High Pre-treatment Plasma D-Dimer Level as a Potential Prognostic Biomarker for Cervical Carcinoma

KOHEI NAKAMURA[1], KENTARO NAKAYAMA[1], MASAKO ISHIKAWA[1], HIROSHI KATAGIRI[1], TOSHIKO MINAMOTO[1], TOMOKA ISHIBASHI[1], NORIYOSHI ISHIKAWA[2], EMI SATO[1], KAORI SANUKI[1], HITOMI YAMASHITA[1], TAKAYOSHI KOMATSU-FUJII[2] and SATORU KYO[1]

Departments of [1]Obstetrics and Gynecology, and [2]Organ Pathology, Shimane University School of Medicine, Izumo, Japan

Abstract. *Background/Aim: We aimed to evaluate the prognostic significance of high pre-treatment plasma D-dimer levels in patients with cervical carcinoma (CC) after adjusting for venous thromboembolism. Patients and Methods: Relationships between the clinicopathological characteristics and the overall (OS) and progression-free (PFS) survival rates of patients with CC (N=129) were examined. Survival was calculated using the Kaplan–Meier method and prognostic indicators assessed using a Cox proportional hazards model. Results: A high pre-treatment plasma level of D-dimers, detected in 42.6% of cases (N=55), was associated with advanced tumour stage. In the multivariate analysis, high pre-treatment plasma D-dimer levels, tumour stage, histological type, and carcinoembryonic antigen (CEA) levels were identified as independent prognostic factors for OS, while tumour stage and CEA levels were identified as independent prognostic factors for PFS. Conclusion: A high pre-treatment plasma level of D-dimers represents an independent prognostic biomarker for CC that could assist in identifying high-risk populations for treatment decisions.*

Uterine cervical carcinoma (CC) represents the second most common form of cancer in women and the fifth most frequent type of malignancy worldwide (1). Uterine CC is a leading cause of cancer-related death among Japanese women. There are two clinically significant variants of uterine CC: squamous cell carcinoma (SCC), accounting for approximately 85-90% of cases and adeno/adenosquamous carcinoma (AD/ASC), accounting for approximately 10-25% of cases (2, 3). The prognosis of SCC is relatively favourable in comparison to AD/ASC. Common prognostic factors for SCC and AD/ASC, however, have yet to be identified.

A high pre-treatment plasma D-dimer level has been reported as a factor indicating a poor prognosis in several types of malignancies, including lung, pancreatic, prostate, gastric, colorectal, breast, and nasopharyngeal carcinoma (4-8). Among gynaecological cancers, high pre-treatment plasma levels of D-dimers have been identified as a negative prognostic factor in ovarian and endometrial carcinoma (9-11). Although high pre-treatment plasma levels of D-dimers are frequently detected in patients with CC, the prognostic significance of this finding is currently unknown. Several studies have revealed that cancer is associated with hypercoagulation (12, 13). In the absence of venous thromboembolism (VTE), the activation of blood coagulation is frequently observed in most patients with cancer (14, 15). Plasma D-dimer is generated *via* degradation of cross-linked fibrin, resulting from the proteolytic actions of plasmin (16). High pre-treatment plasma levels of D-dimer have been identified as a predictor of VTE in cancer patients. Furthermore, the prognosis of patients with cancer with VTE is more likely to be poor (17-19). However, it has not yet been determined whether high pre-treatment plasma levels of D-dimer influence prognosis independently of VTE in patients with CC. In the present study, therefore, we aimed to evaluate the prognostic significance of high pre-treatment plasma levels of D-dimer in patients with CC, after adjusting for VTE.

Materials and Methods

Patients and tumour samples. Patients with CC (N=129) who were scheduled to undergo treatment at Shimane University Faculty of

Correspondence to: Kentaro Nakayama, MD, Ph.D., Department of Obstetrics and Gynecology, Shimane University School of Medicine, Enyacho 89-1, Izumo 6938501, Shimane, Japan. Tel: +81 853202268, Fax: +81 853202264, e-mail: kn88@med.shimane-u.ac.jp

Key Words: Cervical carcinoma, D-dimer, VTE, overall survival, progression-free survival.

Table I. *Clinicopathological characteristics of patients (N=129) with cervical carcinoma.*

Clinicopathological characteristic	Patients (N=129)
Age at diagnosis, N (%)	
<60 Years	66 (51.2)
≥60 Years	63 (48.8)
Histological type, N (%)	
SCC	103 (79.8)
Other	26 (20.2)
FIGO Stage, N (%)	
I-II	72 (55.8)
III-IV	57 (44.2)
Treatment, N (%)	
Surgery alone	24 (18.6)
Surgery with chemotherapy	4 (3.1)
Surgery with radiotherapy	4 (3.1)
Surgery with chemotherapy and radiotherapy	27 (20.9)
Chemotherapy with or without radiotherapy	70 (54.3)
VTE status, N (%)	
Positive	6 (4.7)
Negative	123 (95.3)

FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; VTE, venous thromboembolism.

Table II. *Relationship between pre-treatment plasma D-dimer level (<1.0 vs. ≥1.0 μg/ml) and the clinicopathological characteristics of patients with cervical carcinoma (N=129).*

	Plasma D-dimer level		
Clinicopathological characteristic	<1.0 μg/ml (N=74)	≥1.0 μg/ml (N=55)	*p*-Value
Age at diagnosis, N (%)			
<60 Years	43 (58.1)	23 (41.8)	
≥60 Years	31 (41.9)	32 (58.2)	0.068
Histological type, N (%)			
SCC	61 (82.4)	42 (76.4)	
Other	13 (17.6)	13 (23.6)	0.469
FIGO Stage, N (%)			
I-II	53 (71.6)	19 (34.5)	
III-IV	21 (28.4)	36 (65.5)	<0.001*
VTE status, N (%)			
Positive	0 (0.0)	6 (10.9)	
Negative	74 (100.0)	49 (89.1)	

FIGO, International Federation of Gynecology and Obstetrics; N/A, not available; SCC, squamous cell carcinoma; VTE, venous thromboembolism. *Satistically significant (p<0.05).

Medicine, between March 1997 and December 2013, were enrolled into our study. Diagnoses were based on conventional morphological examination of haematoxylin and eosin-stained sections. Tumours were categorised according to the criteria of the World Health Organization's classification system (20). Tumour staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) classification system (21). Patients with FIGO stage I/II disease (N=72) were primary treated with surgery (*i.e.* radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection) with or without adjuvant therapy (*e.g.* chemotherapy) or radiotherapy. Patients with FIGO stage III/IV (N=57) were primarily treated with chemotherapy and radiotherapy.

The study protocol was approved by the Ethics Committee of Shimane University Faculty of Medicine, Izumo, Japan (no.: 2004-0381). All participants provided informed, written consent. Research was conducted in accordance with the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, effective December 13, 2001.

Measurements of pre-treatment plasma levels of D-dimers. Pre-treatment plasma D-dimer levels were measured ≤4 weeks prior to surgery using the Latex Photometric Immunoassay System and LPIA-ACE D-D dimer II (Mitsubishi Chemical Medience Corp., Tokyo, Japan) as the reagent. The inter-assay variability was <10%. Primary pre-treatment screening for VTE was performed using precise estimates of plasma D-dimer levels and clinical signs, such as leg swelling and tenderness along deep veins. A cut-off threshold of 1.0 μg/ml was used to distinguish between high and normal results.

Statistical analyses. Univariate analysis was performed using binomial logistic regression for ordered categorical variables. Patient clinicopathological characteristics included in the model were age at diagnosis (<60 *vs.* ≥60 years), FIGO classification (stage I/II *vs.* III/IV), histological type (SCC *vs.* other), pre-treatment plasma level of D-dimer (<1.0 *vs.* ≥1.0 μg/ml), plasma fibrinogen level (<450 *vs.* ≥450 mg/dl), platelet counts (<35 *vs.* ≥35×10^4/μl), SCC antigen level (<1.5 *vs.* ≥1.5 U/ml), carcinoembryonic antigen (CEA) levels (<5.0 *vs.* ≥5.0 ng/ml), and VTE status (positive *vs.* negative). The endpoints of the analysis were overall survival (OS) and progression-free survival (PFS). OS was defined as the time from diagnosis to death. Patients alive at last follow-up were censored. PFS was defined as the time from diagnosis to recurrence. Patients without recurrence at last follow-up were censored. Survival data were plotted as Kaplan–Meier curves, and statistical significance was determined by the log-rank test. Variables indicated to be significant (p<0.05) in the univariate analysis were entered into the multivariate analysis.

Multivariate prognostic analysis was performed using a Cox proportional hazards model, and data from patients lost to follow-up were censored. Statistical analyses were conducted using Statistical Package for the Social Sciences for Windows software, Version 19.0 (IBM Corp., Armonk, NY, USA). All reported p-values were two-sided and p-values below 0.05 were considered statistically significant.

Results

Patients' clinicopathological characteristics. A summary of the clinicopathological characteristics of patients with CC (N=129) is provided in Table I. The median age at diagnosis was 60 years (range=22-89 years) with the patients stratified into two groups: <60 years (51.2% of cases) and ≥60 years

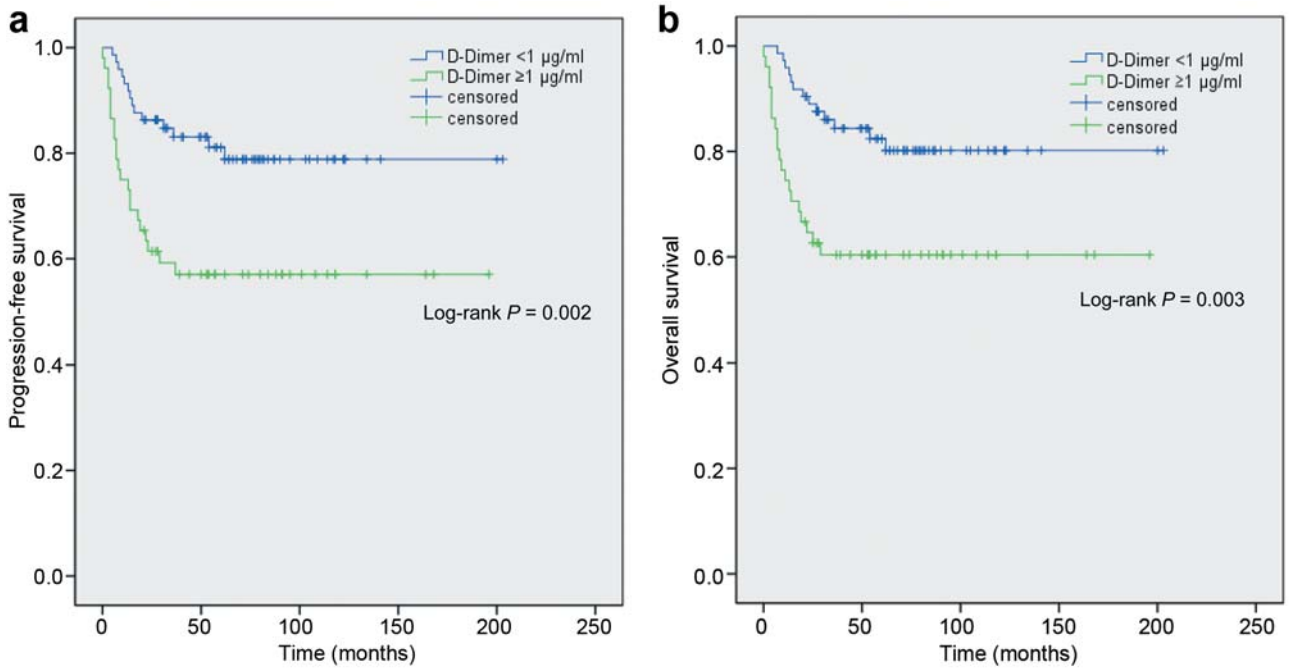

Figure 1. *Kaplan–Meier estimates of the prognostic impact of high pre-treatment plasma D-dimer level on the progression-free (a) and overall (b) survival rate of patients with cervical carcinoma (N=129).*

(48.8% of cases). The majority of patients (79.8%) were diagnosed with SCC. Seventy-two patients (55.8%) were classified as having FIGO stage I/II disease and 57 patients (44.2%) were classified as having FIGO stage III/IV. A high pre-treatment plasma D-dimer level (≥1.0 µg/ml) was detected in 55 patients (42.6%). Platelet count (≥35×10^4/µl), plasma fibrinogen level (≥450 mg/dl), SCC antigen level (≥1.5 U/ml), and CEA level (≥5.0 ng/ml) were elevated in 23 (17.8%), 41 (31.8%), 73 (56.6%), and 55 patients (42.6%), respectively. A positive VTE status was recorded for six patients (4.7%).

Relationships between patients' clinicopathological characteristics and pre-treatment plasma D-dimer levels. Relationships between the clinicopathological characteristics of CC patients and pre-treatment plasma D-dimer levels (<1.0 *vs*. ≥1.0 µg/ml) were assessed using a binomial logistic regression analysis. FIGO stage ($p<0.001$), but not age at diagnosis, histological type, or VTE status, was found to correlate positively with pre-treatment plasma D-dimer level in patients with CC (Table II).

Univariate and multivariate analysis of prognostic factors in patients with cervical carcinoma. In the univariate analysis, FIGO stage ($p<0.001$), pre-treatment plasma D-dimer ($p<0.01$; Figure 1a), platelet count ($p=0.001$), and CEA ($p<0.001$) were identified as potential predictors of PFS in patients with CC. In the multivariate analysis, FIGO stage [hazard ratio (HR)=6.75, 95% confidence interval (CI)=2.499-18.22; $p<0.001$], and CEA level (HR=2.50, 95% CI=1.104-5.674; $p<0.05$) were confirmed as independent risk factors for PFS (Table III). The pre-treatment plasma D-dimer level, however, was not found to be associated with PFS in the multivariate analysis in the present study.

In the univariate analysis, histological type ($p<0.01$), FIGO classification ($p<0.001$), pre-treatment plasma D-dimer level ($p<0.01$; Figure 1b), platelet counts ($p=0.001$), and CEA levels ($p<0.001$) were also identified as potential predictors of OS in patients with CC. In the multivariate analysis, histological type (HR=0.34, 95% CI=0.141-0.834; $p<0.05$), FIGO classification (HR=4.98, 95% CI=1.834-13.51; $p<0.01$), pre-treatment plasma D-dimer level (HR=2.33, 95% CI=1.121-5.504; $p<0.05$), and CEA levels (HR=3.23, 95% CI=1.302-7.992; $p=0.011$) were confirmed as independent risk factors for OS (Table IV).

Discussion

To the best of our knowledge, our study represents the first cohort of patients with CC to be investigated in order to determine whether high pre-treatment plasma D-dimer levels are a significant prognostic factor, independent of VTE. Among patients with CC, the prognosis of SCC is relatively favourable compared to that of AD/ASC, which has a poorer prognosis. Common prognostic factors for SCC and

Table III. *Univariate and multivariate analysis of progression-free survival using a Cox proportional hazards model in patients with cervical carcinoma (N=129).*

Clinicopathological characteristic	Patients (N=129)	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age at diagnosis							
<60 Years	66	ref.					
≥60 Years	63	1.46	(0.757-2.823)	0.254			
Histological type							
SCC	103	ref.					
Other	26	2.03	(0.993-4.416)	0.052			
FIGO Stage							
I-II	72	ref.					
III-IV	57	8.72	(3.621-20.99)	<0.001*	6.75	(2.499-18.22)	<0.001*
VTE status							
Positive	6	2.97	(0.712-12.43)	0.116			
Negative	123	ref.					
Plasma D-dimer							
<1.0 μg/ml	74	ref.					
≥1.0 μg/ml	55	2.71	(1.386-5.303)	0.002*	N/A	N/A	N/A
Platelet count,							
$<35\times10^4$/μl	106	ref.					
$\geq35\times10^4$/μl	23	2.98	(1.509-5.892)	0.001*	N/A	N/A	N/A
Plasma fibrinogen							
<450 mg/dl	88	ref.					
≥450 mg/dl	41	1.60	(0.810-3.176)	0.170			
SCC antigen							
<1.5 ng/ml	56	ref.					
≥1.5 ng/ml	73	1.90	(0.930-3.894)	0.072			
CEA							
<5.0 ng/ml	74	ref.					
≥5.0 ng/ml	55	3.76	(1.846-7.688)	<0.001*	2.50	(1.104-5.674)	0.028*

CEA, Carcinoembryonic antigen; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; N/A, not available; SCC, squamous cell carcinoma; VTE, venous thromboembolism. *Statistically significant ($p<0.05$).

AD/ASC are yet to be determined. In the present study, we aimed to identify inexpensive and convenient prognostic factors in patients with uterine CC.

The relationship between pre-treatment plasma D-dimer level and tumour development has been attracting increasing attention over recent years. Coagulation activation in cancer has been widely implicated in tumour progression and thrombosis (22). An elevated plasma D-dimer level has been associated with a poor prognosis in several types of malignancies, including lung, pancreatic, prostate, gastric, colorectal, breast, and nasopharyngeal carcinomas (4-8). Among gynaecological cancers, the plasma D-dimer level was identified as a negative prognostic factor, independent of VTE, in patients with ovarian carcinomas only (9, 10). Although one study demonstrated a high pre-treatment plasma D-dimer level to be associated with a poor prognosis in patients with CC, VTE was not considered (23). A high pre-treatment plasma D-dimer level has previously been reported to predict VTE in cancer (17, 24).

Our findings revealed, using a Cox proportional hazards model, that high pre-treatment plasma D-dimer levels are an independent prognostic indicator in CC, that is comparable to that of other malignancies. The mechanism(s) underlying the relationship between pre-treatment plasma D-dimer level and the prognosis of CC patients are currently unclear, but may involve abnormalities in the coagulation cascade.

Tissue factor (TF; also known as thromboplastin) is a key element in the initiation of the extrinsic pathway of the coagulation cascade and is considered to play an important role in cancer metastasis and progression. This 47-kDa transmembrane glycoprotein receptor is located on the surface of various cells (*e.g.* platelets, leukocytes, fibroblasts, and endothelial cells, as well as in the smooth muscle cells surrounding the vessel walls); however, TF is not expressed in blood cells or in cells that line the blood vessels. In the extrinsic pathway, TF activates factor VIIa. The TF-VIIa complex in turn activates factor X to produce D-dimer, a fibrin degradation product. In another pathway, TF up-regulates

Table IV. *Univariate and multivariate analysis of overall survival using a Cox proportional hazards model in patients with cervical carcinoma (N=129).*

Clinicopathological characteristic	Patients (N=129)	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age at diagnosis							
<60 Years	66	ref.					
≥60 Years	63	1.45	(0.729-2.874)	0.286			
Histological type							
SCC	103	ref.					
Other	26	0.02	(0.211-0.910)	0.008*	0.34	(0.141-0.834)	0.018*
FIGO Stage							
I-II	72	ref.					
III-IV	57	7.70	(3.172-18.68)	<0.001*	4.98	(1.834-13.51)	0.002*
VTE status							
Positive	6	3.27	(0.778-13.72)	0.086			
Negative	123	ref.					
Plasma D-dimer							
<1.0 μg/ml	74	ref.					
≥1.0 μg/ml	55	2.76	(1.373-5.558)	0.003*	2.33	(1.121-5.504)	0.043*
Platelet count							
$<35\times10^4$/μl	106	ref.					
$\geq35\times10^4$/μl	23	3.05	(1.496-6.198)	0.001*	N/A	N/A	N/A
Plasma fibrinogen							
<450 mg/dl	88	ref.					
≥450 mg/dl	41	1.43	(0.696-2.915)	0.329			
SCC antigen							
<1.5 ng/ml	56	ref.					
≥1.5 ng/ml	73	1.69	(0.814-3.513)	0.153			
CEA							
<5.0 ng/ml	74	ref.					
≥5.0 ng/ml	55	3.70	(1.749-7.836)	<0.001*	3.23	(1.302-7.992)	0.011*

CEA, Carcinoembryonic antigen; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; N/A, not available; SCC, squamous cell carcinoma; VTE, venous thromboembolism. *Statistically significant ($p<0.05$).

vascular endothelial growth factor (VEGF) and down-regulates thrombospondin, an inhibitor of angiogenesis, to promote angiogenesis (25). VEGF is associated with angiogenesis and tumour progression. A previous study conducted by Nakasaki *et al*. (26) reported a correlation between TF and VEGF expression. The expression levels of TF and VEGF may also represent prognostic biomarkers for patients with CC, similar to the pre-treatment plasma D-dimer level. Therefore, future investigations are required to assess the relationship between TF and VEGF expression and pre-treatment plasma D-dimer levels in patients with CC. If the levels of expression of TF and VEGF are also prognostic biomarkers, pre-treatment plasma D-dimer represents the most inexpensive and convenient marker. Our institution has participated in a clinical trial that administered bevacizumab, a VEGF inhibitor, to patients with CC. Moreover, we are interested in determining the different in response rates in patients with CC between those with normal and those with a high pre-treatment plasma D-dimer level.

In the present study, we detected a discrepancy in the correlation between pre-treatment plasma D-dimer levels and PFS or OS rates in the multivariate analysis in patients with CC. Specifically, the pre-treatment plasma D-dimer level exhibited a strong negative association with OS, but not PFS, in patients with CC. Shorter PFS rates are generally considered to be related to poor chemosensitivity. Therefore, our findings, demonstrating the pre-treatment plasma D-dimer level to be related to shorter OS, but not PFS rates, suggest that the pre-treatment plasma D-dimer level is linked to tumour aggressiveness, but not chemoresistance.

Some limitations of our study include its retrospective design and the fact that plasma D-dimer levels were only measured once, as part of a routine examination, before commencing treatment. As the plasma D-dimer level has been indicated as a potential clinical biomarker of aggressive tumour biology, future longitudinal studies are required (with continuous measurements of plasma D-dimer level during different periods of treatment) to elucidate further the

mechanism(s) responsible and the relationship between the plasma D-dimer level and the prognosis of patients with CC.

In conclusion, we identified a high pre-treatment plasma D-dimer level as a potential prognostic biomarker in patients with CC that is independent of VTE.

Conflicts of Interest

The Authors declare that they have no actual or potential conflicts of interest.

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