in vivo *37*: 440-444 (2023)
doi:10.21873/invivo.13097

The Significance of the D-Dimer Level as a Prognostic Marker for Survival and Treatment Outcomes in Patients With Stage IV Colorectal Cancer

MASATSUNE SHIBUTANI[1], SHINICHIRO KASHIWAGI[2], TATSUNARI FUKUOKA[1], YASUHITO ISEKI[1], HIROAKI KASASHIMA[1] and KIYOSHI MAEDA[1]

[1]*Department of Gastroenterological Surgery, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan;*
[2]*Department of Breast and Endocrine Surgery, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan*

Abstract. *Background/Aim: Predictive markers for survival and therapeutic efficacy in stage IV colorectal cancer have not been established. As described in our previous report, D-dimer levels may have potential utility as an indicator of cancer activity. The present study evaluated the significance of the D-dimer level as a marker for the survival and treatment outcomes in patients with stage IV colorectal cancer. Patients and Methods: A total of 34 patients who underwent surgery for stage IV colorectal cancer between February 2017 and October 2019 were enrolled. The D-dimer level was measured using a blood sample obtained at the first visit to our hospital. Results: The median preoperative D-dimer level was 1.2 μg/ml (range=0.5-41.0 μg/ml). We divided patients into two groups using a D-dimer level of 2.0 μg/ml as the cut-off value based on receiver operating characteristic curve analysis. The group with a high-D-dimer-level had a significantly shorter overall survival than that with a low D-dimer level. Progression-free survival after first-line chemotherapy tended to be better in those with a low D-dimer level group than in the high-D-dimer-level group. Conclusion: The preoperative D-dimer level may be a useful indicator for survival and chemotherapeutic outcome in patients with stage IV colorectal cancer.*

Correspondence to: Masatsune Shibutani, Osaka Metropolitan University Graduate School of Medicine, Department of Gastroenterological surgery, 1–4–3 Asahi-machi Abeno-ku, Osaka City, Osaka Prefecture, 545-8585, Japan. Tel: +81 666453835, Fax: +81 666466450, e-mail: fbxbj429@ybb.ne.jp

Key Words: D-Dimer level, colorectal cancer, stage IV, prognostic marker.

Stage IV colorectal cancer includes patients with various conditions, all differing with regard to aspects, such as the number of metastatic organs, number of metastatic lesions, size of metastases, and presence of peritoneal dissemination. Although carcinoembryonic antigen, which has been frequently used as a tumor marker of colorectal cancer in clinical practice (1, 2), is often associated with the tumor burden, its utility as a predictive marker for the survival and treatment efficacy is insufficient.

Although inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR) (3, 4), modified Glasgow Prognostic Score (mGPS) (5, 6), C-reactive protein-to-albumin ratio (CAR) (7, 8) and albumin-to-globulin ratio (9, 10), have been reported to be useful for predicting the prognosis and chemotherapeutic efficacy in various malignancies, predictive markers for the survival and therapeutic efficacy in stage IV colorectal cancer have not been established. We therefore focused on the D-dimer level in this study.

As described in our previous report in which the preoperative D-dimer level was a useful prognostic marker in patients with stage I-III colorectal cancer (11), the D-dimer level may have potential utility as an indicator of cancer activity as well as a screening marker for venous thromboembolism. Furthermore, the D-dimer level has been reported to be useful as a predictor of the survival and treatment outcomes in patients with unresectable gastric cancer (12), cervical carcinoma (13) and high-grade musculoskeletal sarcoma (14).

The present study therefore evaluated the utility of the D-dimer level as a marker for the survival and treatment outcomes in patients with stage IV colorectal cancer.

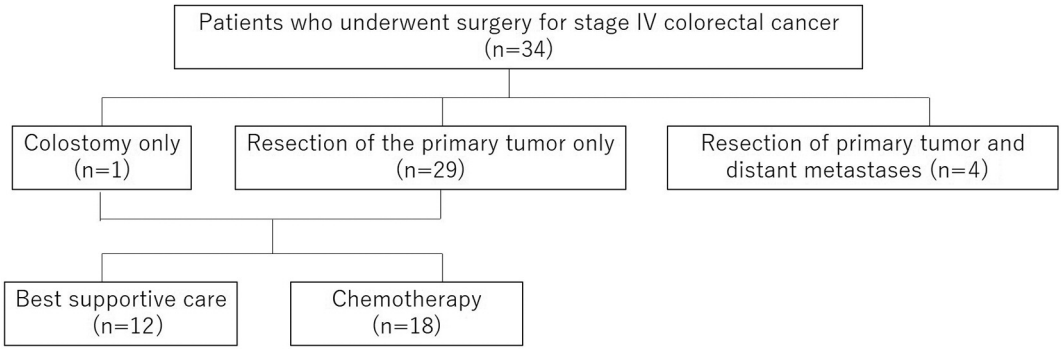

Figure 1. *Treatment flowchart.*

Patients and Methods

Patients. A total of 34 patients who underwent surgery for stage IV colorectal cancer at the Department of Gastroenterological Surgery of Osaka City University Hospital between February 2017 and October 2019 were enrolled in this study. Patients who received chemotherapy first without surgery and cases with recurrence after curative resection were excluded. The associations between the D-dimer level and treatment outcomes, such as the resection of primary tumor/metastatic tumor, chemotherapy introduction and chemotherapeutic efficacy of first-line treatment, were evaluated.

This retrospective study was approved by the Ethics Committee of Osaka City University (approval number: 4182) and was conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent.

Determination of D-dimer level. The D-dimer level was measured on a CN-6000 automated coagulometer analyzer according to the manufacturer's procedure (Sysmex, Kobe, Japan) using a blood sample obtained at the first visit to our hospital. An appropriate cut-off value for the D-dimer level was determined based on a receiver operating characteristic (ROC) curve analysis, and the patients were then classified into low and high D-dimer level groups.

Statistical analyses. All statistical analyses were performed using the SPSS version 26 software package for Windows (IBM Corp., Armonk, NY, USA). The significance of differences in the preoperative D-dimer level and clinicopathological factors was analyzed using a chi-squared test, Fisher's exact test and Mann-Whitney *U*-test.

Overall survival was defined as the interval between the date of operation and the date of death from any cause or of the last follow-up. The progression-free survival was defined as the interval between the date of initiation of first-line chemotherapy and the date of disease progression, death from any cause or of the last follow-up. We adopted the Response Evaluation Criteria in Solid Tumors to classify the treatment response (15). An objective response was defined as a complete or partial response. Disease control was defined as a complete or partial response or stable disease. Survival curves were estimated using the Kaplan-Meier method, and differences in survival curves were assessed with a log-rank test. Values of $p<0.05$ were considered to indicate statistical significance.

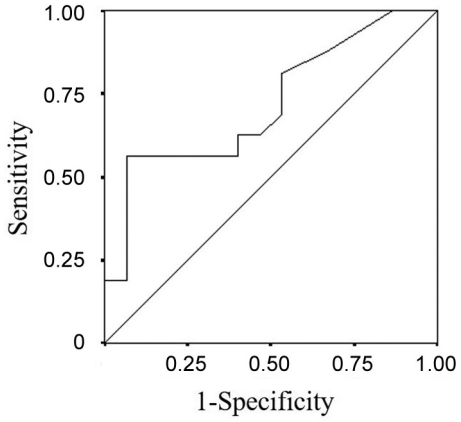

Figure 2. *Receiver operating characteristic curve analysis of the D-dimer levels. Area under the curve=0.719, 95% confidence interval=0.536-0.901, p=0.038.*

Results

The treatment flowchart is shown in Figure 1. The details of operations were as follows: Colostomy only, one patient; resection of the primary tumor only, 29 patients; resection of primary tumor and distant metastases, four patients. Among the 30 patients with residual distant metastases, 18 (60.0%) received chemotherapy. The median preoperative D-dimer level was 1.2 μg/ml (range=0.5-41.0 μg/ml).

Classification according to D-dimer level. The D-dimer level, as a continuous variable, was used as the test variable, and 16.0-month survival (median survival time=16.0 months) was used as the state variable. The ROC curve analysis revealed that the appropriate cut-off D-dimer level was 2.0 μg/ml (sensitivity=56.3%, specificity=93.3%) (Figure 2). We therefore set 2.0 μg/ml as the cut-off value and classified patients into the low (≤2) (n=23) and high (>2) D-dimer level (n=11) groups.

Table I. *Association between D-dimer level and clinicopathological factors.*

Factor	Subgroup	D-Dimer level		*p*-Value
		Low (n=23)	High (n=11)	
Age, n	<75 Years	14	6	<0.999
	≥75 Years	9	5	
Sex, n	Male	9	5	<0.999
	Female	14	6	
Location of the tumor, n	Right side	12	7	0.715
	Left side	11	4	
Histological type, n	Well-/moderately differentiated	22	8	0.212
	Poorly differentiated, mucinous	1	2	
	Unknown	0	1	
Tumor diameter, n	<5 cm	14	3	0.141
	≥5 cm	9	7	
	Unknown	0	1	
Liver metastasis, n	Absent	13	2	0.064
	Present	10	9	
Lung metastasis, n	Absent	19	7	0.388
	Present	4	4	
Peritoneal dissemination, n	Absent	12	6	<0.999
	Present	11	5	
Organs with metastases	1	18	6	0.232
	≥2	5	5	

Table II. *Primers used in quantitative reverse transcriptase polymerase chain reaction.*

Inflammatory marker	Subgroup	Median D-dimer level (range), μg/ml	*p*-Value
NLR	<3	0.8 (0.5-41.0)	0.038
	≥3	3.1 (0.6-12.9)	
mGPS	0, 1	1.0 (0.5-7.3)	0.001
	2	4.4 (0.8-41.0)	

NLR: Neutrophil-to-lymphocyte ratio; mGPS: modified Glasgow prognostic score.

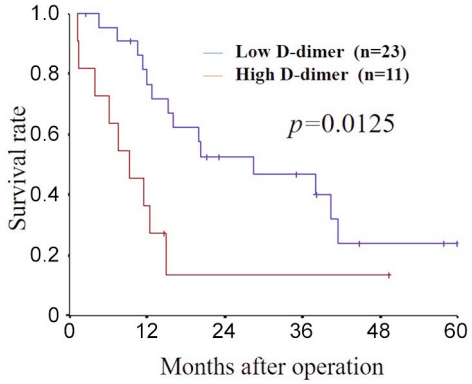

Figure 3. *Kaplan-Meier survival curves for overall survival according to the D-dimer level. The group with a high D-dimer level had a significantly worse overall survival than that with a low level (p=0.0125).*

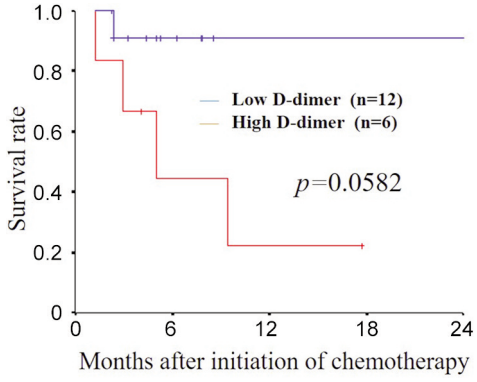

Figure 4. *Kaplan-Meier survival curves for progression-free survival according to the D-dimer level. The group with a high D-dimer level tended to have a worse progression-free survival than that with a low level (p=0.0582).*

Associations between D-dimer level and clinicopathological factors. The D-dimer level had no significant relationship with any of the clinicopathological factors. That is to say, no correlation was observed between the D-dimer level and factors involved in stage determination, such as the number of organs with metastases or peritoneal dissemination (Table I).

Associations between D-dimer level and inflammatory markers. The D-dimer level was significantly positively associated with the NLR and mGPS (p=0.038 and p=0.001, respectively) (Table II).

Results of survival analysis according to the D-dimer level. The group with a high D-dimer level had a significantly lower overall survival than the group with a low level (p=0.0125) (Figure 3).

D-Dimer level by treatment details. One patient who underwent colostomy without excision of the primary tumor had a high D-dimer level of 9.4 μg/ml. Four patients who underwent resection of the primary tumor and distant metastases all had D-dimer levels below 2 μg/ml (0.5, 0.7, 1.3 and 1.7 μg/ml, respectively). The chemotherapy rate tended to be higher in the group with a low D-dimer level (63.2% *vs*. 54.5%), although no statistically significant difference was observed.

Table III. *Comparison of the objective response rate/disease control rate between the groups with low and high D-dimer levels.*

Response	D-Dimer level		*p*-Value
	Low (n=12)	High (n=6)	
Complete response, n	1	0	
Partial response, n	7	2	
Stable disease, n	3	2	
Progressive disease, n	1	2	
Objective response rate	66.7%	33.3%	0.321
Disease control rate	91.7%	66.7%	0.245

Treatment outcomes of first-line chemotherapy. The progression-free survival tended to be better for the group with a low D-dimer level than in the high D-dimer level group (p=0.0582) (Figure 4), although the objective response rates/disease control rates of the two groups did not differ to a statistically significant extent (Table III).

Discussion

This study demonstrated that the D-dimer level at the first visit to the hospital was associated with survival and treatment outcomes of patients with stage IV colorectal cancer.

Due to coagulation-fibrinolysis abnormalities caused by the interaction between cancer cells and endothelial cells, the release of cancer procoagulants and tissue factor, the production of cytokines and activation of blood cells, an increase in the level of D-dimer, a fibrin degradation product, is often observed in patients with cancer (16-20). As cross-linked fibrin produced in coagulation-fibrinolysis abnormalities serves as a framework for processes of cancer progression, such as angiogenesis and invasion, such abnormalities and cancer activity are closely related (20, 21). Therefore, the D-dimer level, which reflects cancer activity, may serve as a prognostic marker for survival and treatment outcomes.

Although in our study D-dimer levels were not associated with the determinants of stage IV subclassification, such as peritoneal dissemination and the number of organs with metastases (22), they were significantly associated with prognosis. Given previous reports that elevated D-dimer levels are associated with a high tumor burden (23), these results are readily accepted. Therefore, the D-dimer level is an excellent marker for evaluating cancer activity, which offers different perspectives from the TNM classification. These findings are supported by the correlation between the D-dimer levels and inflammatory markers, such as the NLR and mGPS, which have also been reported to reflect the tumor burden and cancer activity (8).

The chemotherapy rate tended to be lower in the group with a high D-dimer level. Even with chemotherapy, patients with high D-dimer levels tended to have a short progression-free survival in first-line treatment. This is presumed to be due to the acquisition of chemoresistance associated with a high tumor activity or a tumor growth rate that exceeds the tumor-suppressive effects of chemotherapy. In contrast, it is speculated that patients with low D-dimer levels may have had relatively low cancer activity and low tumor volumes, as all our patients who underwent resection of the primary tumor and distant metastases had low D-dimer levels.

The present study is associated with several limitations. Firstly, this was a retrospective study with a small cohort at a single center. Large prospective studies should be conducted to confirm our findings. Secondly, it was not possible to examine the significance of the D-dimer level in cases where the primary tumor was small and clinical symptoms were poor, as chemotherapy is performed first without surgery in such cases. Thirdly, it was also not possible to examine the relationship between changes in D-dimer levels and therapeutic effects, as the D-dimer level was not routinely measured after the initiation of chemotherapy.

In conclusion, the preoperative D-dimer level may be a useful indicator for survival and chemotherapeutic outcomes of patients with stage IV 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 article. SK, TF, YI, HK and KM designed the study and critically reviewed the article. All Authors read and approved the final article.

References

1 Verazin G, Riley WM, Gregory J, Tautu C, Prorok JJ and Alhadeff JA: Serum sialic acid and carcinoembryonic levels in the detection and monitoring of colorectal cancer. Dis Colon Rectum *33(2)*: 139-142, 1990. PMID: 2298100. DOI: 10.1007/BF02055544

2 Go VL and Zamcheck N: The role of tumor markers in the management of colorectal cancer. Cancer *50(11 Suppl)*: 2618-2623, 1982. PMID: 7139557.

3 Chua W, Charles KA, Baracos VE and Clarke SJ: Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. Br J Cancer *104(8)*: 1288-1295, 2011. PMID: 21448173. DOI: 10.1038/bjc.2011.100

4 Takada K, Kashiwagi S, Asano Y, Goto W, Takahashi K, Shibutani M, Amano R, Takashima T, Tomita S, Hirakawa K and Ohira M: Clinical evaluation of dynamic monitoring of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in

primary endocrine therapy for advanced breast cancer. Anticancer Res *39(10)*: 5581-5588, 2019. PMID: 31570453. DOI: 10.21873/anticanres.13752

5 Kishiki T, Masaki T, Matsuoka H, Kobayashi T, Suzuki Y, Abe N, Mori T and Sugiyama M: Modified Glasgow prognostic score in patients with incurable stage IV colorectal cancer. Am J Surg *206(2)*: 234-240, 2013. PMID: 23827511. DOI: 10.1016/j.amjsurg.2012.07.051

6 Yukihiro K, Teishima J, Goto K, Aoki G, Sekino Y, Hayashi T, Hasegawa Y, Mita K, Kato M, Kajiwara M, Shigeta M, Maruyama S, Kadonishi Y, Fujiwara S and Hinata N: Impact of modified Glasgow prognostic score on predicting prognosis and modification of risk model for patients with metastatic renal cell carcinoma treated with first line tyrosine kinase inhibitor. Urol Oncol *40(10)*: 455.e11-455.e18, 2022. PMID: 35851184. DOI: 10.1016/j.urolonc.2022.06.016

7 Shibutani M, Nagahara H, Fukuoka T, Iseki Y, Matsutani S, Wang EN, Maeda K, Hirakawa K and Ohira M: Prognostic significance of the C-reactive protein-to-albumin ratio in patients with metastatic colorectal cancer treated with trifluridine/thymidine phosphorylase inhibitor as later-line chemotherapy. Anticancer Res *39(2)*: 1051-1057, 2019. PMID: 30711994. DOI: 10.21873/anticanres.13212

8 Shibutani M, Maeda K, Nagahara H, Iseki Y, Hirakawa K and Ohira M: The significance of the C-reactive protein to albumin ratio as a marker for predicting survival and monitoring chemotherapeutic effectiveness in patients with unresectable metastatic colorectal cancer. Springerplus *5(1)*: 1798, 2016. PMID: 27812440. DOI: 10.1186/s40064-016-3529-y

9 Shibutani M, Maeda K, Nagahara H, Ohtani H, Iseki Y, Ikeya T, Sugano K and Hirakawa K: The pretreatment albumin to globulin ratio predicts chemotherapeutic outcomes in patients with unresectable metastatic colorectal cancer. BMC Cancer *15*: 347, 2015. PMID: 25934494. DOI: 10.1186/s12885-015-1375-x

10 Li J, Wang Y, Wu Y, Li J and Che G: Prognostic value of pretreatment albumin to globulin ratio in lung cancer: a meta-analysis. Nutr Cancer *73(1)*: 75-82, 2021. PMID: 32148098. DOI: 10.1080/01635581.2020.1737155

11 Shibutani M, Kashiwagi S, Fukuoka T, Iseki Y, Kasashima H, Kitayama K and Maeda K: Prognostic role of preoperative D-dimer levels in patients with stage I-III colorectal cancer. Cancer Diagn Progn 3(1): 38-43, 2023. DOI: 10.21873/cdp.10177

12 Go SI, Lee MJ, Lee WS, Choi HJ, Lee US, Kim RB, Kang MH, Kim HG, Lee GW, Kang JH, Lee JH and Kim SJ: D-Dimer can serve as a prognostic and predictive biomarker for metastatic gastric cancer treated by chemotherapy. Medicine (Baltimore) *94(30)*: e951, 2015. PMID: 26222870. DOI: 10.1097/MD.0000000000000951

13 Nakamura K, Nakayama K, Ishikawa M, Katagiri H, Minamoto T, Ishibashi T, Ishikawa N, Sato E, Sanuki K, Yamashita H, Komatsu-Fujii T and Kyo S: High pre-treatment plasma D-dimer level as a potential prognostic biomarker for cervical carcinoma. Anticancer Res *36(6)*: 2933-2938, 2016. PMID: 27272807.

14 Morii T, Tajima T, Aoyagi T and Ichimura S: D-dimer level changes during systemic chemotherapy can predict prognosis of high-grade musculoskeletal sarcoma patients. Anticancer Res *35(12)*: 6781-6786, 2015. PMID: 26637896.

15 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45(2)*: 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026

16 Noble S and Pasi J: Epidemiology and pathophysiology of cancer-associated thrombosis. Br J Cancer *102 Suppl 1(Suppl 1)*: S2-S9, 2010. PMID: 20386546. DOI: 10.1038/sj.bjc.6605599

17 Falanga A, Marchetti M and Vignoli A: Coagulation and cancer: biological and clinical aspects. J Thromb Haemost *11(2)*: 223-233, 2013. PMID: 23279708. DOI: 10.1111/jth.12075

18 Khorana AA: Cancer and coagulation. Am J Hematol *87 Suppl 1(Suppl 1)*: S82-S87, 2012. PMID: 22389165. DOI: 10.1002/ajh.23143

19 Kuderer NM, Ortel TL and Francis CW: Impact of venous thromboembolism and anticoagulation on cancer and cancer survival. J Clin Oncol *27(29)*: 4902-4911, 2009. PMID: 19738120. DOI: 10.1200/JCO.2009.22.4584

20 Wojtukiewicz MZ, Sierko E, Klement P and Rak J: The hemostatic system and angiogenesis in malignancy. Neoplasia *3(5)*: 371-384, 2001. PMID: 11687948. DOI: 10.1038/sj.neo.7900184

21 Ruf W, Yokota N and Schaffner F: Tissue factor in cancer progression and angiogenesis. Thromb Res *125 Suppl 2(0 2)*: S36-S38, 2010. PMID: 20434002. DOI: 10.1016/S0049-3848(10)70010-4

22 Brierley JD GM, Wittekind C: TNM Classification of Malignant Tumours. Union for International Cancer Control. Eighth Edition. John Wiley & Sons, Ltd., 2017.

23 Lu SL, Ye ZH, Ling T, Liang SY, Li H, Tang XZ, Xu YS and Tang WZ: High pretreatment plasma D-dimer predicts poor survival of colorectal cancer: insight from a meta-analysis of observational studies. Oncotarget *8(46)*: 81186-81194, 2017. PMID: 29113378. DOI: 10.18632/oncotarget.20919

Received November 11, 2022
Revised December 5, 2022
Accepted December 7, 2022