D-dimer as a more effective marker for detecting thrombosis in patients with ovarian clear cell carcinoma compared with high-grade serous carcinoma

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Abstract. The present retrospective cohort study aimed to examine the effectiveness of D-dimer in detecting cancer-associated thromboembolism (CAT) in clear cell carcinoma (CCC) compared with that in high-grade serous carcinoma (HGSC) to develop an effective screening method. Patients diagnosed with CCC or HGSC who underwent primary surgery at National Defense Medical College Hospital (Tokorozawa, Japan) between January 2009 and December 2023 were included in the present study, and their clinical records were analyzed. Patients with a history of thrombosis and anticoagulation and those with acute infection at the initial visit were excluded. In the CCC and HGSC groups, 20 out of 79 patients (25.3%) and 15 out of 123 patients (12.2%) developed CAT, respectively, indicating that CAT was more common in patients with CCC (P=0.022). D-dimer was a significantly better predictor in CCC [area under the curve (AUC), 0.92] than in HGSC (AUC, 0.75). Multivariate analysis demonstrated that the International Federation of Gynecology and Obstetrics (FIGO) stage was an independent risk factor for CAT (odds ratio, 3.28; 95% CI, 1.04-10.3; P=0.042) in the CCC group. For CAT detection, combining D-dimer with FIGO stage further improved the predictive accuracy in early-stage CCC (AUC, 0.97). These results may be useful for CAT screening in clinical practice.

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Abbreviations: CAT, cancer-associated thrombosis; EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; CCC, clear cell carcinoma; HGSC, high-grade serous carcinoma; TF, tissue factor; CA 125, carbohydrate antigen 125; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PE, pulmonary embolism; DVT, deep vein thrombosis; OR, odds ratio; ROC, receiver operating characteristic; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value

Key words: EOC, cancer-associated thromboembolism, venous thromboembolism, CCC, D-dimer

Introduction

The incidence of cancer-associated thromboembolism (CAT) depends on the type of cancer and is relatively high in gynecological cancers (1,2). CAT complications are associated with worse prognosis in patients with epithelial ovarian cancer (EOC) (3,4). The prevalence of pretreatment CAT in patients with EOC ranges from 10.4 to 26.4%, and many cases are asymptomatic (4-6). As untreated CAT can lead to life-threatening conditions, early detection and treatment are essential for the comprehensive care of patients with EOC.

D-dimer testing has been recommended as a cost-effective and rapid screening tool for CAT in EOC (7,8); however, D-dimer levels reflect a variety of conditions, including inflammation caused by cancer cells and cancer treatments such as surgery and chemotherapy (9-11). In addition, cancer cells and EOC treatment may create an environment for recurrent inflammation, where the level of inflammation is influenced by the histological subtype and International Federation of Gynecology and Obstetrics (FIGO) stage (12-14). This condition can affect the effectiveness of D-dimer as a screening method (15,16).

Clear cell carcinoma (CCC) and high-grade serous carcinoma (HGSC) are two histological subtypes of ovarian cancer that exhibit several differences in biological and clinical characteristics. CCC is more common in Asia than in Western countries, often detected in earlier stages, and has a platinum-resistant nature (17). In contrast, HGSC is the most common histological type, frequently discovered at an advanced stage, and is sensitive to platinum (18). Although HGSC is often complicated with CAT, CCC exhibits the highest complication rate among all histological subtypes (3-6). In CCC, CAT formation is caused by hypercoagulation due to overexpression of tissue factor (TF) and interleukin-6 (IL-6) (19,20). CAT formation in HGSC is naturally related to hypercoagulation, but it may also be associated

with dehydration and inflammation due to massive ascites and malnutrition because HGSC is usually discovered at a more advanced stage than CCC (21). Thus, the tumor microenvironment and status of patients with CCC differ from those of patients with HGSC.

Considering these distinct characteristics, the diagnostic accuracy of biomarkers for CAT may differ between histological subtypes such as CCC and HGSC. However, this possibility has not been systematically evaluated. If D-dimer does not prove effective as a biomarker for CAT, a screening test for CAT detection is required. Therefore, we aimed to examine the effectiveness of CAT screening in patients with CCC compared with HGSC to develop a new system for CAT detection.

Materials and methods

Patients and blood samples. Patients diagnosed with CCC or HGSC who underwent primary surgery at our hospital between January 2009 and December 2023 were identified. Clinical data were retrospectively collected from medical records. Patients with acute infections at the initial visit were excluded because of strong inflammatory responses. Additionally, patients with a history of thrombosis or anticoagulation therapy at the initial visit, those with other cancers, and those without medical records were excluded. This study was approved by the Ethics Committee of National Defense Medical College, Tokorozawa, Japan (No4933). Written informed consent for all participation was obtained before the treatment.

To identify the risk factors for CAT in CCC and HGSC, the following variables were assessed: age at diagnosis, body mass index, cardiovascular risk factors and comorbidities, the World Health Organization Performance Status Scale (22), and 2014 FIGO (23). Additional factors included the histological type diagnosed according to the 2020 WHO Health Organization criteria (24), tumor size measured using magnetic resonance imaging (MRI) before primary treatment, and the presence of ascites, which was assessed intraoperatively or through preoperative percutaneous abdominal puncture. Cardiovascular risk factors and comorbidities included previous or concurrent ischemic stroke, peripheral arterial disease, coronary artery disease, hypertension, diabetes mellitus, and hyperlipidemia.

Peripheral blood samples were obtained during the initial visit. Data on white blood cell differential counts and platelet, hemoglobin, C-reactive protein (CRP), albumin, D-dimer, fibrinogen, and carbohydrate antigen 125 (CA 125) levels were retrospectively obtained from medical records. D-dimer was measured using a latex coagulation reaction by sensitization with an anti-D-dimer mouse monoclonal antibody, and turbidity was assessed using a spectrophotometer (CN-6500; SYSMEX, Hyogo, Japan). The cutoff value for D-dimer was set at 1.0 μg/l. In addition, we calculated the neutrophil-lymphocyte ratio (NLR), defined as the absolute neutrophil count divided by the absolute lymphocyte count, and the platelet-lymphocyte ratio (PLR), defined as the absolute platelet count divided by the absolute lymphocyte count, as biomarkers of inflammation (25).

CAT evaluation protocol. In our study, CAT was defined as CAT that developed before primary treatment. CAT was classified as venous thromboembolisms, including pulmonary embolism (PE) and deep vein thrombosis (DVT). All patients underwent computed tomography before the primary treatment to detect CAT. If patients had symptoms suggestive of CAT, such as lower extremity edema, chest pain, and dyspnea, we performed additional examinations, including ultrasonography, MRI, and angiography.

Statistical analysis. All statistical analyses were performed using JMP Pro 14 software (SAS Institute Inc., Cary, NC, USA). Chi-square tests and Fisher's exact tests were used to compare clinical and pathological characteristics between patients with and without CAT. In addition, the incidence and risk factors for CAT in patients with CCC and HGSC were examined. Univariate and multivariate analyses were performed using logistic regression analysis. Serologic and hematologic biomarkers were compared using the Mann Whitney U test. Receiver operating characteristic (ROC) curves were used to predict CAT development. The Youden index (sensitivity + specificity-1) was calculated, and the cutoff value corresponding to the highest Youden index was used as the optimal cutoff value. Statistical significance was set at $P<0.05$.

Results

Clinical characteristics. In total, we analyzed the data of 79 patients with CCC and 123 with HGSC. Of them, 20 patients with CCC (25.3%) and 15 with HGSC (12.2%) developed CAT (P=0.022). The CCC group included 6 patients (7.6%) with DVT, 6 (7.6%) with PE, and 8 (10.1%) with PE and DVT, whereas the HGSC group included 8 patients (6.5%) with DVT and 7 (5.7%) with PE.

Table I presents the clinical characteristics of patients with and without CAT. In the CCC group, patients with CAT were diagnosed at a more advanced FIGO stage (P=0.004) and had larger tumors (P=0.030) and massive ascites (P=0.013). However, no significant differences in CAT complications were observed in the HGSC group. Table II summarizes the univariate and multivariate analyses of risk factors for CAT in the CCC group. Univariate analysis identified advanced stage [odds ratio (OR) 4.40, 95% confidence intervals (CI) 1.51 12.8, P=0.007], larger tumor size (OR 4.46, 95% CI 1.18 16.9, P=0.028), and increased ascites volume (OR 14.5, 95% CI 1.51 139.0, P=0.020) as significant risk factors for CAT. Multivariate analysis confirmed that an advanced disease stage (OR 3.28, 95% CI 1.04 10.3, P=0.042) was an independent risk factor for CAT. Risk factors for CAT in the HGSC group could not be determined.

Biomarker analysis. Comparison of serological and hematological biomarkers between patients with and without CAT is presented in Table III. In the CCC group, significant differences were observed in NLR, PLR, hemoglobin, albumin, CRP, D-dimer, CA125, and CA19-9 levels. Conversely, in the HGSC group, only D-dimer levels were significantly different. D-dimer had the highest area under the curve (AUC) (0.92, P<0.001) in the CCC group and highest AUC (0.75, P=0.002) in the HGSC group; the AUC in the HGSC group was lower than that in the CCC group (Fig. 1). The cutoff value of

Table I. Characteristics of patients with CCC and HGSC with or without CAT.

	Patients with CCC			Patients with HGSC		
Variables	CAT (+), n (%) (n=20)	CAT (-), n (%) (n=59)	P-value	CAT (+), n (%) (n=15)	CAT (-), n (%) (n=108)	P-value
Age at diagnosis, years			0.588			0.584
≥65	13 (65.0)	42 (71.2)		5 (33.3)	46 (42.6)	
<65	7 (35.0)	17 (28.8)		10 (66.6)	62 (57.4)	
Body mass index, kg/m^2			0.999			0.739
≥25	3 (15.0)	9 (15.3)		4 (26.7)	23 (21.3)	
<25	17 (85.0)	50 (84.7)		11 (73.3)	85 (78.7)	
Cardiovascular risk factors and comorbidities			0.490			0.720
Yes	3 (15.0)	7 (11.9)		3 (20.0)	18 (16.7)	
No	17 (85.0)	52 (88.1)		12 (80.0)	90 (83.3)	
FIGO stage			0.004			0.054
I	8 (40.0)	44 (74.6)		3 (20.0)	18 (16.7)	
II	2 (10.0)	7 (11.9)		7 (46.7)	73 (67.6)	
III	9 (45.0)	8 (13.5)		3 (20.0)	9 (8.3)	
IV	1 (5.0)	0 (0.0)		2 (13.3)	8 (7.4)	
Tumor size, cm			0.030			0.342
≥10	17 (85.0)	33 (55.9)		5 (33.3)	24 (22.2)	
<10	3 (15.0)	26 (44.1)		10 (66.7)	84 (77.8)	
Ascites, ml			0.013			0.382
≥1,000	4 (20.0)	1 (1.7)		9 (60.0)	61 (56.5)	
<1,000	16 (80.0)	58 (98.3)		6 (40.0)	47 (43.5)	

CAT, cancer-associated thromboembolism; CCC, clear cell carcinoma; HGSC, high-grade serous carcinoma; FIGO, International Federation of Gynecology and Obstetrics.

Table II. Univariate and multivariate analysis for the incidence of cancer-associated thromboembolism in clear cell carcinoma.

	Univariate analysis			Multivariate analysis		
Variables	OR	95% CI	P-value	OR	95% CI	P-value
Age at diagnosis (≥65 vs. <65 years)	1.33	0.45-3.91	0.588			
Body mass index (≥25 vs. <25 kg/m^2)	0.98	0.24-4.05	>0.999			
Cardiovascular risk factors and comorbidities (yes vs. no)	1.31	0.30-5.64	0.716			
FIGO stage (II-IV vs. I)	4.40	1.51-12.76	0.007	3.28	1.04-10.32	0.042
Tumor size (≥10 vs. <10 cm)	4.46	1.18-16.88	0.028	3.22	0.80-12.87	0.098
Ascites (≥1,000 vs. <1,000 ml)	14.48	1.51-139.02	0.020	6.61	0.63-70.01	0.116

FIGO, International Federation of Gynecology and Obstetrics; OR, odds ratio.

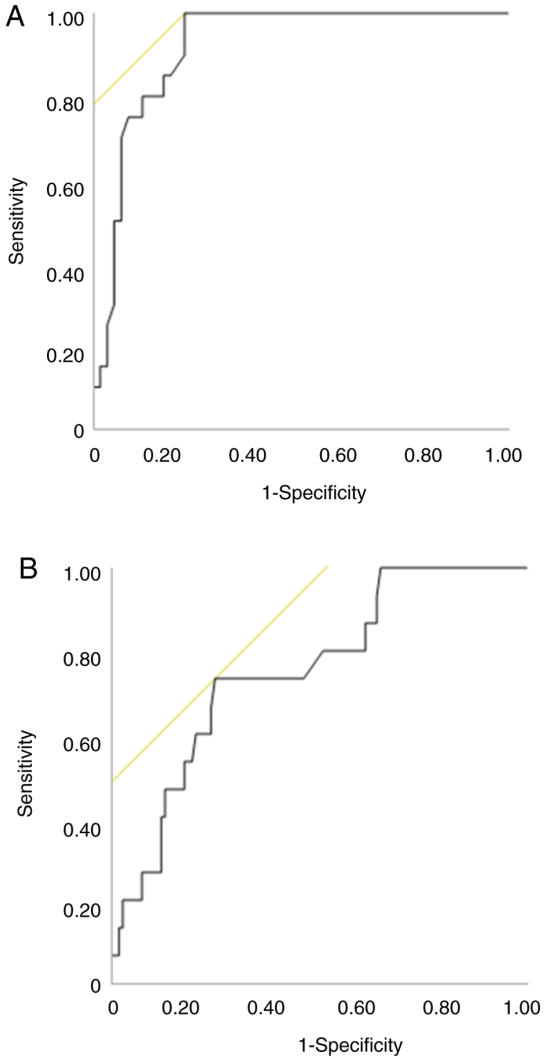

Figure 1. Receiver operating characteristic curves demonstrating the area under the curve of D-dimer for predicting cancer-associated thrombosis in the (A) clear cell carcinoma and (B) high-grade serous carcinoma groups. The yellow line indicates the Youden Index as the optimal cutoff value.

D-dimer as a predictor of CAT was 1.5 μg/ml in CCC and 5.8 μg/ml in HGSC.

Diagnostic performance of D-dimer. Tables IV and V show the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of D-dimer in predicting CAT in the CCC and HGSC groups. the AUC for predicting CAT was 0.75 in HGSC group, and according to the cutoff values corresponding to the highest Youden index, the sensitivity, specificity, PPV, and NPV were 73.3, 75.0, 28.9, and 95.3%, respectively. In contrast, the AUC, sensitivity, specificity, PPV, and NPV for predicting CAT in the CCC group were 0.91, 100, 83.0, 50.0, and 100%, respectively. The combination of FIGO stage I and D-dimer ≥1.5 μg/l improved the predictive ability to an AUC of 0.97 in the CCC group.

Discussion

Our study showed that CCC was more frequently complicated by CAT. Advanced stage was the only risk factor identified

Table III. Comparison of serologic and hematologic biomarkers in patients with CCC and HGSC before primary treatment.

	CCC				HGSC			
Variable	CAT (+) (n=20)	CAT (-) (n=59)	P-value	AUC	CAT (+) (n=15)	CAT (-) (n=108)	P-value	AUC
Neutrophil count, 10^9/l	5.21 (3.05-27.28)	4.82 (1.56-8.28)	0.120	0.62	4.55 (1.69-12.11)	5.41 (1.94-13.41)	0.120	0.62
Lymphocyte count, 10^9/l	1.21 (0.49-2.20)	1.47 (0.73-3.03)	0.111	0.62	1.21 (0.42-1.92)	1.25 (0.37-4.27)	0.444	0.56
NLR	3.89 (2.37-25.77)	3.15 (1.02-7.09)	0.005	0.71	3.62 (1.13-22.73)	4.18 (1.22-24.73)	0.716	0.47
Platelet count, 10^9/l	32.65 (22.70-69.80)	27.6 (10.50-57.50)	0.099	0.62	28.70 (10.10-61.30)	32.60 (16.00-69.20)	0.152	0.61
PLR	281.50 (116.06-659.48)	182.6 (74.12-576.51)	0.015	0.68	202.02 (78.84-1293.89)	265.48 (61.33-1217.98)	0.599	0.46
Hemoglobin, g/l	10.70 (8.20-13.70)	12.30 (6.80-14.40)	0.008	0.70	12.40 (7.50-15.30)	12.70 (8.70-16.70)	0.948	0.49
Albumin, g/l	3.50 (2.10-4.70)	4.00 (2.60-5.10)	0.002	0.73	3.30 (2.00-4.40)	3.10 (2.00-4.90)	0.278	0.59
CRP, mg/dl	2.25 (0.30-19.70)	0.30 (0.30-8.70)	0.004	0.71	1.70 (0.30-11.50)	1.50 (0.14-27.10)	0.651	0.54
D-dimer, μg/l	8.35 (1.60-28.10)	0.70 (0.10-25.30)	<0.001	0.91	8.00 (2.00-27.50)	3.50 (0.10-27.30)	0.002	0.75
Fibrinogen, mg/dl	454.50 (163.00-719.00)	372.50 (174.00-847. 00)	0.725	0.53	368.00 (217.00-744.00)	412.00 (196.00-2,565.00)	0.749	0.53
CA125, U/ml	400.30 (13.00-1,423.00)	44.10 (5.40-2,206.00)	<0.001	0.80	1,367.10 (5.20-32,547.00)	592.20 (6.60-15,665.00)	0.243	0.59

Data are presented as the mean (range). CAT, cancer-associated thromboembolism; CCC, clear cell carcinoma; HGSC, high-grade serous carcinoma; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; CA125, cancer antigen 125; AUC, area under the curve.

Table IV. Diagnostic performance of D-dimer cutoffs and FIGO stage for detecting cancer-associated thromboembolism in clear cell carcinoma before treatment.

Marker combination	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC
D-dimer (1.00 μg/ml)[a]	100.0	61.0	46.5	100.0	0.91
D-dimer (1.50 μg/ml)[b]	100.0	78.0	60.6	100.0	0.91
Plus FIGO stage I	100.0	88.6	61.5	100.0	0.97
Plus FIGO stage II-IV	100.0	60.0	66.7	100.0	0.81

[a]The cutoff value of D-dimer based on the reference value provided by the manufacturer. [b]The optimal cutoff value corresponding to the highest Youden index. FIGO, International Federation of Gynecology and Obstetrics; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

Table V. Diagnostic performance of D-dimer cutoffs for detecting cancer-associated thromboembolism in high-grade serous carcinoma before treatment.

Marker	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC
D-dimer (1.00 μg/ml)[a]	100.0	13.9	13.9	100.0	0.75
D-dimer (5.80 μg/ml)[b]	73.3	75.0	28.9	95.3	0.75

[a]The cutoff value of D-dimer based on the reference value provided by the manufacturer. [b]The optimal cutoff value corresponding to the highest Youden index. PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

for CAT in the CCC group, whereas no significant risk factors were found in the HGSC group. Furthermore, D-dimer showed the highest AUC for detecting CAT in both the CCC and HGSC groups, with the CCC group having a higher AUC than the HGSC group. Additionally, a model combining D-dimer levels and early-stage disease exhibited improved sensitivity and specificity for detecting CAT.

Our results indicated that CAT incidence before treatment in patients with CCC and those with HGSC fell within the range reported in previous studies, ranging from 13.4 to 33.1% in CCC (3,4,6,26) and 11.8 to 24.0% in HGSC (5,6,26). Patients with EOC and CAT do not usually present with symptoms (5), which were consistent with the findings of our study. Therefore, imaging studies such as CT angiography or ultrasound sonography are necessary for thrombosis screening.

Some risk factors for CAT have been reported, including age, massive ascites, FIGO stage, and cardiovascular disease (4,6,26,27). Our analysis revealed that advanced FIGO stage was an independent risk factor for CAT formation in the CCC group. In contrast, no significant risk factors were identified in the HGSC group. Therefore, particular attention is needed for patients with CCC experiencing risk factors and for all patients with HGSC.

Although we attempted to identify new biomarkers, the D-dimer test remained the most useful tool for detecting CAT in both the CCC and HGSC groups, consistent with previous findings (4,15,16). Notably, the D-dimer test was more effective in detecting CAT in patients with CCC than in those with HGSC. We assumed that these results were due to the different characteristics of CCC and HGSC. Overexpression of TF and IL-6 plays a pivotal role in CAT development in CCC (14,19,27). TF, Factor III, initiates the extrinsic coagulation pathway by binding to Factor VIIa and Factor Xa, leading to thrombin generation. Meanwhile, IL-6 is a proinflammatory cytokine that promotes coagulation by increasing TF expression and fibrinogen synthesis (28). In HGSC, while these factors also contribute to CAT, CAT is strongly associated with ascites, tumor pressure on the veins, and dehydration (6). Our reports suggest that a strategy for detecting CAT can be established according to the histological subtypes. The constructed predictive model, combining disease stage and D-dimer levels, may be useful for detecting CAT in CCC.

The limitations of our study included the retrospective design, single-institution analysis, and small sample size. Further studies with larger sample sizes are warranted to confirm the clinical significance of the association between CCC and CAT.

In conclusion, advanced stage is an independent risk factor for the development of CAT in CCC. D-dimer is an excellent screening tool for CAT in CCC, in particular when combined with FIGO stage; however, it is less reliable in HGSC, suggesting a need for histology-specific screening strategies. Further studies are required for preoperative diagnosis using imaging, tumor markers, and molecular biological methods for early detection of CAT.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TI, MM and MT contributed to the conception and design of the study. Material preparation, and data collection and analysis were carried out by TI, NK, JS and TH. TI, MM, RT, SN, JS, TH, YO, KK, HS, KO, YH and MT contributed to the interpretation of the data. The first draft of the manuscript was written by TI. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of the National Defense Medical College, Tokorozawa, Saitama, Japan on January 20, 2024 (confirmation no. 4933). All patient records and information were completely anonymized prior to analysis to prevent the disclosure of their identities. Before the treatment, written informed consent was obtained from all patients with ovarian cancer who underwent surgery.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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