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Fibrin/fibrinogen Degradation Products Are Associated With Tumor Stage and Prognosis in Patients Undergoing Resection of Esophageal Cancer

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Abstract. *Background/Aim: To investigate the significance of preoperative fibrin/fibrinogen degradation products (FDP) in patients with esophageal cancer (EC), we examined the association between the preoperative FDP level and clinicopathological features in patients with EC who underwent McKeown esophagectomy with gastric tube reconstruction without neoadjuvant therapy. Patients and Methods: Ninety patients with EC who underwent surgery between 2006 and 2014 were included in this study. We investigated the association of FDP levels with clinicopathological features and prognosis. Results: Multivariate analysis revealed increased FDP level and pathological tumor depth to be independent prognostic factors for overall survival (OS) (p=0.008 and p=0.002, respectively). In addition, FDP levels were significantly positively associated with more advanced pathological TNM stage as a continuous variable (p for trend=0.002). Conclusion: The preoperative FDP level was associated with a poor prognosis and was an independent prognostic factor for the OS of EC patients who underwent esophagectomy. Furthermore, the tumor stage-related increase in FDP indicated that a high FDP level is associated with tumor progression in patients with EC.*

Esophageal cancer (EC) is the seventh most common cancer and the sixth leading cause of death from cancer worldwide (1). Although chemoradiotherapy has been reported to be effective for EC (2), esophagectomy remains the predominant treatment modality (3). However, esophagectomy for thoracic EC is widely recognized as one of the most invasive surgical procedures, with a morbidity rate from 40-50% (4-6). Thus, investigating preoperative prognostic factors is essential to improve surgical outcomes. Abnormalities of coagulation and fibrinolysis regulate the pathogenesis of several disorders such as deep vein thrombosis, pulmonary thromboembolism, atherosclerosis, disseminated intravascular coagulation (DIC), sepsis, and cancer (7). Fibrinogen and its degradation products subsequently generated after coagulation and secondary fibrinolysis, such as D-dimer, are associated with tumor stage and prognosis in several types of cancer of the digestive system (8). Higher fibrinogen levels were reported to be positively correlated with tumor progression, metastasis, and poor prognosis of patients with EC (9). D-Dimer levels were also reported to be an independent negative prognostic factor in patients with EC (10). This suggests that both coagulation and fibrinolysis play essential roles in tumor progression in EC.

Fibrin degradation under plasmin activation cleaves fibrin into many fragments of differing molecular weights, termed fibrinogen/fibrin degradation products (FDP) (7). Although D-dimer is an FDP and is considered to be a final product of fibrinolysis, it is known that a variety of differently sized cross-linked FDPs exist in the blood (7). Furthermore, under specific pathological conditions, such as DIC, fibrinogen is degraded by plasmin before fibrin monomer formation and the degradation products do not include D-dimer. Commercially available FDP assays recognize degradation products from both fibrin clots and fibrinogen (11). Thus, we hypothesized that the pretreatment FDP level is also correlated with tumor progression and prognosis in patients with EC. We examined the association between the

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Key Words: Esophageal neoplasms, fibrin/fibrinogen degradation products, prognosis.

Table I. *Patient characteristics*.

Characteristic		All patients (n=90)	Grouping by FDP		
			<2.9 μg/ml (n=48)	≥2.9 μg/ml (n=42)	*p*-Value
Age, years	Mean±SD	65.5±8.7	64.1 (9.7)	67.2 (7.1)	0.096
Sex, n (%)	Female	9 (10.0)	5 (10.4)	4 (9.5)	>0.99
	Male	81(90.0)	43 (89.6)	38 (90.5)	
Location of tumor, n (%)	Upper	10 (11.1)	6 (12.5)	4 (9.5)	0.869
	Middle	44 (48.9)	24 (50.0)	20 (47.6)	
	Lower	36 (40.0)	18 (37.5)	18 (42.9)	
Pathological tumor depth, n (%)	T1	35 (38.9)	21 (43.8)	14 (33.3)	0.251
	T2	15 (16.7)	7 (14.6)	8 (19.0)	
	T3	34 (37.8)	19 (39.6)	15 (35.7)	
	T4	6 (6.7)	1 (2.1)	5 (11.9)	
Pathological lymph node metastasis, n (%)	Negative	32 (35.6)	22 (45.8)	10 (23.8)	0.046
	Positive	58 (64.4)	26 (54.2)	32 (76.2)	
Histology, n (%)	Squamous	82 (91.1)	41 (85.4)	41 (97.6)	0.063
	Other	8 (8.9)	7 (14.6)	1 (2.4)	

FDP: Fibrin/fibrinogen degradation products; SD: standard deviation.

preoperative FDP level and clinicopathological features in patients who underwent esophagectomy for EC to investigate this hypothesis. We also evaluated the prognostic value of FDP.

Patients and Methods

Patients. This retrospective study was approved by the Ethics Committee of the Graduate School of Medicine, Gunma University (Protocol number HS2019-025). Informed consent was obtained in the form of an opt-out on a web-site. We examined 90 patients with thoracic EC undergoing esophagectomy between 2006 and 2014 at our Institute. Inclusion and exclusion criteria except for blood chemistry were described elsewhere (12). Patients were excluded from this study when they no data of FDP in peripheral blood within one month before surgery. We reviewed the hospital medical records to confirm clinicopathological characteristics and patient outcomes. Tumors were classified according to the seventh edition of the TNM classification of the International Union Against Cancer (13). The tumor stage determination and follow-up were performed as previously described (12).

Measurement of FDP. The levels of FDP were measured at our central laboratory by an immunoturbidimetric method as previously described (14).

Statistical analysis. Patient characteristics were compared using chi-squared tests for categorical variables the Student's *t*-test for continuous variables. Correlation analysis was performed using Spearman's rank coefficients. The Jonckheere–Terpstra test was used for trend analysis. Univariate and multivariate survival analyses were carried out using the Cox proportional hazards regression model. Kaplan-Meier curves were generated for overall survival (OS), which was defined as the time from surgery to the date of the last follow-up or death from any cause, and significance was assessed using the log-rank test. Receiver operating characteristics (ROC) curves were generated, and the area under the curve was used to evaluate the discriminatory ability of FDP to predict OS. A probability value of less than 0.05 was considered significant. All statistical analyses were performed using EZR (15).

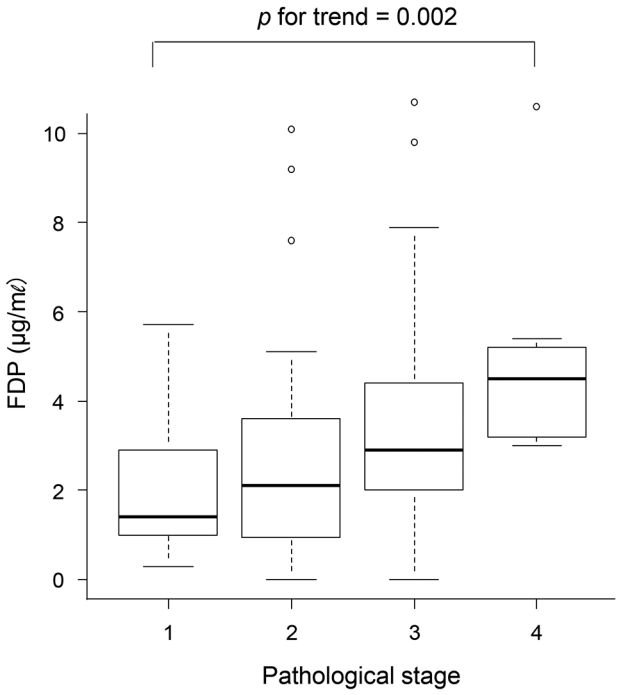

Figure 1. *Association between serum level of fibrin/fibrinogen degradation products (FDP) and pathological stage*.

Table II. *Univariate and multivariate analyses for overall survival.*

Characteristic		Univariate		Multivariate	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	Per-year increment	1.02 (0.98-1.07)	0.330	1.01 (0.96-1.06)	0.640
Gender	Female (Reference)	1			
	Male	1.35 (0.4-4.56)	0.630	1.39 (0.41-4.68)	0.600
Pathological tumor depth	T1 (Reference)	1			
	T2-4	4.20 (1.59-11.07)	0.004	4.92 (1.81-13.37)	0.002
Pathological lymph node metastasis	Negative (Reference)	1			
	Positive	1.11 (0.51-2.41)	0.790	0.60 (0.26-1.39)	0.240
FDP	<2.9 μg/ml (Reference)	1			
	≥2.9 μg/ml	2.62 (1.22-5.64)	0.014	2.99 (1.32-6.73)	0.008

FDP: Fibrin/fibrinogen degradation products.

Results

Relationship between FDP and clinicopathological variables. The baseline patient characteristics are summarized in Table I. The mean (range) level of FDP in patients with EC was 3.04 (0-10.7 μg/ml) (normal range=0-4.0 μg/ml). The best cut-off value of the FDP level for OS based on ROC curves was 2.9 μg/ml (area under the curve=0.659, 95% confidence intervaI=0.540 to 0.778). Using this cut-off, 48 patients were assigned to the group with a low FDP level and 42 to the high-level group. The FDP level was significantly positively associated with pathological lymph node metastasis (p=0.046). FDP level as a continuous variable was higher with higher TNM stage (p for trend=0.002) (Figure 1).

Survival analysis. We found the FDP level and pathological tumor depth were significant prognostic factors for OS by univariate analysis. Multivariate analysis demonstrated the FDP level and pathological tumor depth to be independent prognostic factors for OS (Table II). The OS rate was significantly lower for patients with an FDP level ≥2.9 μg/ml than for those with an FDP level <2.9 μg/ml (p=0.011) (Figure 2).

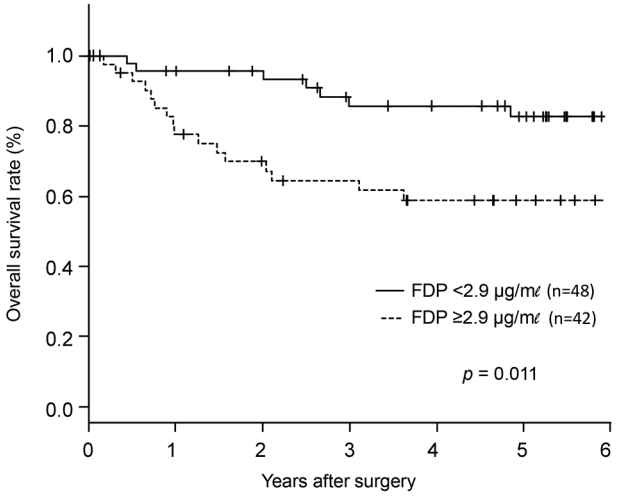

Figure 2. *Kaplan-Meier curves for overall survival according to serum level of fibrin/fibrinogen degradation products (FDP).*

Discussion

The most important finding of the present study was that the preoperative FDP level was associated with a poor prognosis and appears to be an independent prognostic factor for the OS of patients with EC. In addition, we confirmed that as a continuous variable, FDP increased in association with tumor stage. This association suggests that a high FDP level is associated with tumor progression patients with EC regardless of the cut-off value used. To our knowledge, this is the first study to demonstrate an association between FDP and tumor progression and prognosis in EC.

The mechanism underlying the association between an increased FDP level and tumor progression has not been thoroughly investigated. Cancer cells produce and release procoagulants (*e.g.* tissue factor, cancer procoagulant, and factor VII) and fibrinolytic proteins [*e.g.* urokinase plasminogen activator and tissue plasminogen activator (tPA)], their inhibitors (*e.g.* plasminogen activator inhibitor-1 and -2), receptors, and inflammatory cytokines (16). These factors activate the coagulation and fibrinolytic system in patients with cancer and cause an increase in the serum levels of plasma soluble fibrin monomer complex, fibrinogen, and FDP. Of note, most of these factors also promote tumor growth and metastasis and are associated

with tumor progression and a poor prognosis (17-19). Thus, FDP may reflect tumor-mediated activation of the coagulation and fibrinolytic system, and tumor progression. Furthermore, due to heightened pro-coagulative activity, the serum levels of the plasma soluble fibrin monomer complex, fibrinogen, and FDP were found to be significantly increased in patients with cancer compared with those with nonmalignant disease and healthy controls (19). Thus, patients with cancer may have chronic or subclinical DIC without symptoms. FDP may reflect the impact of preoperative aberrant coagulo-fibrinolytic activation on the prognosis of patients with EC.

Several clinical applications of FDP in cancer treatment are expected. The FDP level was found to be an independent prognostic factor for OS of patients with EC who underwent surgery. This suggests that FDP levels can identify a subgroup of patients who risk a poor prognosis after surgical resection independently of pathological staging. As the coagulation and fibrinolytic system is closely related to cancer development and progression, the antitumor effects of coagulation or fibrinolytic inhibitors have been investigated. Recombinant hirudin, a potent inhibitor of thrombin, was reported to inhibit tumor implantation and growth of human lung and breast cancer in nude mice (20). Direct thrombin inhibitor peptide and recombinant hirudin were reported to inhibit thrombin-promoted cell migration, invasion, and angiogenesis of lung cancer cell lines *in vitro* (21). Although the clinical utility of these anticoagulants for antitumor therapy is a future perspective, FDP may be a potential biomarker for the antitumor effects of anticoagulants.

Our study had several limitations. Firstly, this study was a retrospective single-center analysis. Secondly, the cut-off value for the FDP level may have been biased because it was obtained by ROC analysis.

In conclusion, the preoperative FDP level was associated with a poor prognosis and was an independent prognostic factor for the OS of patients with EC who underwent esophagectomy. Furthermore, the tumor stage-related increase in FDP indicated that a high FDP level is associated with tumor progression in patients with EC.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Study conception and design: M. Sakai; acquisition of data: S. Uchida, A. Yamaguchi, T. Watanabe, H. Saito, Y. Ubukata, N. Nakazawa and K. Kuriyama; analysis and interpretation of data: M. Sakai, M. Sohda, A. Sano, H. Ogawa and T. Yokobori; drafting of manuscript: M. Sakai, critical revision: K. Shirabe and H. Saeki.

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