Acta Med. Okayama, 2022
Vol. 76, No. 2, pp. 129–135

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

The Combination of D-dimer and Glasgow Prognostic Score Can Be Useful in Predicting VTE in Patients with Stage IIIC and IVA Ovarian Cancer

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Cancer patients have increased risk of venous thromboembolism (VTE) that must be assessed before treatment. This study aimed to determine effective VTE biomarkers in gynecologic cancer (GC). We investigated the correlation between D-dimer levels, Khorana risk score (KRS), Glasgow prognostic score (GPS), and VTE in 1499 GC patients (583 cervical cancer (CC), 621 endometrial cancer (EC), and 295 ovarian cancer (OC) patients) treated at our institution between January 2008 and December 2019. χ^2 and Mann–Whitney *U*-tests were used to determine statistical significance. We used receiver operating characteristic-curve analysis to evaluate the discriminatory ability of each parameter. D-dimer levels were significantly correlated with KRS and GPS in patients with GC. VTE was diagnosed in 11 CC (1.9%), 27 EC (4.3%), and 39 OC patients (13.2%). Optimal D-dimer cut-off values for VTE were 3.1, 3.2, and 3.9 μg/ml in CC, EC and OC patients, respectively. D-dimer could significantly predict VTE in all GC patients. Furthermore, D-dimer combined with GPS was more accurate in predicting VTE than other VTE biomarkers in stage IIIC and IVA OC (AUC: 0.846; $p < 0.001$). This study demonstrates that combined D-dimer and GPS are useful in predicting VTE in patients with OC.

Key words: D-dimer, gynecologic cancer, venous thromboembolism

Patients with cancer have an increased risk of venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism. VTE is a common cause of morbidity and mortality in patients with various cancers [1,2]. The risk of VTE differs depending on the type and stage of cancer. Patients with stomach and pancreatic cancer are at very high risk, while patients with lung, gynecological, bladder, testicular cancer and lymphoma are considered to be at high risk [3,4].

Therefore, screening tests to predict VTE are imperative: D-dimer, C-reactive protein (CRP), albumin, and the Khorana risk score (KRS) are generally used as VTE biomarkers. D-dimer, a signal of activation of the coagulation pathway and an end-product of fibrinogen degradation, has been accepted as a useful diagnostic and prognostic parameter in several malignancies [5-8]. CRP, a nonspecific marker of inflammation produced by the liver, plays a central role in the etiopathogenesis of atherothrombosis [9]. Therefore, CRP may also be linked to VTE [10,11]. Reduced serum albumin levels are also associated with a moderately increased risk of VTE [12], and albumin has been suggested as a novel risk factor of VTE in patients with cancer [13]. In this study, we examined the ability of the Glasgow Prognostic Score (GPS), which combines albumin and CRP, to predict VTE.

Received May 14, 2021; accepted October 7, 2021.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

The KRS has also been used to identify patients at high risk of VTE [3]. The KRS has been recommended by the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology to identify cancer patients at risk for VTE, and those who would be eligible for thromboprophylaxis [14]. By applying five risk factors, the KRS classifies cancer patients based on three risk stratifications, *i.e.*, low- (score = 0), intermediate- (score = 1-2) and high-risk (score ≥ 3) groups. Previous studies have reported that the incidence of VTE varies among the risk levels, with rates of 0.8-13%, 1.8-15.9% and 6.7-41.4% in the low-, intermediate- and high-risk groups, respectively [15].

In the present study, we examined whether VTE is correlated with D-dimer levels, GPS, and KRS in gynecologic cancer (GC) patients. The main purpose of this study was to determine which of three markers — the D-dimer levels, GPS, or KRS — was the most effective VTE biomarker in GC patients.

Materials and Methods

In this retrospective study, we reviewed the medical records of 1499 GC patients (583 cervical cancer (CC), 621 endometrial cancer (EC), and 295 ovarian cancer (OC) patients) who were treated at the Department of Obstetrics and Gynecology of Okayama University Hospital between January 2008 and December 2019. The study protocol was approved by the institutional review board of Okayama University Hospital (2020-005). Patients with GC who did not receive treatment, and those with a history of VTEs, using anticoagulants, or diagnosed with double cancers were excluded from the study. Disease staging was performed according to the International Federation of Gynecology and Obstetrics criteria.

White blood cell (WBC) count, hemoglobin (Hb), platelet count, albumin, CRP, and D-dimer levels were measured from 1-7 days before the start of treatment. WBC, Hb, and platelet counts were measured using automated blood cell counters (Bayer HealthCare, Diagnostics Division, Tarrytown, NY, USA). Serum albumin and CRP levels were assessed using latex nephelometry (LT Auto; Wako, Osaka, Japan). D-dimer levels were measured by latex photometric immunoassay using LPIA-ACE D-D dimer II (Mitsubishi Chemical Medience Corporation, Tokyo) as the reagent. GPS was estimated as previously described [16]. Patients with elevated CRP levels (> 1.0 mg/dL) and hypoalbuminemia (< 3.5 g/dL) were assigned a score of 2 and classified in the high GPS group. Patients with only one of these biochemical abnormalities were assigned a score of 1, and those with neither were assigned a score of 0. The latter were assigned to the low GPS group.

To calculate the KRS, we used blood count data obtained immediately before treatment. Per the KRS, GC is associated with a significantly increased risk of VTE development; therefore, the base score was 1. In addition, platelet count > 350,000/μL, WBC count > 11,000/μL, Hb level < 10 g/dL, and body mass index (BMI) ≥ 35 kg/m^2 are significant risk factors of VTE, and each added an additional point to the score [3].

Mochizuki *et al.* reported that a D-dimer cut-off level of 3 μg/ml might be a useful indicator level to exclude VTE or show an increased risk for VTE in colorectal cancer patients treated with bevacizumab-containing chemotherapy [17]. In this study, the cut-off value of D-dimer was set to over 3.0 μg/ml. Patients with D-dimer higher than the cut-off underwent computed tomography of the chest, abdomen, and lower extremities using multidetector row computed tomography (MDCT; Toshiba, Tokyo) within 6 h after blood sampling, and VTE was differentiated. After the MDCT, a radiologist or cardiologist made a VTE diagnosis within 30 min. Patients diagnosed with VTE were immediately administered anticoagulant therapy.

Data were analyzed using χ^2 and Mann-Whitney *U*-tests for group-wise comparisons. One-factor analysis of variance, followed by Fisher's protected least significant difference test, was used for all pairwise comparisons. A receiver operating characteristic (ROC) curve was generated for each parameter, and the area under the curve (AUC) was calculated to evaluate the discriminatory ability of each parameter. We also examined the data in a cross-tabulated form to explore the characteristics associated with VTE. Analyses were performed using SPSS software (version 26.0; IBM Corp., Armonk, NY). Statistical significance was set at $p < 0.05$.

Results

Table 1 shows the age, BMI, stage of cancer, histology, hypertension, and smoking status of the patients at diagnosis. The median pretreatment D-dimer levels in the CC, EC, and OC groups were 0.5, 0.5, and

Table 1 Characteristics with gynecologic cancers

Baseline characteristics

	CC		EC		OC	
	Numbers	%	Numbers	%	Numbers	%
Age (year)					295	
<40	99	17	48	7.7	29	9.8
40–49	137	23.5	73	11.8	45	15.3
50–59	132	22.6	208	33.5	82	27.8
60–69	115	19.7	179	28.8	88	29.8
≥70	100	17.2	113	18.2	51	17.3
BMI						
<18.5	91	15.6	43	6.9	21	7.1
18.5–24.9	357	61.2	345	55.6	215	72.9
25.0–29.9	103	17.7	128	20.6	46	15.6
30.0–34.9	25	4.3	64	10.3	9	3.1
≥35.0	7	1.2	41	6.6	4	1.3
Stage						
I+II	371	63.6	467	75.2	136	46.1
III+IV	212	36.4	154	24.8	159	53.9
Histology						
CC; SCC, EM; Low grade, OV; non-CCC	428	73.4	402	64.7	243	82.4
CC; Non- SCC, EC; High grade, OC; CCC	155	26.6	219	35.3	52	17.6
Hypertension						
Present	482	82.7	443	71.3	246	83.4
Absent	101	17.3	178	28.7	49	16.6
Smoking						
Negative	447	76.7	581	93.6	278	94.2
Positive	136	23.3	40	6.4	17	5.8

CC, cervical cancer; EC, endometrial cancer; OC, ovarian cancer; SCC, squamous cell carcinoma; BMI, body mass index; CCC, clear cell carcinoma.
*$p<0.05$

2.3 μg/ml, respectively. We subsequently investigated the correlation between D-dimer levels and GPS and KRS in CC, EC, and OC patients. For this purpose, we set the VTE cut-off to 3.0 μg/ml and divided patients into two groups based on their D-dimer levels (< 3.0 μg/ml and ≥ 3.0 μg/ml). Correlations between D-dimer levels and clinical characteristics (BMI, age, stage, histology, hypertension, and smoking) were assessed for patients with CC, EC, and OC. High D-dimer levels were significantly more common in elderly patients with EC and OC ($p<0.001$ and $p=0.001$, respectively). They were also significantly more common in patients with advanced-stage CC, EC, and OC ($p=0.003$, $p<0.001$, and $p<0.001$, respectively). When examining D-dimer levels based on histology, high D-dimer levels were significantly more common in patients with EC and non-clear cell carcinoma ($p<0.001$ and $p=0.017$, respectively) (Table 2).

In the low D-dimer group (< 3.0 μg/ml), the average KRS was 1.34 in CC patients, 1.28 in EC patients, and 1.26 in OC patients. Meanwhile, in the high D-dimer group (≥ 3.0 μg/ml), the average KRS was 1.84 in CC patients, 1.67 in EC patients, and 1.67 in OC patients. Average GPS values were 0.16 in CC patients, 0.14 in EC patients, and 0.25 in OC patients in the low D-dimer group, and 0.64 in CC patients, 0.92 in EC patients, and 1.04 in OC patients in the high D-dimer group. D-dimer levels were thus significantly correlated with KRS and GPS both in patients in the low and those in the high D-dimer group (CC: $p=0.030$ and $p=0.010$,

Table 2 Correlations between D-dimer and clinical characteristics with gynecologic cancers

Baseline characteristics	CC			EC			OC		
D-Dimer	<3.0	≥3.0		<3.0	≥3.0		<3.0	≥3.0	
	Numbers	Numbers	*p*-value	Numbers	Numbers	*p*-value	Numbers	Numbers	*p*-value
BMI			0.605			0.075			0.739
<30.0	527	23		470	47		165	117	
≥30.0	31	2		100	4		7	6	
Age (year)			0.105			<0.001*			0.001*
<65	409	14		396	23		129	70	
≥65	149	11		174	28		43	53	
Stage			0.003*			<0.001*			<0.001*
I+II	362	9		448	19		105	31	
III+IV	196	16		122	32		67	92	
Histology			0.87			<0.001*			0.017*
CC; SCC, EC; Low grade, OC; non-CCC	410	18		384	18		134	109	
CC; Non- SCC, EC; High grade, OC; CCC	148	7		286	33		38	14	
Hypertension			0.149			0.082			0.891
Present	464	18		412	31		143	103	
Absent	94	7		158	20		29	20	
Smoking			0.125			0.307			0.663
Negative	431	16		535	46		171	117	
Positive	127	9		35	5		11	6	

CC, cervical cancer; EC, endometrial cancer; OC, ovarian cancer; SCC, squamous cell carcinoma; BMI, body mass index; CCC, clear cell carcinoma.
*$p<0.05$

respectively; EC: $p=0.004$ and $p<0.001$, respectively; and OC: $p<0.001$ and $p<0.001$, respectively) (Table 3).

Patients with D-dimer above 3.0 μg/ml were diagnosed with VTE using MDCT. VTE was diagnosed in 11 CC (1.9%), 27 EC (4.3%), and 39 OC patients (13.2%). The rate of correct diagnosis of VTE by MDCT was 11 of 25 (44.0%) for CC, 27 of 51 (52.9%) for EC, and 39 of 123 (31.7%) for OC patients. Table 4 shows the distribution of clinical parameters (BMI, age, stage, and histology) based on the development of VTE in patients with CC, EC, and OC. BMI and age were examined by dividing patients into two groups at 30 kg/m^2 and 65 years, which are the World Health Organization (WHO) definitions of obese and elderly, respectively. In patients with OC, VTE was significantly associated with clear cell carcinoma ($p=0.023$; Mann-Whitney *U*-test). However, there was no relationship between other clinical characteristics and D-dimer levels in any type of GC.

We used ROC-curve analyses to determine the cut-off value of the KRS, D-dimer, and GPS to predict VTE. In CC patients, the analyses identified KRS≥2.0 (AUC: 0.640, $p=0.110$, 95%CI 0.465-0.816), D-dimer ≥3.1 μg/ml (AUC: 0.990, $p=0.004$, 95%CI 0.982-0.992), and GPS≥1.0 (AUC: 0.672, $p=0.050$, 95%CI 0.483-0.861) as optimal cut-offs. In EC patients, the analyses identified KRS≥1.5 (AUC: 0.585, $p=0.133$, 95%CI 0.467-0.703), D-dimer≥3.2 μg/ml (AUC: 0.985, $p<0.001$, 95%CI 0.976-0.993), and GPS≥1.0 (AUC: 0.698, $p<0.001$, 95%CI 0.581-0.816) as optimal cut-offs. In OC patients, the analyses identified KRS≥1.5 (AUC: 0.660, $p=0.001$, 95%CI 0.563-0.756), D-dimer≥3.9 μg/ml (AUC: 0.876, $p<0.001$, 95%CI 0.835-0.917), and GPS≥1.0 (AUC: 0.768, $p<0.001$, 95%CI 0.692-0.843) as optimal cutoffs. Based on these results, D-dimer was able to significantly predict VTE in all CC, EC, and OC patients (Fig. 1). We further investigated correlations among D-dimer, KRS, GPS, D-dimer+KRS, D-dimer+GPS, KRS+GPS, D-dimer+KRS+GPS, and VTE in patients with stage IIIC and IVA OC. The combination of D-dimer and GPS had a significantly higher AUC (0.846) than other

Table 3 Correlations between D-dimer and Khorana risk score/Glasgow prognostic score with gynecologic cancers

Baseline characteristics

	CC			EC			OC		
D-Dimer	<3.0	≥3.0		<3.0	≥3.0		<3.0	≥3.0	
	Numbers	Numbers	*p*-value	Numbers	Numbers	*p*-value	Numbers	Numbers	*p*-value
KRS			0.030*			0.004*			<0.001*
1	409	13		458	30		134	54	
2	111	5		73	10		32	56	
3	33	6		32	9		4	13	
4	5	0		7	2		2	0	
5	0	1		0	0		0	0	
GPS			0.010*			<0.001*			<0.001*
0	492	15		510	21		142	36	
1	44	4		39	13		16	46	
2	22	6		21	17		14	41	

CC, cervical cancer; EC, endometrial cancer; OC, ovarian cancer; KRS, Khorana risk scor; GPS, glasgow prognostic score.
*$p<0.05$

Table 4 Correlations between venous thromboembolism and clinical characteristics with gynecologic cancers

Baseline characteristics

	CC			EC			OC		
VTE	(−)	(+)		(−)	(+)		(−)	(+)	
	Numbers	Numbers	*p*-value	Numbers	Numbers	*p*-value	Numbers	Numbers	*p*-value
BMI			0.867			0.265			0.355
<30.0	13	10		21	26		79	38	
≥30.0	1	1		3	1		5	1	
Age (year)			0.371			0.204			0.646
<65	9	5		9	14		49	21	
≥65	5	6		15	13		35	18	
Stage			0.437			0.593			0.289
I+II	6	3		8	11		19	12	
III+IV	8	8		16	16		65	27	
Histology			0.653			0.396			0.023*
CC; SCC, EM; Low grade, OV; non-CCC	9	8		7	11		79	30	
CC; Non- SCC, EM; High grade, OV; CCC	5	3		17	16		5	9	

CC, cervical cancer; EC, endometrial cancer; OC, ovarian cancer; VTE, venous thromboembolism; SCC, squamous cell carcinoma; BMI, body mass index; CCC, clear cell carcinoma.
*$p<0.05$

characteristics in terms of predicting VTE in patients with stage IIIC and IVA OC ($p<0.001$) (Table 5).

Discussion

VTE needs to be vigorously addressed, not only because it can jeopardize patient survival and quality of life, but also so that physicians can focus on active cancer therapy. Therefore, the ability to predict VTE is crucial. The predictive parameters determined by this study included D-dimer, GPS, and KRS.

D-dimer is clinically useful as a biological marker of

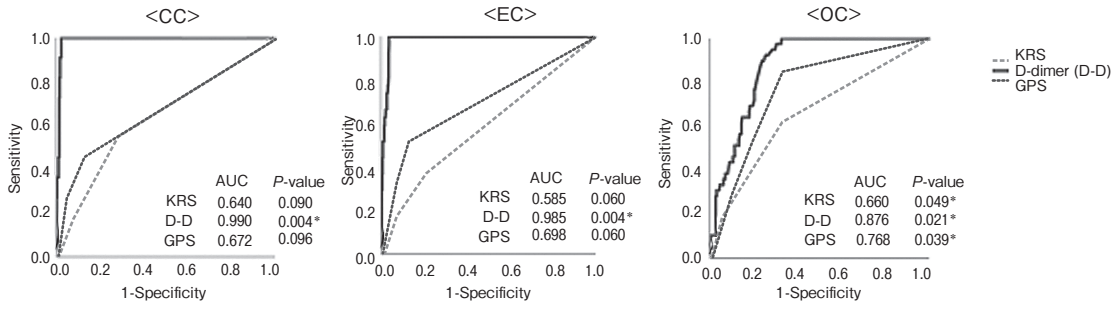

Fig. 1 Receiver operating characteristic curve analyses to determine optimal cut-off values for KRS, D-dimer, and GPS to predict VTE in patients with gynecologic cancers, such as CC, EC, and OC.

Table 5 Comparaision of AUC for diagnostic venous thromboembolism with Stage IIIC and IVA ovarian caner patients

Period	AUC	95%CI	*P*-value
KRS (≥2)	0.587	0.428–0.746	0.296
GPS (≥1)	0.719	0.587–0.851	0.009*
D-Dimer (≥3.9)	0.808	0.700–0.916	<0.001*
KRS (≥2) plus D-Dimer (≥3.9)	0.713	0.554–0.871	0.011*
KRS (≥2) plus GPS (≥1.0)	0.61	0.449–0.770	0.189
D-Dimer (≥3.9) plus GPS (≥1)	0.846	0.732–0.960	<0.001
D-Dimer (≥3.9) plus GPS (≥1) plus KRS (≥2)	0.721	0.582–0.879	0.008

BMI, body mass index; CCC, clear cell carcinoma; KRS, khorana risk score; GPS, glasgow prognostic score.
*$p<0.05$

hemostasis and hemostatic abnormalities, especially as an indicator of intravascular thrombosis. Several other inflammatory markers, such as interleukins and tumor necrosis factor alpha, have been shown to be associated with VTE [18,19]. CRP may also be linked to VTE [10,11]. Additionally, reduced serum albumin levels are associated with a moderately increased risk of VTE [12]. In this study, we examined GPS, which reflects both CRP and albumin levels, as a predictor of VTE. KRS has also been correlated with VTE in several studies [20-22]. Hence, we aimed to assess the correlation between VTE and D-dimer, KRS, and GPS in patients with GC.

We additionally investigated the correlation between D-dimer levels and clinical characteristics. High D-dimer levels were significantly more common in elderly patients with EC and OC. They were also significantly more frequent in patients with advanced-stage CC, EC, and OC; in EC patients with high grade cancer; and in OC patients with non-clear cell carcinoma. Furthermore, D-dimer was shown to be significantly correlated with KRS and GPS in patients with all three types of GC.

Finally, we investigated the correlation between VTE and clinical characteristics. VTE was significantly associated with histology in patients with OC. D-dimer was the most predictable biomarker for VTE in all CC, EC, and OC patients. The optimal D-dimer cut-off value for VTE was 3.1 μg/ml for CC, 3.2 μg/ml for EC, and 3.9 μg/ml for OC. If the D-dimer is ≥4 μg/ml, the possibility of VTE must be carefully addressed with gynecologic cancers. Furthermore, in patients with advanced stage IIIC and IVA OC associated with ascites and pleural effusion, the combination of D-dimer and GPS was significantly more accurate in predicting VTE than other characteristics. If ascites or pleural effusion appear, D-dimer is 3.0 or higher, and GPS is 1 or higher, a more detailed MDCT is necessary.

Our study has some limitations. The number of patients was relatively small, and it was a single-institution study. Further prospective studies with more patients and/or involving multiple institutions would provide more definitive data to clarify the significance of our findings.

In conclusion, this report shows that D-dimer and GPS can be useful tools in the prediction of VTE in patients with OC.

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