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Prognostic Role of Preoperative D-dimer Levels in Patients With Stage I-III Colorectal Cancer

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Abstract. *Background/Aim: As D-dimer levels have been reported to reflect cancer activity, preoperative D-dimer levels may serve as a prognostic marker in patients with colorectal cancer. The aim of this study was to evaluate the prognostic significance of preoperative D-dimer levels in patients with stage I-III colorectal cancer who underwent curative surgery. Patients and Methods: A total of 264 patients who underwent curative surgery for stage I-III colorectal cancer between January 2015 and December 2019 were enrolled in this study. Results: The median preoperative D-dimer level was 0.8 μg/ml (range=0.4-42.5 μg/ml). Based on the results of a receiver operating characteristic curve analysis, we set 1.45 as the cut-off value and classified patients into the low (n=215) and high D-dimer (n=49) groups. The high D-dimer group had significantly lower relapse-free and overall survival in comparison to the low D-dimer group (p<0.0001, p<0.0001, respectively). Conclusion: Preoperative D-dimer levels can serve as a prognostic marker for stage I-III colorectal cancer.*

As D-dimer, a degradation product of fibrin, increases in the presence of venous thromboembolism, D-dimer is often used as a marker for screening for venous thromboembolism in clinical practice (1-3). On the other hand, cancer patients sometimes have elevated D-dimer levels regardless of the presence of venous thromboembolism (4, 5), since they are hypercoagulable. Previous studies have reported that high D-dimer levels are associated with advanced stage and reflect a high tumor burden (4, 6-10).

Based on the above, preoperative D-dimer levels may have the potential to be a prognostic marker for colorectal cancer as well as a biomarker for predicting venous thromboembolism. The aim of this study was to evaluate the prognostic significance of preoperative D-dimer levels in patients with stage I-III colorectal cancer who underwent curative surgery.

Patients and Methods

Patients. A total of 264 patients who underwent curative surgery for stage I-III colorectal cancer at the Department of Gastroenterological Surgery of Osaka City University Hospital between January 2015 and December 2019 were enrolled in this study. Patients who received preoperative treatment, such as neoadjuvant chemoradiotherapy, were excluded. This retrospective study was approved by the Ethics Committee of Osaka City University (approval number: 4182) and conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent.

Methods. Blood samples were obtained within a period of one month prior to the operation. If the preoperative D-dimer levels were ≥1.0 μg/ml, contrast enhanced computed tomography or ultrasonography was performed to confirm the presence of venous thromboembolism. An appropriate cut-off value for the D-dimer levels was determined based on a receiver operating characteristic (ROC) curve analysis, and the patients were then classified into the low D-dimer and high D-dimer groups.

Statistical analysis. All statistical analyses were performed using the SPSS software package for Windows (SPSS, Chicago, IL, USA). The significance of differences in the preoperative D-dimer level and

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Key Words: D-dimer, colorectal cancer, prognostic marker.

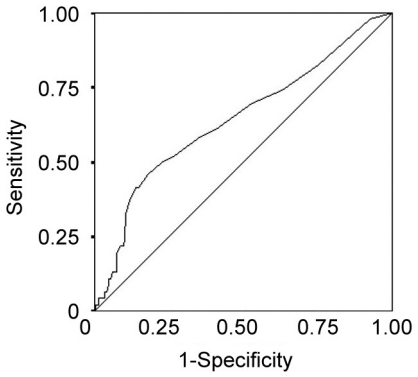

Figure 1. *A receiver operating characteristic curve analysis of the preoperative D-dimer levels. Area under the curve (AUC)=0.643; 95% confidence interval=0.549-0.737; p=0.002.*

clinicopathological factors was analyzed using a chi-squared test and Fisher's exact test. Relapse-free survival was defined as the interval between the date of operation and the date of diagnosis of first recurrence, death from any cause, or last follow-up. Overall survival was defined as the interval between the date of operation and date of death from any cause or last follow-up. Survival curves were estimated using the Kaplan-Meier method, and differences in the survival curves were assessed with a log-rank test. Factors with a *p*-value of <0.1 in a univariate analysis were included in a multivariate analysis. A multivariate Cox proportional hazard model was used to evaluate the prognostic factors associated with survival. *p*-Values of <0.05 were considered to indicate statistical significance.

Table I. *Associations between preoperative D-dimer levels and clinicopathological factors.*

	Low D-dimer group (n=215)	High D-dimer group (n=49)	*p*-Value
Age (years), n			
<75	140	24	
≥75	75	25	0.049
Sex, n			
Male	123	29	
Female	92	20	0.873
Location of the tumor, n			
Right side	72	22	
Left side	143	27	0.140
Histological type, n			
Well/moderately differentiated	208	48	
Poorly differentiated, Mucinous, Signet	7	1	<0.999
Tumor diameter (cm), n			
<5	154	28	
≥5	61	21	0.060
Depth of tumor, n			
T1-3	199	42	
T4	16	7	0.157
Lymph node metastasis, n			
Negative	163	37	
Positive	52	12	<0.999
Serum CEA levels (ng/ml), n			
≤5.0	164	30	
>5.0	51	19	0.047

CEA: Carcinoembryonic antigen.

Results

The median preoperative D-dimer level was 0.8 μg/ml (range=0.4-42.5 μg/ml). Among the 105 patients with a preoperative D-dimer level of ≥1.0 μg/ml, venous thromboembolism was found in 5 patients. The median duration of follow-up was 37.0 months. Thirty-two patients (12.1%) relapsed, and 22 patients (8.3%) died during the follow-up period. Among the patients enrolled in this study, no patients died within 30 days after surgery.

Classification according to the preoperative D-dimer levels. The preoperative D-dimer level, as a continuous variable, was used as the test variable and recurrence was used as the state variable. A ROC curve analysis revealed that the appropriate cut-off value of the preoperative D-dimer levels was 1.45 (sensitivity=41.3%, specificity=86.2%) (Figure 1). We therefore set 1.45 as the cut-off value and classified patients into the low D-dimer (n=215) and high D-dimer (n=49) groups.

Associations between preoperative D-dimer levels and clinicopathological factors. The associations between the preoperative D-dimer levels and clinicopathological factors are shown in Table I. High preoperative D-dimer levels were significantly associated with higher age and higher carcinoembryonic antigen (CEA) levels and tended to be associated with larger tumor diameter.

Survival analysis according to preoperative D-dimer levels. The high D-dimer group had significantly lower relapse-free and overall survival in comparison to the low D-dimer group ($p<0.0001$, $p<0.0001$, respectively) (Figure 2).

Analysis of the prognostic value of preoperative D-dimer levels by stage. In patients with stage I colorectal cancer, the high D-dimer group had significantly lower relapse-free and overall survival in comparison to the low D-dimer group ($p=0.0086$, $p=0.0037$, respectively) (Figure 3A and B). In patients with stage II colorectal cancer, the high D-dimer group had significantly lower relapse-free survival ($p=0.0037$) and tended to have lower overall survival in comparison to the low D-dimer group ($p=0.0782$) (Figure 3C and D). In patients with stage III colorectal cancer, the high D-dimer group had significantly lower relapse-free and overall survival in comparison to the low D-dimer group ($p=0.0182$, $p=0.0009$, respectively) (Figure 3E and F).

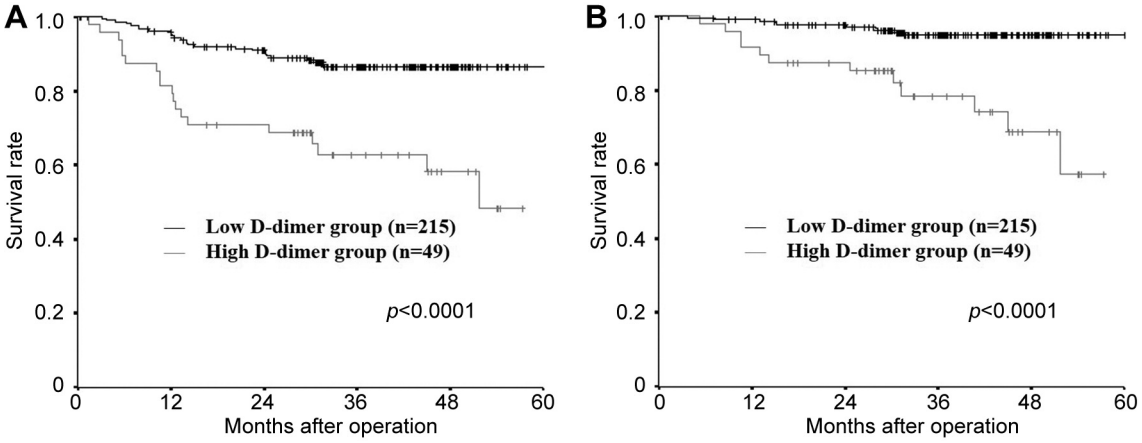

Figure 2. *Kaplan-Meier survival curves for relapse-free and overall survival according to the preoperative D-dimer levels of all patients enrolled in this study. (A) The high D-dimer group had significantly worse relapse-free survival than the low D-dimer group (p<0.0001). (B) The high D-dimer group had significantly worse overall survival than the low D-dimer group (p<0.0001).*

Table II. *Associations between relapse-free survival and various clinicopathological factors.*

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	*p*-Value	Hazard ratio	95%CI	*p*-Value
Sex (Male *vs*. Female)	1.204	0.666-2.179	0.539			
Age (≥75 years *vs*. <75 years)	1.138	0.629-2.058	0.669			
Tumor location (Right sided *vs*. Left sided)	0.611	0.317-1.181	0.143			
Tumor diameter (>5 *vs*. ≤5 cm)	1.080	0.583-2.000	0.808			
Histological type (Poorly, Mucinous *vs*. Well, Moderately)	0.727	0.100-5.276	0.753			
Tumor depth (T4 *vs*. T1-3)	4.320	2.141-8.716	<0.001	3.874	1.859-8.071	<0.001
Lymph node metastasis (Positive *vs*. Negative)	2.320	1.283-4.196	0.005	1.878	1.017-3.466	0.044
Serum CEA levels (>5 *vs*. ≤5 ng/ml)	2.414	1.348-4.325	0.003	1.725	0.953-3.123	0.072
Preoperative D-dimer level (>1.45 *vs*. ≤1.45 μg/ml)	3.660	2.032-6.592	<0.001	3.754	2.065-6.823	<0.001

CI: Confidence interval; CEA: carcinoembryonic antigen.

Table III. *Associations between overall survival and various clinicopathological factors.*

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	*p*-Value	Hazard ratio	95%CI	*p*-Value
Sex (Male *vs*. Female)	1.384	0.580-3.301	0.464			
Age (≥75 *vs*. <75 years)	1.832	0.793-4.231	0.156			
Tumor location (Right sided *vs*. Left sided)	0.841	0.343-2.064	0.705			
Tumor diameter (>5 *vs*. ≤5 cm)	0.820	0.321-2.096	0.678			
Histological type (Poorly, Mucinous *vs*. Well, Moderately)	1.606	0.216-11.951	0.644			
Tumor depth (T4 *vs*. T1-3)	4.981	1.947-12.739	0.001	4.771	1.841-12.365	0.001
Lymph node metastasis (Positive *vs*. Negative)	1.596	0.650-3.917	0.308			
Serum CEA level (>5 *vs*. ≤5 ng/ml)	2.047	0.875-4.789	0.099	1.440	0.610-3.397	0.405
Preoperative D-dimer level (>1.45 *vs*. ≤1.45 μg/ml)	5.939	2.561-13.775	<0.001	5.738	2.455-13.411	<0.001

CI: Confidence interval; CEA: carcinoembryonic antigen.

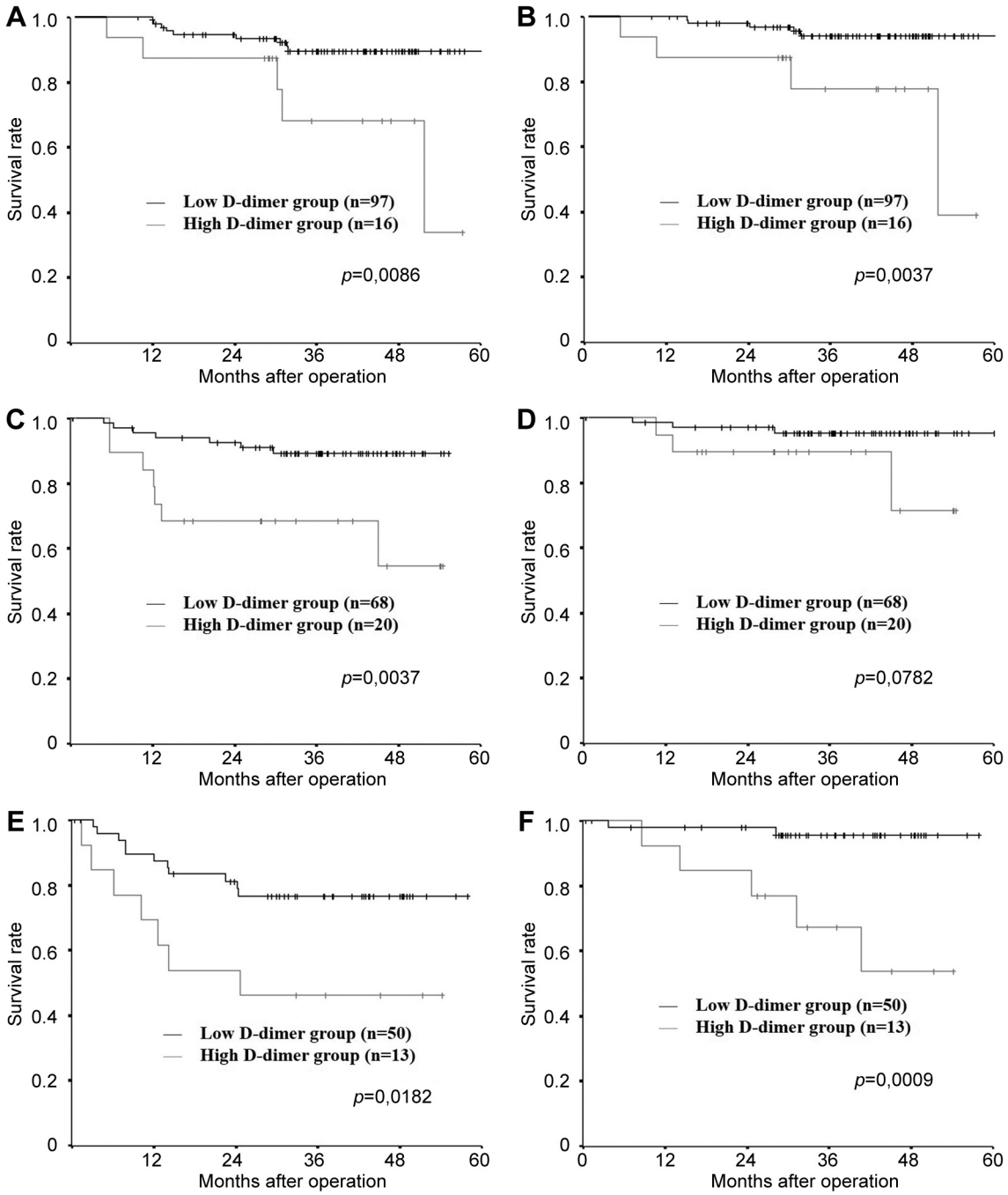

Figure 3. *Kaplan-Meier survival curves according to preoperative D-dimer levels in patients with stage I, II, and III colorectal cancer. Relapse-free (A) and overall (B) survival in patients with stage I colorectal cancer. The high D-dimer group had significantly worse relapse-free and overall survival than the low D-dimer group (p=0.0086, 0.0037, respectively). Relapse-free (C) and overall (D) survival in patients with stage II colorectal cancer. The high D-dimer group had significantly worse relapse-free survival (p=0.0037) and tended to have worse overall survival (p=0.0782) than the low D-dimer group. Relapse-free (E) and overall (F) survival in patients with stage III colorectal cancer. The high D-dimer group had significantly worse relapse-free and overall survival than the low D-dimer group (p=0.0182, 0.0009, respectively).*

Prognostic factors for relapse-free/overall survival identified by the univariate and multivariate analyses. The associations between relapse-free survival and various clinicopathological factors are shown in Table II. According to the results of the univariate analysis, relapse-free survival was significantly associated with tumor depth, lymph node

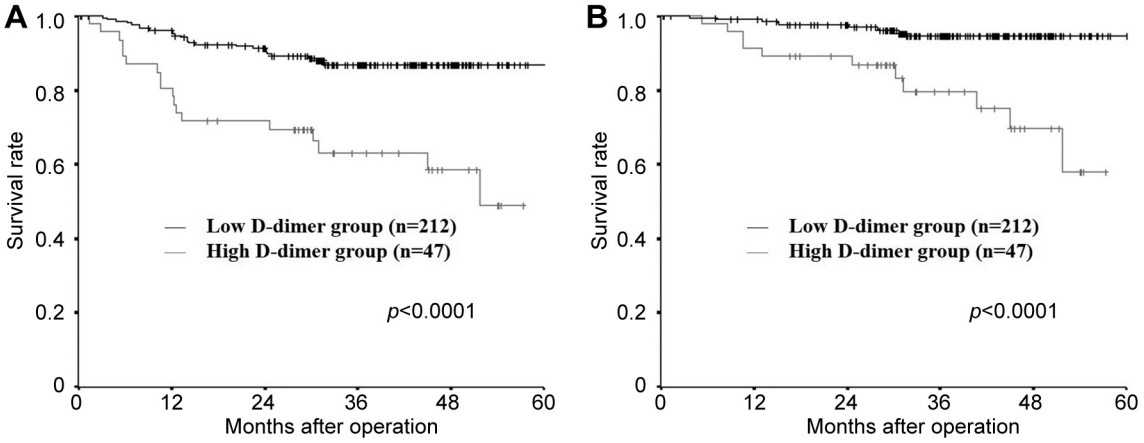

Figure 4. *Kaplan-Meier survival curves for relapse-free and overall survival according to the preoperative D-dimer level in an analysis limited to patients without venous thromboembolism. (A) The high D-dimer group had significantly worse relapse-free survival than the low D-dimer group (p<0.0001). (B) The high D-dimer group had significantly worse overall survival than the low D-dimer group (p<0.0001).*

metastasis, CEA and preoperative D-dimer levels. The multivariate analysis indicated that higher T stage (T4), the presence of lymph node metastasis, and higher preoperative D-dimer levels were independent prognostic factors for worse relapse-free survival. The associations between overall survival and various clinicopathological factors are shown in Table III. According to the results of the univariate analysis, overall survival was significantly associated with tumor depth and preoperative D-dimer levels, and tended to be associated with CEA. The multivariate analysis indicated that higher T stage (T4) and higher preoperative D-dimer levels were independent prognostic factors for worse overall survival.

Survival analysis limited to patients without venous thromboembolism. Similar to the results of the analysis of the overall study population, the high D-dimer group had significantly lower relapse-free and overall survival rates in comparison to the low D-dimer group in patients without venous thromboembolism ($p<0.0001$, $p<0.0001$, respectively) (Figure 4).

Discussion

This study demonstrated that high preoperative D-dimer levels were associated with poor survival in patients with stage I-III colorectal cancer who underwent curative surgery. Furthermore, from the results of the analyses to evaluate the prognostic value of the preoperative D-dimer by stage, the preoperative D-dimer level was revealed to be an excellent prognostic marker regardless of the cancer stage.

Cancer patients are hypercoagulable due to the direct interaction between cancer cells and endothelial cells, release of cancer procoagulants and tissue factor, production of cytokines, and activation of blood cells, such as monocytes, macrophages, and platelets (11-15), Therefore, an increase in the levels of D-dimer, a fibrin degradation product, is often observed in cancer patients (4, 5). As cross-linked fibrin serves as a framework for endothelial cell proliferation in angiogenesis and tumor cell proliferation in invasion (15, 16), tumor-induced coagulation and fibrin formation are required for angiogenesis, invasion and metastasis (17, 18). Thus, the D-dimer level can be an indicator of cancer activity (8). Based on the above, increased preoperative D-dimer levels in patients with stage I-III colorectal cancer may imply the presence of systemic micrometastases that cannot be detected by imaging examinations (5).

Seitawan *et al*. reported that venous thromboembolism was associated with poor survival (1). In this study, the prognosis was significantly poorer in the high D-dimer group, even after excluding 5 patients with venous thromboembolism. Based on these findings, it is speculated that high preoperative D-dimer levels are associated with a poor prognosis regardless of the presence or absence of venous thromboembolism.

The present study is associated with several limitations. First, this was a retrospective study with a small cohort, in a single center. Since it has been several years since the preoperative D-dimer level was routinely measured, the number of cases to be analyzed is not sufficient. Large prospective studies should be conducted to confirm our findings. Second, the cut-off value used in this study is a provisional value calculated from the data of patients enrolled in this study. It is expected that large-scale studies will determine a more accurate cut-off value for D-dimer as a prognostic marker.

In conclusion, preoperative D-dimer levels can serve as a prognostic marker for stage I-III colorectal cancer.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

Authors' Contributions

MS designed the study, performed the statistical analysis and drafted the manuscript. SK, TF, YI, HK, KK and KM designed the study and critically reviewed the manuscript. All Authors read and approved the final manuscript.

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