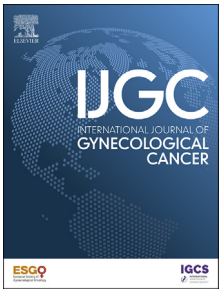
ORIGINAL RESEARCH

Association of clinical and laboratory variables with risk of venous thromboembolism in high-grade serous ovarian cancer



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ABSTRACT

Objectives: This study aimed to assess the incidence and time course of venous thromboembolism and to survey clinical and laboratory features predicting the risk for these complications in patients with high-grade serous ovarian cancer.

Methods: Patients with high-grade serous ovarian cancer treated in a prospective ovarian cancer study at the Turku University Hospital between 2009 and 2020 were retrospectively analyzed for the incidence of venous thromboembolism. This diagnosis was based on the International Classification of Diseases, 10th Revision Coding, and confirmed from hospital electronic health records. Analyses combined multiple variables including treatment strategies and laboratory variables.

Results: Among the 146 patients with high-grade serous ovarian cancer, 24 (16.4%) had a confirmed venous thromboembolism. In 5 patients (3.4%), venous thromboembolism preceded the cancer diagnosis. The median time from cancer diagnosis to the venous thromboembolism event was 12.8 months. Patients with venous thromboembolism had shorter median survival (30.6 versus 41.6 months, $p = .014$), but age, disease stage at diagnosis, and co-morbidities were similar. In a multivariable analysis, short platinum-free interval ($p < .005$) and increased leukocyte ($p = .004$) and neutrophil ($p = .013$) counts both indicated an increased probability of venous thromboembolism event. Conversely, longer carbohydrate antigen 125 doubling time ($p = .036$), along with higher hemoglobin ($p < .0001$) and albumin levels ($p = .015$), were linked to a reduced risk of venous thromboembolism.

Conclusions: The combination of these findings in high-grade serous ovarian cancer patients could be incorporated into their venous thromboembolism risk stratification.

WHAT IS ALREADY KNOWN ON THIS TOPIC

High-grade serous ovarian cancer is associated with a risk for venous thromboembolism that is considerably elevated. However, the methods of risk assessment for targeted thromboprophylaxis are not comprehensive.

WHAT THIS STUDY ADDS

In high-grade serous ovarian cancer patients, venous thromboembolism is associated with reduced survival time and is more frequent in patients treated with neoadjuvant chemotherapy. Patients with a short platinum-free interval show a significantly increased risk for venous thrombosis. Also, increased leukocyte and neutrophil counts, higher carbohydrate antigen 125 value, and reduced carbohydrate antigen 125 doubling time are associated with an increased risk of venous thromboembolism.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

Because common laboratory tests and treatment strategies (primary debulking surgery versus

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Given the reduced overall survival in patients with venous thromboembolism, future studies should prioritize proactively targeted thromboprophylaxis.

neoadjuvant chemotherapy) can predict venous thromboembolism risk in a high-grade serous ovarian cancer patient they should be considered in decisions on thromboprophylaxis.

Keywords:
Venous Thromboembolism;
Ovarian Cancer;
Retrospective Study;
Pulmonary Embolism

INTRODUCTION

Ovarian cancer is the gynecologic malignancy associated with the highest incidence of venous thromboembolism.[1,2] For ovarian cancer patients, the highest probability for thromboembolic events is after primary debulking surgery and during chemotherapy.[3-5] High-grade serous ovarian cancer, the most common ovarian cancer type frequently diagnosed at an advanced stage, carries a significant risk for venous thromboembolic events.[5,6]

Venous thromboembolism can delay the start of cancer treatment, reduce quality of life, increase economic burden, and contribute to mortality.[7-10] Targeted thromboprophylaxis in cancer patients is therefore likely to both improve quality of life and overall survival and reduce health care costs.[11] Risk-directed thromboprophylaxis is an appropriate approach, but the methods for risk assessment are not yet sufficiently accurate.[12]

Several biomarkers such as circulating levels of tissue factor, D-dimer levels, thrombocytosis, and plasma levels of CA125, are likely to predict the risk of venous thromboembolism in ovarian cancer patients.[13-17] Despite considerable research, in the clinic we still lack biomarkers to predict venous thromboembolism in these patients, especially regarding high-grade serous ovarian cancer.

This study is based on clinical data collected in a prospective study setting, with the aim of understanding the biological characteristics of high-grade serous ovarian cancer.[18] We utilized the longitudinal clinical information in the study database and retrospectively surveyed the incidence and time course of the development of venous thromboembolism. We evaluated whether clinical and laboratory biomarkers used in routine medical care could offer tools to predict thromboembolic events in high-grade serous ovarian cancer patients.

METHODS

Data supporting the results of this study are available from the corresponding author upon request. Data are not publicly available due to privacy or ethical constraints.

Data Source

This retrospective study utilized research data from a prospective observational clinical trial of ovarian cancer (HERCULES, ClinicalTrials.gov identifier: NCT01276574) that aimed to study drug resistance in high-grade serous ovarian cancer.[18] All participating patients provided informed consent. The study was registered and approved by the Turku Clinical Research Center (permission number: T07/009/15), and the Ethics Committee of the Hospital District of Southwest Finland (ETMK 53/180/2009§238)

Study Population

The study population comprised patients treated in a single regional tertiary hospital (Turku University Hospital). All 146 patients included had their comprehensive clinical and electronic health record data available for the duration of the entire follow-up between January 2009 and August 2020 at the Turku University Hospital, with each patient followed for at least 6 months after their ovarian cancer diagnosis, or until death. Clinical information, including disease stage (as per International Federation of Gynecology and Obstetrics 2014 [FIGO 2014]), treatment, and survival data were collected from the data repository, as described by Isoviita and colleagues.[18]

From this data set, we identified a venous thromboembolism diagnosis according to the International Classification of Disease, 10th Revision (ICD-10) codes for deep vein thrombosis I80.2, I80.3, I80.8, I80.9, I82, pulmonary embolism I26, or portal vein thrombosis I81. Confirmation of thromboembolic events was by linking the register to the Turku University Hospital Patient Discharge Data, with only diagnoses based on radiologic imaging included. M.H.P. collected information from individual electronic health records on those patient characteristics involving venous thromboembolism (Table S1).

Co-variates

The treating physician, at the diagnosis of high-grade serous ovarian cancer, reported body mass index and co-morbidities. Co-morbidities were categorized into 5 groups as described in Table S2. Additionally, we created a variable to indicate whether a patient had any co-morbidities or none.

Blood samples obtained during treatment and follow-up visits were one part of routine clinical care. The variables included were comprehensive blood cell counts, plasma levels of creatinine, alanine transaminase, alkaline phosphatase, albumin, and CA125. Laboratory values were log-transformed as needed (skewness above +1 or below -1) for further analyses. The Khorana score, a risk assessment tool for predicting risk for chemotherapy-associated venous thromboembolism, we calculated by disease type (gynecologic cancer [1 point]), hematologic factors (platelet count $\geq 350 \times 10^9$/L [1 point], hemoglobin level <10 g/dL [1 point], leukocyte count $>11 \times 10^9$/L [1 point]), and body mass index (≥ 35 kg/m^2 [1 point]), if these pre-chemotherapy measures were available.[19] Additionally, we adapted our previous approach to studying the time-dependent correlation

between CA19-9 values and venous thromboembolism in pancreatic cancer,[20] and we calculated CA125 doubling time (CA125-DT) (Supplementary Material A).

Patients were treated with either primary debulking surgery followed by platinum-based adjuvant chemotherapy or with platinum-based neoadjuvant chemotherapy followed by interval debulking surgery and by additional cycles of platinum-based adjuvant chemotherapy. The outcome of primary therapy was defined according to the Response Evaluation Criteria in Solid Tumors 1.1.[21] The number of primary chemotherapy cycles was recorded and standardized for analysis by dividing by the total duration (in weeks) of primary chemotherapy treatment. The platinum-free interval (months) was defined as the range of platinum-free months from the date of the last platinum-based chemotherapy dose until the date of progression, death, or the end of follow-up.

Statistical Analysis

Patients were stratified by the occurrence of venous thromboembolism (no or yes); the latter was further subdivided by the time of occurrence (prior to or post-ovarian cancer diagnosis). The 5 patients with venous thromboembolism prior to their cancer diagnosis we excluded from inferential analyses due to the small sample size and due to the lack of comprehensive pre-venous thromboembolism data on risk factors relevant to this study.

We summarized continuous patient characteristics with medians and interquartile ranges (IQRs). Differences between patient groups we assessed with the Mann-Whitney U test. Categorical variables were observed in frequencies and proportions, with differences between groups analyzed with the Fisher exact test. Overall survival we explored with the Kaplan-Meier estimator and compared the differences in survival distributions with the log-rank test. Analysis of time-to-venous thromboembolism and its associated risk factors utilized the cumulative incidence function and Gray test, considering the competing event of death, and we reported median overall survival and median time-to-venous thromboembolism, along with their corresponding 95% CIs, if applicable.

We further analyzed risk factors for venous thromboembolism by use of 2 distinct cause-specific hazard models: a multivariate model incorporating patient characteristics together with CA125-DT, and a univariate model treating each laboratory measurement as a time-varying variable.[22] The results we reported using HRs, along with their corresponding 95% CIs and *p*-values. To assess the proportional hazards assumption, we utilized Schoenfeld residuals, and additionally, we compared nested models with the likelihood-ratio test.

Missing data for the variables we described and used without imputation in the analyses. A *p*-value of 0.05 was considered statistically significant. We conducted analyses with R software version 3.6.3 (R Core Team, 2021).

RESULTS

Table 1 presents the characteristics of the study cohort, which comprised 146 patients diagnosed with high-grade serous ovarian cancer. Among these, 24 (16.4%) had venous thromboembolism, with 5 occurring before the initial cancer diagnosis. The median age of the cohort was 68 years (IQR 62-74), and 137 patients (93.8%) had metastatic disease (FIGO stage III-IV) already at the time of cancer diagnosis (Table 1). The median follow-up period was 28.3 months (IQR 14.1-43.9).

No significant difference emerged in treatment responses ($p = 0.32$), Khorana score ($p = 0.70$), nor in co-morbidities ($p = 0.42$; further details in Table S2), nor in FIGO disease stage ($p = 0.60$) between the patients with and without venous thromboembolism (Table 1). However, venous thromboembolism was more prevalent in patients receiving neoadjuvant chemotherapy than in those undergoing primary debulking surgery (OR 5.6, CI 95% CI 1.50 to 31.7; $p = .005$). Additionally, between those groups, standardized chemotherapy cycles ($p = .018$) differed.

The median time from diagnosis of high-grade serous ovarian cancer to the occurrence of a venous thromboembolism event was 12.8 months (IQR 2.7-22.8 months). Of 24 patients, in 6 (25.0%), venous thromboembolism was asymptomatic and diagnosed incidentally by computed tomography scan during routine follow-up examination, 2 were diagnosed with venous thromboembolism before systemic anticancer treatment, 13 during treatment or 1 month after last dose, and 4 received the diagnosis after treatment ended (over a month). The characteristics related to the 24 venous thromboembolism patients we detailed in Table S1. Seven patients were diagnosed with a venous thromboembolic event during primary therapy, 4 patients during the first disease relapse, and 8 patients at a later phase of cancer. The responses of all patients to primary chemotherapy are shown in Figure 1.

Platinum-free interval was associated with venous thromboembolism risk (part A in Table 2), this probability decreasing by 17% for every platinum-free month (HR 0.84, 95% CI 0.74 to 0.96; $p = .012$). In a comparison of the full model to a reduced model that includes only the platinum-free interval, the models provided similar results ($\chi^2(7) = 2.10$; $p = 0.96$), and the HR for the platinum-free interval was 0.81 (95% CI 0.72 to 0.91; $p < .001$). Additionally, CA125-DT (Fig. 2), was linked to the risk of thromboembolism (part B in Table 2). The median CA125-DT for patients with venous thromboembolism was 8.8 months (IQR; 6.3-12.5), compared to 12.5 months (IQR; 6.8-27.7) for those without, a difference not statistically significant. Furthermore, CA125 levels at high-grade serous ovarian cancer diagnosis were higher in patients who later developed venous thromboembolism (848 U/mL, IQR; 526-1700 versus 385 U/mL, IQR; 151-901, $p = .0073$). Other laboratory variables did not show significant differences between groups at cancer diagnosis (Table S3).

In a simple cause-specific hazard model that treated laboratory variables as time-varying and that utilized all available measurements throughout follow-up (part C in Table 2), higher leukocyte count (HR 6.05, 95% CI 1.78 to 20.57, $p = .0039$) and specifically neutrophil count (HR 3.81, 95% CI 1.33 to 10.92, $p = .013$), along with elevated CA125 (HR 1.79, 95% CI 1.35 to 2.38, $p < .0001$) were associated with an increased risk for venous thromboembolism. Conversely, higher levels of hemoglobin (HR 0.95, 95% CI 0.93 to 0.97, $p < .0001$) and albumin (HR 0.90, 95% CI 0.83 to 0.98, $p = .015$) were associated with a decreased risk for venous thromboembolism (part C in Table 2). We were unable to establish cut-off values for variables to predict an individual risk.

Patients with venous thromboembolism had a shorter median overall survival of 30.6 months (95% CI 18.20-not reported) compared with 41.6 months (95% CI 33.94 to 60.48) of those without ($p = .01$) (Fig. 3). However, no difference appeared as to the cause of death between groups (Table 1).

Table 1 Baseline Clinical Characteristics of Study Patients

Variable	All patients	Non-venous thromboembolism	Venous thromboembolism prior[a]	Venous thromboembolism post[b]	*p*-Value[c]
Total (number)	***N* = 146**	***n* = 122**	***n* = 5**	***n* = 19**	
Age, median (IQR)	68.0 (62.0-74.0)	67.5 (62.0-74.0)	77.0 (76.0-77.0)	65.0 (60.5-71.0)	0.29
Body mass index, median (IQR)	25.4 (23.2-28.6)	25.2 (23.0-28.5)	27.6 (24.0-29.0)	26.0 (23.9-28.6)	0.47
Co-morbidities[d]					0.42
No. (%)	41 (28.1)	33 (27.0)	1 (20.0)	7 (36.8)	
Yes (%)	105 (71.9)	89 (73.0)	4 (80.0)	12 (63.2)	
Previous cancer, any type					0.53
No. (%)	119 (81.5)	100 (82.0)	2 (40.0)	17 (89.5)	
Yes (%)	28 (18.9)	23 (18.5)	3 (60.0)	2 (10.5)	
Stage (FIGO 2014)					0.60
I-II (%)	9 (6.2)	8 (6.6)	1 (20.0)	0 (0.0)	
III-IV (%)	137 (93.8)	114 (93.4)	4 (80.0)	19 (100.0)	
Khorana risk score[e]					0.70
1-2 (%)	109 (75.7)	96 (78.7)	NA	13 (68.4)	
≥3 (%)	25 (16.7)	21 (17.2)	NA	4 (21.1)	
Primary treatment strategy					0.00539
Primary debulking surgery (%)	68 (46.6)	63 (51.6)	2 (40.0)	3 (15.8)	
Neoadjuvant chemotherapy (%)	78 (53.4)	59 (48.4)	3 (60.0)	16 (84.2)	
Primary chemotherapy cycles [f] median (IQR)					
Non-standardized	6.00 (6.00-7.00)	6.00 (6.00-6.75)	6.00 (6.00-6.00)	8.00 (6.00-9.00)	
Standardized	0.32 (0.29- 0.40)	0.35 (0.29-0.40)	0.28 (0.28-0.39)	0.30 (0.28-0.32)	0.0177
Platinum-free interval, median (IQR), mos	7.00 (3.1-18.8)	9.02 (4.0-20.2)	2.45 (0.8-16.1)	4.24 (2.2-6.1)	0.00617
Doubling time of plasma levels of CA125 (P-CA125-dT) median (IQR), mos	12.1 (6.7-26.5)	12.5 (6.8-27.7)	NA	8.75 (6.3-12.5)	0.0644
Survival at the end of follow-up time [g]					0.18
Alive (%)	67 (45.9)	59 (48.4)	3 (60.0)	5 (26.3)	
Death due to cancer (%)	74 (50.7)	59 (48.4)	1 (20.0)	14 (73.7)	
Death due to other reason (%)	5 (3.4)	4 (3.2)	1 (20.0)	0 (0.0)	
Time to death [h]					0.87
Median (IQR), mos	25.5 (13.5-36.2)	26.2 (13.7-36.6)	12.6 (8.3-16.8)	23.4 (13.6-36.0)	
Time to death after venous thromboembolism					
Median (IQR), mos	3.11 (0.6-7.8)	NA	13.0 (8.8-17.3)	1.6 (0.7-6.6)	

Abbreviations: CA, carbohydrate antigen; FIGO, International Federation of Gynecology and Obstetrics; ICD-10, International Classification of Diseases, 10th revision; IQR, interquartile range; NA, not applicable.

[a] Venous thromboembolism observed prior to the high-grade serous ovarian cancer diagnosis.

[b] Venous thromboembolism observed after the high-grade serous ovarian cancer diagnosis.

[c] *p*-Values of Fisher exact test for categorical attributes and Mann-Whitney U test for continuous attributes tested between 19 post-venous thromboembolism patients and 122 without venous thromboembolism.

[d] Categorized into groups based on vital organs and disease groups as classified by ICD-10 (Table S2).

[e] Based on the 139 patients with pre-chemotherapy measurements (117 with non-venous thromboembolism; 22 with venous thromboembolism).

[f] Duration of 1 cycle: 3 to 4 weeks.

[g] Follow-up period: January 1, 2009 to August 31, 2020.

[h] Calculated from the start of follow-up (1.1.2009) to death.

DISCUSSION

Summary of Main Results

Our study showed that of patients with high-grade serous ovarian cancer, 16.4% developed a venous thromboembolism event during follow-up. Venous thromboembolism was significantly more frequent in patients treated with neoadjuvant chemotherapy than in those with primary debulking surgery. Median overall survival and platinum-free intervals in patients with venous thromboembolism were shorter than in those without. Additionally, associated with a higher risk of venous

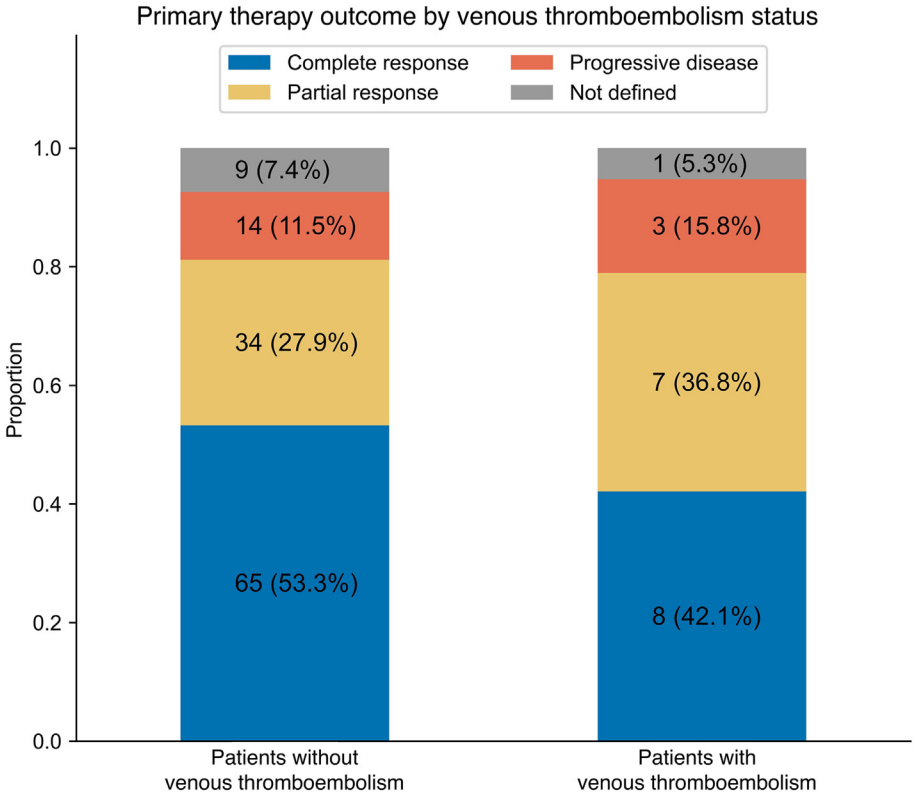

Figure 1 Incidence of the primary therapy outcome of patients having high-grade serous ovarian cancer with and without venous thromboembolism[a] ; ($p = .32$)[b]. [a] Venous thromboembolism was observed after the high-grade serous ovarian cancer diagnosis. [b] *p*-value of the Fisher exact test.

thromboembolism were higher baseline CA125 values, shorter CA125-DT, and increased leukocyte and neutrophil levels throughout follow-up, whereas higher hemoglobin and albumin levels were linked to a lower risk.

Results in the Context of Published Literature

A recent review by Black and colleagues[23] reported that the incidence of venous thromboembolism in ovarian cancer, with several histological subtypes combined, can range from 0.0% to 18.0%. Most studies that have examined the relationship between ovarian cancer and venous thromboembolism have grouped all epithelial ovarian cancer subtypes and even non-epithelial ovarian cancers into the same analysis.[5,14,24] To the best of our knowledge, this is the first cohort study focusing on venous thromboembolism in the most common and deadliest ovarian cancer subtype: high-grade serous ovarian carcinoma; its profile clinically, biologically, and molecularly, differs from the other subtypes. This means that our relatively high rate of venous thromboembolism (16.4%) as compared with figures from other studies demonstrating half the rate or even less of our venous thromboembolism (3.0%-10.0%), is likely explained by differing patient cohorts.[4,25-27] A common risk factor for venous thromboembolism is aging, and our study population's median age was slightly above that of other studies.[25,26] Additionally, a great majority (93.8%) of our study patients were of advanced disease stage (FIGO III-IV), consistent with real-life data for this subtype; which is associated with risk for venous thromboembolism.[10] In other studies, a notable proportion of the patients were at stage I or II,[4,25] and in addition, Mokri and colleagues[4] focused on ovarian cancer patients undergoing primary cytoreduction and excluded patients who received neoadjuvant chemotherapy from the analyses. However, here we noticed the venous thromboembolism risk to be significantly increased in patients receiving neoadjuvant chemotherapy, and a similar finding was recently reported in patients with advanced ovarian or pancreatic cancer.[23,27,28] In a meta-analysis by Weeks and colleagues,[24] 769 venous thromboembolism events occurred in 6324 patients with unselected ovarian cancer, an incidence of 12.1%. A similar 11.0% incidence of venous thromboembolism in ovarian cancer patients was reported by Zhou and colleagues.[15]

The platinum-free interval is prognostic for survival in high-grade serous ovarian cancer,[29] and to our knowledge, the direct association between platinum-free interval and venous thromboembolism events is a novel finding. Other studies have reported an increased risk for venous thromboembolism in ovarian cancer patients with partial or no response to treatment, when compared with patients reaching complete remission,[16] who are surrogates for platinum-free interval. Several mechanisms could explain the link between platinum-free interval and increased venous thromboembolism risk. These include endothelial activation, along with the release of von Willebrand factor and enhanced platelet activation during cancer relapse and progression.[30] In addition to their being thrombogenic, activated platelets in high-grade serous ovarian cancer have been shown to promote cancer dissemination, resulting in early relapse and short platinum-free intervals.[31]

Short CA125-DT has been an independent prognostic factor for survival after first-line chemotherapy for ovarian cancer patients,[32] but to the best of our knowledge, this is the first study to indicate its potential risk for venous thromboembolism. Similarly, CA19-9-

Table 2 Risk Factors for Venous Thromboembolism After Diagnosis of High-Grade Serous Ovarian Cancer

A) Multivariate cause-specific hazard model (full)		
Variables	**HR (95% CI)**	***p*-Value**
Age	0.98 (0.92-1.04)	0.44
Body mass index	1.03 (0.92-1.14)	0.65
Co-morbidities	1.16 (0.43-3.09)	0.77
Previous cancer	0.92 (0.19-4.37)	0.92
Platinum-free interval	0.84 (0.74-0.97)	**0.0123**
Primary treatment strategy: neoadjuvant chemotherapy	6.56 (1.86-23.17)	**0.00347**
Doubling time of plasma levels of CA125 (P-CA125-DT)	0.96 (0.93-0.99)	**0.0334**
B) Multivariate cause-specific hazard model (reduced)		
Variable	**HR (95% CI)**	***p*-Value**
Primary treatment strategy: Neoadjuvant chemotherapy	6.52 (1.87-22.74)	**0.00325**
Doubling time of plasma levels of CA125 (P-CA125-DT)	0.96 (0.93-0.99)	**0.0359**
C) Simple cause-specific hazard model with time-varying variable		
Variable	**HR (95% CI)**	***p*-Value**
Platelet count, 10^9/L[a]	2.12 (0.64-7.00)	0.22
Hemoglobin level, g/dL	0.95 (0.93-0.97)	**< 0.0001**
Leukocyte count, 10^9/L[a]	6.05 (1.78-20.57)	**0.00398**
Neutrophil count), 10^9/L[a]	3.81 (1.33-10.92)	**0.0126**
Plasma creatinine, μmol/L[a]	0.48 (0.07-3.35)	0.46
Alanine transaminase, U/L[a]	0.94 (0.35-2.56)	0.91
Alkaline phosphatase, U/L[a]	2.99 (1.20-7.50)	**0.0192**
Albumin, g/L	0.90 (0.83-0.98)	**0.0151**
Plasma level of carbohydrate antigen 125 (P-CA125), U/mL[a]	1.79 (1.35-2.38)	**< 0.0001**

Abbreviations: CA, carbohydrate antigen; P-CA125-DT, Doubling time of plasma levels of carbohydrate antigen 125.
Statistically significant *p*-values ($p \leq .050$) are in bold.
[a] Values log-transformed.

DT is known to correlate with this risk in pancreatic cancer.[20] Whereas the baseline CA125-DT did not significantly differ between patient groups, further analysis indicated that an outlier (Fig. 2) influenced this result because removing that patient rendered the difference statistically significant. In addition, patients who developed venous thromboembolism had higher baseline CA125 values. In earlier studies, plasma levels of CA125 may predict venous thromboembolism, and they describe CA125 as associated with coagulation activity in epithelial ovarian cancer.[14,15,33] Thus, based on both prior studies and our findings, patients with higher CA125 and shorter CA125-DTs may have an increased propensity to develop venous thromboembolism. Although the progression of ovarian cancer is associated with a confirmed rise in CA125 level,[21] further elucidation is required of the correlation between platinum-free interval and CA125-DT.

The Khorana predictive score is the most internationally validated assessment model for ambulatory cancer patients during chemotherapy, but its prediction ability in ovarian cancer patients is debatable, because, among the population to derive and validate the Khorana score, only 10.4% had a gynecologic

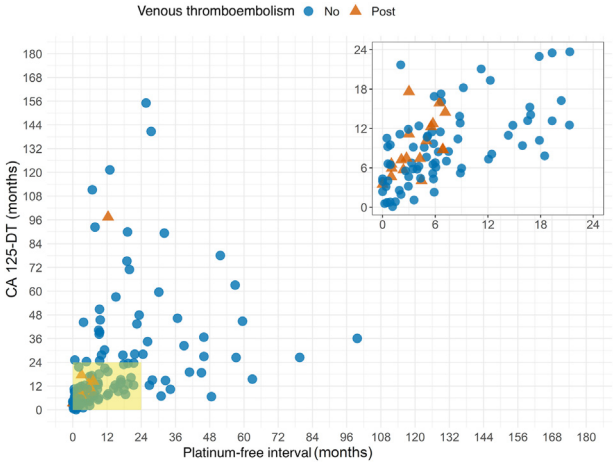

Figure 2 Scatterplot of platinum-free interval and CA125-DT showing that CA125 doubling times and platinum-free intervals were shorter in patients with venous thromboembolism after diagnosis of high-grade serous ovarian cancer (orange) than in those without venous thromboembolism (blue). CA, carbohydrate antigen; DT, doubling time.

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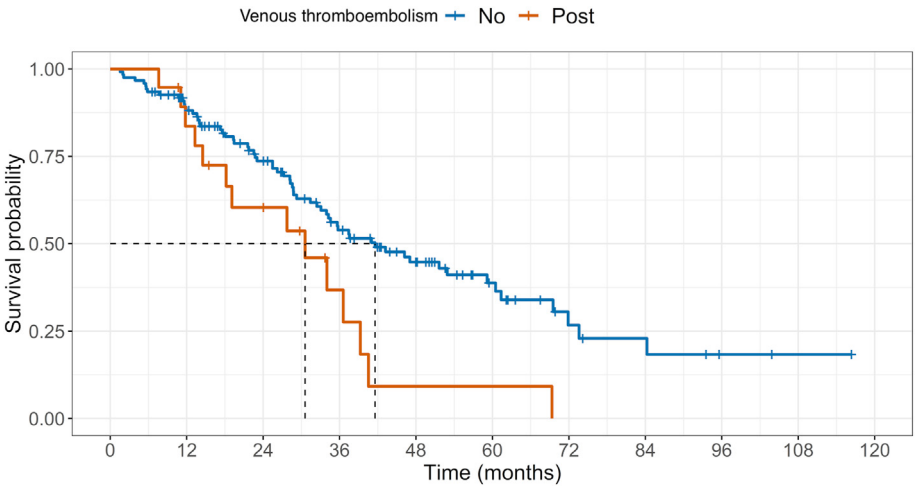

Figure 3 Kaplan-Meier estimate of overall survival of the high-grade serous ovarian cancer patients with venous thromboembolism[a] (orange line) and without (blue line) ($p = .01$)[b]. Dashed lines indicate the median survival and tick marks censoring. [a]Venous thromboembolism was observed after the high-grade serous ovarian cancer diagnosis. [b]*p*-value of the log-rank test.

malignancy.[19,34] Our study revealed no significant difference in Khorana score ($p = 0.70$) between patients with and without venous thromboembolism; this supports others' results. The other risk assessment models are developed (eg, Prophylaxis of thromboembolism during chemotherapy (PROTECHT), Vienna cancer and thrombosis study (Vienna-CATS), the CONKO score, Comparison of methods for thromboembolic risk assessment with clinical perceptions and awareness - Cancer associated thrombosis (COMPASS-CAT)) and have attracted debate as to their clinical use. Our results on other laboratory values and venous thromboembolism risk are in line with those of earlier studies. As others' findings show, decreased albumin and hemoglobin levels are related to venous thromboembolism events.[15,19] However, unlike previous findings, ours showed no correlation between platelet count and venous thromboembolism.[16] At cancer diagnosis, patients who later developed venous thromboembolism had thrombocytosis (platelet count above 350×10^9/L; Table S3). One must note that the timing of the assessment of platelet counts and the start of cancer treatment was not standardized; this may explain the discrepancy. These values should be evaluated together with the other features to assess an individual patient's risk of developing venous thromboembolism.

Strengths and Weaknesses

Our study has certain limitations. First, whereas the proportion who developed venous thromboembolism is similar to that seen earlier,[23,24] our relatively small cohort of patients and the absolute number of venous thromboembolism events limited statistical analyses. For instance, being unable to stratify our analyses according to disease stage, we performed a sensitivity analysis excluding patients with FIGO I-II; the results remained consistent. Second, due to the nature of the study, patients were not routinely scanned for venous thromboembolism. Consequently, some with asymptomatic may have been missed. Consistent monitoring by medical imaging and clinical examination during treatment and follow-up, focusing also on symptoms, reduces the probability of undetected venous thromboembolism events. Third, utilizing the real-life electronic health record data posed statistical challenges, due to considerable variability in the quantification of distinct markers. This was then reflected in the CIs. Fourth, the study lacked some relevant information, in particular, any documentation of inherited and acquired thrombophilias,[35] of plasma D-dimer values, and other coagulation biomarkers[15] known to be associated with increased thromboembolism risk in cancer patients. Despite these weaknesses, the analysis of longitudinal data from a carefully selected and well-documented high-risk high-grade serous ovarian cancer patient cohort enabled us to differentiate some individual biomarker associations with venous thromboembolism, for improved analytical precision.

Implications for Practice and Future Research

Our study indicates that valuable tools for assessing venous thromboembolism risk include the length of the platinum-free interval and also routine laboratory variables, including the CA125 and its DT. While some of these variables are already incorporated into established scoring calculators, none utilizes the full set, suggesting that amendments to scoring systems could improve predictive accuracy. However, such advancements require confirmatory studies in larger clinical cohorts. Furthermore, the potential role in the pathogenesis of venous thromboembolism of coagulation activity linked to CA125 and CA125-DT, as well as the correlation between platinum-free interval and CA125-DT both warrant further analysis.

CONCLUSIONS

In summary, we found that 1 in 6 high-grade serous ovarian cancer patients develops venous thromboembolism. These results demonstrate that elevated venous thromboembolism risk is associated with short platinum-free intervals and increased leukocyte and neutrophil counts, along with higher CA125 levels and shorter CA125-DT. These findings may have implications for the clinical care of patients with high-grade serous ovarian cancer, and these risk markers should be incorporated into risk stratification models for venous thromboembolism.

Ethics Approval This study involves human participants and was approved by the Ethics Committee of the Hospital District of Southwest Finland (ETMK): (ETMK 5 80/2009 §238) and the Turku Clinical Research Center (permission number: T07/009/15). All of the participating patients gave an informed consent.

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Data Availability Statement The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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