen (P=0.877), neoadjuvant chemotherapy (P=0.114), hypertension (P=0.511), diabetes (P=0.534), coronary heart disease (P=0.232), prior VTE history (P=0.907), CA125 (P=0.585), platelet count (P=0.882), prothrombin time (P=0.139), hemoglobin (P=0.170), and albumin (P=0.254) showed no significant associations.

Variables with P<0.1 in univariate analysis were entered into multivariate Fine-Gray competing-risk modeling. As D-dimer and fibrinogen exhibited strong collinearity (r=0.645, exceeding the |r|>0.6 threshold), both were excluded from multivariate modeling to avoid redundancy, given that neither reached conventional significance in univariate analysis for this endpoint (D-dimer: P=0.053; fibrinogen: P=0.029). VIF values for all retained variables were <5. Multivariate analysis showed that VTE was an independent risk factor for VTE-related death (SHR=4.086, 95% CI: 1.881-8.876, P<0.001). Absence of PARP inhibitor maintenance therapy did not reach significance (P=0.064) (**Table 7**).

Subgroup analysis of VTE's impact on mortality outcomes

To further explore whether VTE's effects on different mortality outcomes varied across clinically meaningful subgroups, we performed subgroup analyses based on six pre-specified variables: FIGO stage (key prognostic staging system), histological type (distinct biological behavior of high-grade serous carcinoma), cytoreductive surgery status (major determinant of residual disease and prognosis), age (poten-

Table 6. Fine-Gray competing risk regression analysis for tumor-related death in ovarian cancer patients

Variable	Univariate Fine-Gray			Multivariate Fine-Gray		
	Beta	*P* value	SHR (95% CI)	Beta	*P* value	SHR (95% CI)
VTE (Yes vs No)	0.633	<0.001	1.884 (1.303-2.724)	0.485	0.014	1.624 (1.104-2.388)
Age (<65 vs ≥65 years)	0.017	0.912	1.017 (0.755-1.369)	-	-	-
BMI (<28 vs ≥28 kg/m^2)	0.039	0.825	1.040 (0.736-1.469)	-	-	-
FIGO stage (III-IV vs I-II)	0.575	<0.001	1.777 (1.324-2.386)	0.464	0.003	1.590 (1.177-2.150)
Histological type (HGSC vs Others)	0.346	0.027	1.413 (1.039-1.921)	0.380	0.017	1.463 (1.069-2.001)
Cytoreduction (Suboptimal vs Optimal)	0.570	<0.001	1.767 (1.333-2.343)	0.473	0.001	1.605 (1.199-2.147)
Operative time (<240 vs ≥240 min)	0.064	0.650	1.066 (0.809-1.406)	-	-	-
Blood loss (<1000 vs ≥1000 ml)	-1.081	<0.001	0.339 (0.226-0.509)	-	-	-
Chemotherapy (TC vs Others)	0.260	0.138	1.297 (0.920-1.828)	-	-	-
Neoadjuvant chemotherapy (Yes vs No)	-0.051	0.761	0.950 (0.683-1.322)	-	-	-
PARP inhibitor (No vs Yes)	0.207	0.174	1.229 (0.913-1.656)	-	-	-
Hypertension (Yes vs No)	0.165	0.321	1.179 (0.852-1.632)	-	-	-
Diabetes (Yes vs No)	-0.028	0.884	0.972 (0.664-1.424)	-	-	-
Coronary heart disease (Yes vs No)	-0.063	0.811	0.939 (0.559-1.576)	-	-	-
Prior VTE history (Yes vs No)	0.363	0.272	1.438 (0.752-2.751)	-	-	-
CA125 (>500 vs ≤500 U/ml)	0.423	0.003	1.527 (1.154-2.019)	0.407	0.006	1.502 (1.124-2.007)
D-dimer (mg/L)	0.157	0.009	1.170 (1.041-1.316)	-	-	-
Fibrinogen (g/L)	0.177	0.014	1.194 (1.036-1.376)	-	-	-
Platelet count (×10^9/L)	0.001	0.111	1.001 (1.000-1.003)	-	-	-
Prothrombin time (s)	-0.014	0.828	0.986 (0.872-1.116)	-	-	-
Hemoglobin (g/L)	-0.006	0.216	0.994 (0.985-1.003)	-	-	-
Albumin (g/L)	-0.010	0.471	0.990 (0.963-1.018)	-	-	-

Note: SHR, Subdistribution Hazard Ratio; CI, Confidence Interval; VTE, Venous Thromboembolism; BMI, Body Mass Index; FIGO, International Federation of Gynecology and Obstetrics; HGSC, High-Grade Serous Carcinoma; TC, Paclitaxel plus Carboplatin; PARP, Poly ADP-Ribose Polymerase; CA125, Cancer Antigen 125. D-dimer, fibrinogen, and intraoperative blood loss were excluded from multivariate analysis due to collinearity. VTE-related death and other causes of death were treated as competing events.

tial differences in coagulation status), CA125 level (surrogate of tumor burden that may modulate competing mortality dynamics), and chemotherapy regimen (differential effects on coagulation and thrombotic risk). Variables excluded from subgroup analysis included D-dimer (strong correlation with VTE, r=0.368), fibrinogen (collinearity with D-dimer, r=0.645), intraoperative blood loss (collinearity with operative time, r=0.668), PARP inhibitor maintenance therapy (insufficient VTE-related death events for stable estimates), and prior VTE history (subgroup size too small, n=22).

For tumor-related death, VTE showed significant adverse prognostic effects in most subgroups. VTE was significantly associated with increased tumor-related mortality risk in FIGO stage III-IV (SHR=1.99, P=0.001), high-grade serous carcinoma (SHR=2.17, P<0.001), optimal cytoreduction (SHR=2.12, P=0.002), age <65 years (SHR=2.03, P=0.001), CA125≤500 U/ml (SHR=2.29, P=0.008), and both chemotherapy subgroups (other regimens: SHR=1.78, P=0.005; TC regimen: SHR=2.80, P=0.024). In subgroups of FIGO stage I-II (P=0.667), other histological types (P=0.577), suboptimal cytoreduction (P=0.153), and aged ≥65 years (P=0.244), VTE association with tumor-related death did not achieve significance probably due to smaller sample size or lack of VTE events. No interaction effects with any subgroup variable were significant (P interaction >0.05), which suggests that the impact of VTE on tumor-related death is fairly consistent across clinical subgroups.

For VTE-related death, VTE showed strong adverse prognostic effects across subgroups. VTE was significantly associated with increased VTE-related mortality risk in FIGO stage I-II (SHR=6.60, P=0.008), stage III-IV (SHR=3.18, P=0.013), high-grade serous carcinoma (SHR=5.02, P<0.001), optimal cytoreduction (SHR=4.84, P=0.002), age <65 years (SHR=3.84, P=0.002), CA125≤500 U/ml (SHR=8.63, P<

Table 7. Fine-Gray competing risk regression analysis for VTE-related death in ovarian cancer patients

Variable	Univariate Fine-Gray			Multivariate Fine-Gray		
	Beta	*P* value	SHR (95% CI)	Beta	*P* value	SHR (95% CI)
VTE (Yes vs No)	1.412	<0.001	4.106 (1.908-8.833)	1.408	<0.001	4.086 (1.881-8.876)
Age (<65 vs ≥65 years)	-0.488	0.289	0.614 (0.249-1.512)	-	-	-
BMI (<28 vs ≥28 kg/m^2)	0.088	0.848	1.092 (0.445-2.680)	-	-	-
FIGO stage (III-IV vs I-II)	0.539	0.196	1.714 (0.758-3.879)	-	-	-
Histological type (HGSC vs Others)	0.551	0.229	1.734 (0.707-4.255)	-	-	-
Cytoreduction (Suboptimal vs Optimal)	0.369	0.333	1.446 (0.685-3.051)	-	-	-
Operative time (<240 vs ≥240 min)	0.116	0.758	1.123 (0.537-2.352)	-	-	-
Blood loss (<1000 vs ≥1000 ml)	-0.614	0.213	0.541 (0.206-1.421)	-	-	-
Chemotherapy (TC vs Others)	0.076	0.877	1.079 (0.411-2.830)	-	-	-
Neoadjuvant chemotherapy (Yes vs No)	0.961	0.114	2.614 (0.794-8.609)	-	-	-
PARP inhibitor (No vs Yes)	0.894	0.066	2.446 (0.943-6.343)	0.888	0.064	2.429 (0.949-6.220)
Hypertension (Yes vs No)	-0.324	0.511	0.723 (0.275-1.902)	-	-	-
Diabetes (Yes vs No)	-0.378	0.534	0.685 (0.208-2.253)	-	-	-
Coronary heart disease (Yes vs No)	0.638	0.232	1.893 (0.665-5.387)	-	-	-
Prior VTE history (Yes vs No)	-0.120	0.907	0.887 (0.119-6.586)	-	-	-
CA125 (>500 vs ≤500 U/ml)	0.206	0.585	1.229 (0.586-2.577)	-	-	-
D-dimer (mg/L)	0.217	0.053	1.243 (0.997-1.548)	-	-	-
Fibrinogen (g/L)	0.340	0.029	1.404 (1.036-1.904)	-	-	-
Platelet count (×10^9/L)	0.000	0.882	1.000 (0.995-1.004)	-	-	-
Prothrombin time (s)	0.203	0.139	1.225 (0.936-1.603)	-	-	-
Hemoglobin (g/L)	-0.020	0.170	0.980 (0.953-1.008)	-	-	-
Albumin (g/L)	0.040	0.254	1.041 (0.971-1.116)	-	-	-

Note: SHR, Subdistribution Hazard Ratio; CI, Confidence Interval; VTE, Venous Thromboembolism; BMI, Body Mass Index; FIGO, International Federation of Gynecology and Obstetrics; HGSC, High-Grade Serous Carcinoma; TC, Paclitaxel plus Carboplatin; PARP, Poly ADP-Ribose Polymerase; CA125, Cancer Antigen 125. D-dimer and fibrinogen were excluded from multivariate analysis due to collinearity. Tumor-related death and other causes of death were treated as competing events.

0.001), and both chemotherapy subgroups (other regimens: SHR=3.82, P=0.002; TC regimen: SHR=5.84, P=0.046). Notably, there was a trend toward significant interaction between CA125 stratification and VTE (P interaction =0.070), suggesting VTE's impact on VTE-related death may be more pronounced in patients with CA125≤500 U/ml. Reliable effect estimates could not be obtained for the other histological types subgroup due to insufficient VTE-related death events (only 6 cases). No significant interaction effects were detected for other subgroup variables (P interaction >0.05) (**Figure 6**).

Baseline characteristics and prognosis comparison between anticoagulation groups among VTE patients

Among 68 ovarian cancer patients who developed VTE, 48 received guideline-adherent anticoagulation and 20 received non-adherent anticoagulation. Main reasons for non-adherence included high bleeding risk, poor patient compliance, treatment abandonment due to tumor progression, and financial constraints. No significant differences existed between groups for age (P=0.897), BMI (P=0.558), FIGO stage (P=0.402), histological type (P=0.272), cytoreductive surgery status (P=0.974), operative time (P=0.721), intraoperative blood loss (P=0.291), chemotherapy regimen (P=0.241), neoadjuvant chemotherapy (P=0.670), PARP inhibitor maintenance therapy (P=0.403), hypertension (P=0.103), diabetes (P=0.801), coronary heart disease (P=1.000), prior VTE history (P=0.444), CA125 (P=0.340), VTE type (P=0.534), or perioperative VTE rate (P= 0.322). Coagulation and hematological parameters, including D-dimer (P=0.072), fibrinogen (P=0.203), platelet count (P=0.108), prothrombin time (P=0.838), hemoglobin (P=0.361), and albumin (P=0.744), also showed no significant differences (**Table 8**).

Impact of anticoagulation therapy on mortality outcomes in VTE patients

We used the Fine-Gray competing-risk model to analyze how anticoagulation adherence affect-

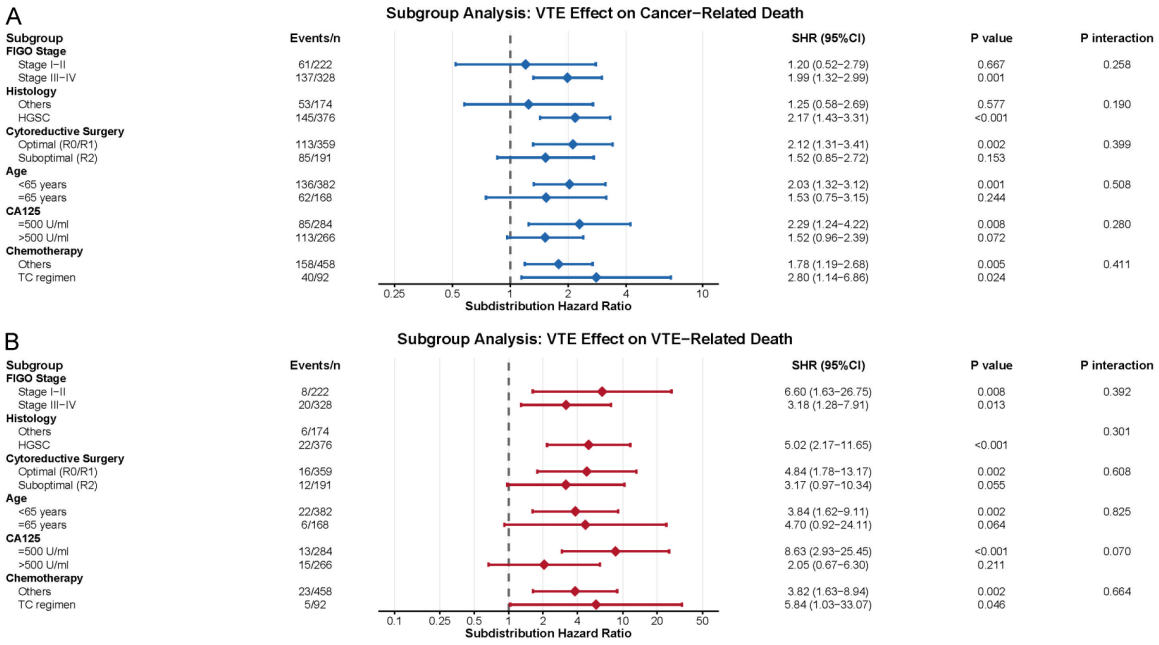

Figure 6. Forest plots of subgroup analysis for the effect of VTE on cancer-related death and VTE-related death in ovarian cancer patients. A. Subgroup analysis for VTE effect on cancer-related death; B. Subgroup analysis for VTE effect on VTE-related death. VTE-related death and other causes of death were treated as competing events for cancer-related death analysis; cancer-related death and other causes of death were treated as competing events for VTE-related death analysis. SHR, Subdistribution Hazard Ratio; CI, Confidence Interval; VTE, Venous Thromboembolism; FIGO, International Federation of Gynecology and Obstetrics; HGSC, High-Grade Serous Carcinoma; TC, Paclitaxel plus Carboplatin; CA125, Cancer Antigen 125.

ed different mortality outcomes in VTE patients. VTE-related death was analyzed with tumor-related death and other-cause death as competing events; tumor-related death was analyzed with VTE-related death and other-cause death as competing events. CIF curves were plotted.

Results showed that cumulative incidence of VTE-related death was significantly higher in the non-adherent group than in the adherent group (Gray's test χ^2=14.725, P<0.001). The difference originated early in follow-up and widened over time. The difference in the cumulative incidence of tumor-related death among the groups was not statistically significant (Gray's test χ^2=0.169, P=0.681). According to these findings, VTE-realted mortality risk is significantly decreased with guideline-adherent anticoagulation and not significantly increased in tumor-related death (**Figure 7**).

Discussion

This study systematically evaluated VTE incidence, risk factors, and cause-specific mortality outcomes in a large cohort of ovarian cancer patients using competing-risk methodology, and further quantified the survival benefit of guideline-adherent anticoagulation in real-world practice. Three clinically meaningful findings emerged from this analysis.

The overall VTE incidence of 12.4% places this cohort at the high end of previously reported ranges for ovarian cancer during treatment. Compared with the approximately 9% incidence reported by Ye et al. during chemotherapy [7] and the 10%-13% reported in neoadjuvant chemotherapy settings by Black et al. [8, 9], our higher rate likely reflects the inclusion of more advanced-stage patients undergoing complex cytoreductive procedures. This elevated thrombotic burden is not incidental but rather reflects the unique biological behavior of epithelial ovarian cancer. Unlike endometrial or cervical cancer, ovarian cancer is characterized by peritoneal dissemination, which promotes pelvic and abdominal venous compression. Tumor cells expressing high levels of tissue factor generate procoagulant microparticles that directly activate the coagulation cascade, while pro-

Table 8. Comparison of baseline characteristics and prognosis between adherent and non-adherent anticoagulation groups in VTE patients

Variable	Total	Non-adherent group (n=20)	Adherent group (n=48)	χ^2/t	*P* value
Age group				0.017	0.897
<65 years	52 (76.47%)	16 (80.00%)	36 (75.00%)		
≥65 years	16 (23.53%)	4 (20.00%)	12 (25.00%)		
BMI group				0.342	0.558
≥28 kg/m^2	53 (77.94%)	17 (85.00%)	36 (75.00%)		
<28 kg/m^2	15 (22.06%)	3 (15.00%)	12 (25.00%)		
FIGO stage				0.701	0.402
I-II	19 (27.94%)	7 (35.00%)	12 (25.00%)		
III-IV	49 (72.06%)	13 (65.00%)	36 (75.00%)		
Histological type				1.209	0.272
Others	20 (29.41%)	4 (20.00%)	16 (33.33%)		
High-grade serous carcinoma	48 (70.59%)	16 (80.00%)	32 (66.67%)		
Cytoreductive surgery				0.001	0.974
Optimal (R0/R1)	41 (60.29%)	12 (60.00%)	29 (60.42%)		
Suboptimal (R2)	27 (39.71%)	8 (40.00%)	19 (39.58%)		
Operative time				0.128	0.721
<240 min	25 (36.76%)	8 (40.00%)	17 (35.42%)		
≥240 min	43 (63.24%)	12 (60.00%)	31 (64.58%)		
Intraoperative blood loss				1.115	0.291
<1000 ml	41 (60.29%)	14 (70.00%)	27 (56.25%)		
≥1000 ml	27 (39.71%)	6 (30.00%)	21 (43.75%)		
Chemotherapy regimen				1.372	0.241
Others	58 (85.29%)	15 (75.00%)	43 (89.58%)		
TC regimen	10 (14.71%)	5 (25.00%)	5 (10.42%)		
Neoadjuvant chemotherapy				0.181	0.670
No	18 (26.47%)	6 (30.00%)	12 (25.00%)		
Yes	50 (73.53%)	14 (70.00%)	36 (75.00%)		
PARP inhibitor maintenance				0.700	0.403
No	22 (32.35%)	5 (25.00%)	17 (35.42%)		
Yes	46 (67.65%)	15 (75.00%)	31 (64.58%)		
Hypertension				2.665	0.103
No	50 (73.53%)	12 (60.00%)	38 (79.17%)		
Yes	18 (26.47%)	8 (40.00%)	10 (20.83%)		
Diabetes				0.063	0.801
No	54 (79.41%)	15 (75.00%)	39 (81.25%)		
Yes	14 (20.59%)	5 (25.00%)	9 (18.75%)		
Coronary heart disease				0.000	1.000
No	62 (91.18%)	18 (90.00%)	44 (91.67%)		
Yes	6 (8.82%)	2 (10.00%)	4 (8.33%)		
Prior VTE history				0.585	0.444
No	64 (94.12%)	20 (100.00%)	44 (91.67%)		
Yes	4 (5.88%)	0 (0.00%)	4 (8.33%)		
CA125				0.911	0.340
≤500 U/ml	28 (41.18%)	10 (50.00%)	18 (37.50%)		
>500 U/ml	40 (58.82%)	10 (50.00%)	30 (62.50%)		
VTE type				1.256	0.534
DVT only	42 (61.76%)	14 (70.00%)	28 (58.33%)		
PE only	12 (17.65%)	3 (15.00%)	9 (18.75%)		
DVT with PE	14 (20.59%)	3 (15.00%)	11 (22.92%)		
Perioperative VTE	38 (55.88%)	13 (65.00%)	25 (52.08%)	0.982	0.322
Reasons for non-adherence					
High bleeding risk	8 (11.76%)	8 (40.00%)	-		
Poor compliance	6 (8.82%)	6 (30.00%)	-		
Treatment abandonment	4 (5.88%)	4 (20.00%)	-		
Financial constraints	2 (2.94%)	2 (10.00%)	-		

D-dimer (mg/L)	3.19±1.79	2.58±1.66	3.44±1.80	1.831	0.072
Fibrinogen (g/L)	4.58±1.27	4.27±1.07	4.70±1.33	1.287	0.203
Platelet count (×10⁹/L)	329.15 [261.85, 370.30]	301.45 [241.80, 357.30]	333.75 [290.80, 378.78]	1.608	0.108
Prothrombin time (s)	11.88±1.20	11.83±0.83	11.90±1.33	0.205	0.838
Hemoglobin (g/L)	104.86±16.47	102.01±18.58	106.05±15.56	0.920	0.361
Albumin (g/L)	35.03±5.55	34.69±5.42	35.17±5.65	0.328	0.744

Note: VTE, Venous Thromboembolism; BMI, Body Mass Index; FIGO, International Federation of Gynecology and Obstetrics; HGSC, High-Grade Serous Carcinoma; TC, Paclitaxel plus Carboplatin; PARP, Poly ADP-Ribose Polymerase; CA125, Cancer Antigen 125; DVT, Deep Vein Thrombosis; PE, Pulmonary Embolism.

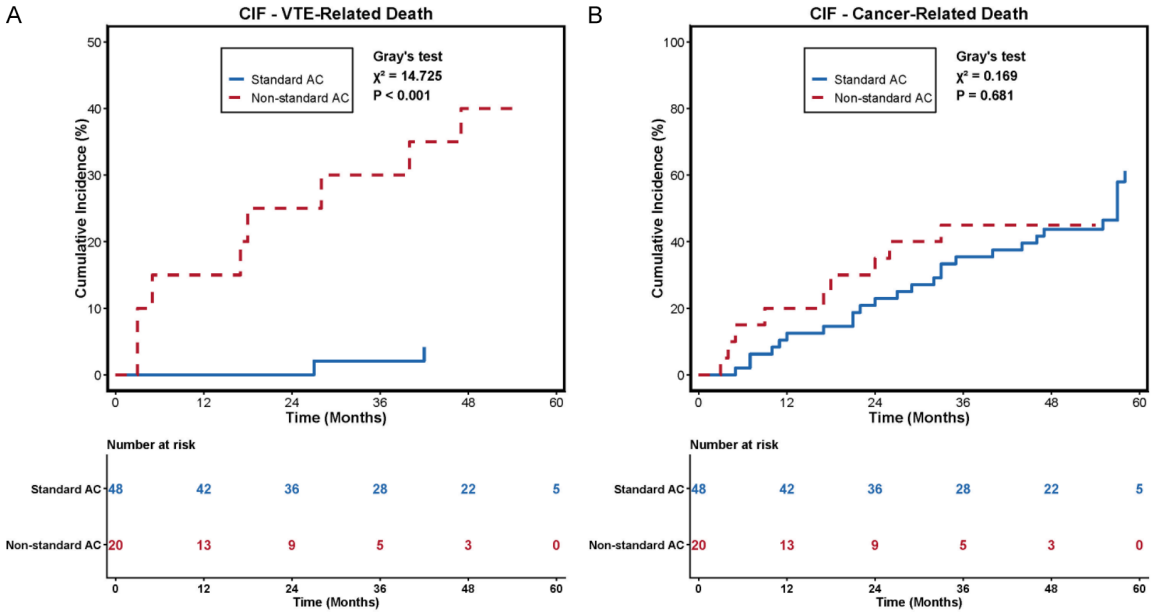

Figure 7. Cumulative incidence function curves of death outcomes between standard and non-standard anticoagulation groups in VTE patients. A. Cumulative incidence of VTE-related death; B. Cumulative incidence of cancer-related death. Note: Cancer-related death and other causes of death were treated as competing events for VTE-related death analysis; VTE-related death and other causes of death were treated as competing events for cancer-related death analysis. CIF, Cumulative Incidence Function; AC, Anticoagulation; VTE, Venous Thromboembolism.

inflammatory cytokines within the tumor microenvironment - including IL-6 and TNF-α - sustain a prothrombotic endothelial phenotype [5]. In a real-world study by Abdol Razak et al., patients with ovarian cancer were found to be at risk not only for DVT and PE but also for arterial thrombotic events [12], suggesting that the hypercoagulable state may be systemic. Clinicians should therefore recognize VTE as an integral component of the systemic disease course in ovarian cancer, and remain vigilant throughout the perioperative period and chemotherapy cycles.

Among identified risk factors, elevated D-dimer, increased platelet count, and operative time ≥240 minutes were independently associated with VTE occurrence. D-dimer reflects real-time hypercoagulability and fibrinolytic activation; despite baseline elevation being common in cancer patients, it retained the strongest predictive value after multivariable adjustment (AUC=0.823, sensitivity=73.5%, specificity=90.7%, PPV=52.6%, NPV=96.0%), endorsing its utility for dynamic risk monitoring. Thrombocytosis in ovarian cancer represents a paraneoplastic phenomenon wherein activated platelets coat circulating tumor cells, facilitating immune evasion and promoting distant metastasis, while simultaneously amplifying coagulation through granule release [18-21]. Elevated platelet count thus signals both thrombotic risk and more aggressive tumor biology, consistent with findings by Nadeem et al. linking platelet aggregation to advanced disease and poor prognosis through paraneoplastic mechanisms [22]. Prolonged operative time reflects the extensive multi-organ resection,

peritoneal stripping, and major vessel-adjacent lymph node dissection required for cytoreduction, during which lithotomy position, pneumoperitoneum pressure, vascular endothelial injury, and postoperative immobility collectively elevate thrombotic risk [23, 24]. These findings underscore the need for combined pharmacological and mechanical prophylaxis - particularly intermittent pneumatic compression devices initiated intraoperatively - in patients undergoing major cytoreductive procedures, as pharmacological prophylaxis alone appears insufficient for this high-risk group.

One notable finding warrants methodological clarification: CA125 appeared as a protective factor in multivariate logistic regression despite trending toward increased risk in univariate analysis. This reversal reflects a suppression effect arising from multivariate model adjustment rather than any biological antithrombotic property of elevated tumor burden. When proximal coagulation-related variables such as D-dimer and platelet count - which lie closer to the thrombosis causal pathway - are simultaneously adjusted for, the shared variance between CA125 and VTE risk is absorbed, and the residual coefficient direction may reverse due to unmeasured treatment selection bias or nonlinear relationships distorted by dichotomization. This finding should not be interpreted as a causal reversal, but rather as a reminder of the complexity of multivariate model interpretation in observational studies.

The prognostic analysis revealed that VTE independently worsened overall survival (HR= 2.533, P<0.001) and significantly increased the cumulative incidence of both tumor-related and VTE-related death. At 60 months, absolute differences of 20.4% and 11.2% were observed for tumor-related and VTE-related mortality respectively between VTE and non-VTE patients. Employing the Fine-Gray competing-risk model was methodologically essential in this context. Conventional Kaplan-Meier and Cox approaches treat competing events as censored, implicitly assuming that patients dying of tumor progression would have experienced the same VTE mortality trajectory as survivors - an assumption that systematically overestimates cause-specific cumulative incidence [25]. The Fine-Gray model directly estimates the subdistribution hazard, providing more accurate absolute risk estimates in the presence of multiple competing outcomes. The interaction trend between CA125 stratification and VTE-related mortality (P interaction=0.070) further illustrates the dynamic nature of competing risks: in patients with relatively lower tumor burden (CA125≤500 U/ml), the tumor exerts less competing mortality pressure, allowing VTE to emerge more prominently as a direct cause of death (SHR=8.63 vs 2.05 in the higher CA125 group). This has practical implications - for patients with well-controlled disease and longer expected survival, VTE prevention may yield proportionally greater survival benefit than in those with dominant tumor mortality risk. Beyond direct fatal events such as massive PE and cerebral embolism, VTE indirectly accelerates tumor progression through multiple mechanisms: treatment interruption allowing tumor growth during chemotherapy hiatus; coagulation factor-mediated promotion of angiogenesis, invasion, and metastasis via protease-activated receptors (PARs) and growth factor release; amplification of systemic inflammation creating a tumor-promoting microenvironment; and reduction in performance status precluding aggressive anticancer therapy [23].

Guideline-adherent anticoagulation - defined as at least 3 months of therapeutic-dose treatment per ITAC 2022 [26], ASCO 2023 [27], and ASH 2021 [28] recommendations - was associated with significantly reduced VTE-related mortality in this cohort (P<0.001), without a significant effect on tumor-related death (P= 0.681). This finding aligns with randomized evidence from the CARAVAGGIO trial demonstrating non-inferiority of apixaban to LMWH for cancer-associated VTE [29]. Real-world implementation, however, remains challenging. Chemotherapy-induced thrombocytopenia, gastrointestinal bleeding risk from tumor invasion of bowel or pelvic vessels, financial constraints, and injection-related non-compliance collectively impede adherence. Our data support a more individualized approach: dose modification per ISTH guidance when thrombocytopenia occurs (<50×10^9/L), and preferential use of DOACs when bleeding risk is manageable, to maximize protection against fatal thrombotic events while minimizing treatment burden.

Several limitations of this study merit acknowledgment. As a single-center retrospective study, selection and information biases are inher-

ent. VTE diagnosis relied on a symptom-driven rather than systematic screening approach, likely underestimating true incidence by missing asymptomatic cases - a non-differential misclassification that biases effect estimates toward the null, if anything underestimating the true impact of VTE on mortality. Dynamic biomarker changes across chemotherapy cycles and germline mutation status, including BRCA1/2 - which may modulate thrombotic risk through tumor microenvironment effects - were not captured, and should be examined in future studies. The effects of concomitant medications influencing coagulation, such as NSAIDs, herbal medicines, and antiplatelet agents, could not be comprehensively assessed in this retrospective setting; prospective studies are needed to address this deficiency. Additionally, certain subgroups had limited VTE-related death events: FIGO stage I-II (8 events), non-serous carcinoma (6 events, precluding reliable estimation), and age ≥65 years (6 events). While effect directions remained consistent with full-cohort findings, wide confidence intervals in these subgroups limit definitive conclusions, and interaction findings should be validated in larger prospective cohorts. Future research should develop dynamic, integrated prediction models incorporating surgical risk scores, tissue factor, P-selectin, and germline risk scores, leveraging longitudinal biomarker monitoring and machine learning to enable real-time thrombosis risk stratification and ultimately improve long-term survival outcomes in ovarian cancer patients.

Conclusion

In conclusion, VTE represents a frequent and clinically significant complication in ovarian cancer, with an incidence of 12.4% in this cohort. Elevated D-dimer, increased platelet count, and prolonged operative time are independently associated with VTE occurrence and should inform perioperative risk stratification. From a competing-risk perspective, VTE independently increases the cumulative incidence of both tumor-related and VTE-related mortality, with the latter effect being particularly pronounced in patients with relatively lower tumor burden - a finding that highlights the dynamic interplay between thrombotic and oncological competing risks. Guideline-adherent anticoagulation significantly reduces VTE-related mortality without adversely affecting tumor-related outcomes, underscoring the importance of standardized thrombosis management alongside antitumor therapy. Clinicians should prioritize early VTE recognition and individualized anticoagulation strategies as integral components of comprehensive ovarian cancer care, and future prospective studies with larger cohorts are warranted to validate and refine these findings.

Disclosure of conflict of interest

None.

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