D-dimer as a potential clinical marker for predicting metastasis and progression in cancer

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Abstract. D-dimer is a widely used biomarker for indicating the activation of coagulation and fibrinolysis, and is reported to serve important roles in cancer progression. The aim of the current retrospective study was to investigate the association of D-dimer plasma level with the development of various cancers. Patients with breast (n=86), gastric (n=317), pancreatic (n=37), colon (n=153) and rectal (n=137) cancers and 92 healthy volunteers were assessed in the present study. Plasma levels of D-dimer in the patients and healthy controls were measured by immunoturbidimetric assays. The association of D-dimer levels with the clinicopathological features of patients were also determined. The plasma levels of D-dimer were significantly higher in patients with breast cancer (P=0.0022), gastric cancer (P<0.0001), pancreatic cancer (P=0.0003), colon cancer (P=0.0001) and rectal cancer (P=0.0028), compared with the healthy controls. It was also determined that the plasma D-dimer levels were positively associated with clinical cancer stage (P<0.05) and metastasis (P<0.05). These findings suggested that the plasma D-dimer level may be used as marker for predicting cancer metastasis and progression.

Introduction

D-dimer is the cleavage product of cross-linked fibrin that is formed by activation of the coagulation system, which signals hyperfibrinolysis in response to clot activation and fibrin formation (1). Elevated levels of D-dimer have been detected in patients exhibiting diffuse intravascular coagulation (2), vascular occlusion crisis in sickle cell disease (3), thromboembolic events (4,5) and myocardial infarction (6). D-dimer is a widely used biomarker for indicating the activation of coagulation and fibrinolysis (7,8). Coagulation disorders are among the most common complications in cancer patients (7,9). D-dimer levels are elevated in the plasma of patients with various solid cancers, including of the prostate (10-12), cervix (13-15) and esophageal squamous cells (16). However, the association of D-dimer levels and cancer progression remains to be a focus of study.

In the present retrospective study, the plasma levels of D-dimer in patients with breast, gastric, pancreatic, colon and rectal cancers and in healthy controls were firstly measured. Subsequently, associations between the D-dimer levels and clinical features were assessed. The results suggested that the plasma level of D-dimer was notably associated with the extent of tumor metastasis and tumor stage in cancer patients.

Materials and methods

Study population. Enrolled patients had been diagnosed with breast cancer (n=86; age range, 35-79 years; all female), gastric cancer (n=317; age range, 32-83 years; male: female, 208:109), pancreatic cancer (n=37; age range, 34-82 years; male: female, 22:15), colon cancer (n=153; age range, 26-90 years; male: female 73:80) or rectal cancer (n=137; age range, 44-79 years; male: female, 81:56) at the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou, China, from January 2010 to December 2014. A total of 92 healthy volunteers (age range, 23-69 years; male: female, 43:49) undergoing physical examination at Changzhou No. 2 People's Hospital in January 2016 were also enrolled. The cancers were defined according to pathological findings. Other inclusion criteria were measurable disease by magnetic resonance imaging. Disease clinical staging (I-IV) depended on the systems recommended by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (17-21). Exclusion criteria were intravascular disseminated coagulation, which was diagnosed on the parameters issued by the Chinese Hematology Society (22-24). The present retrospective

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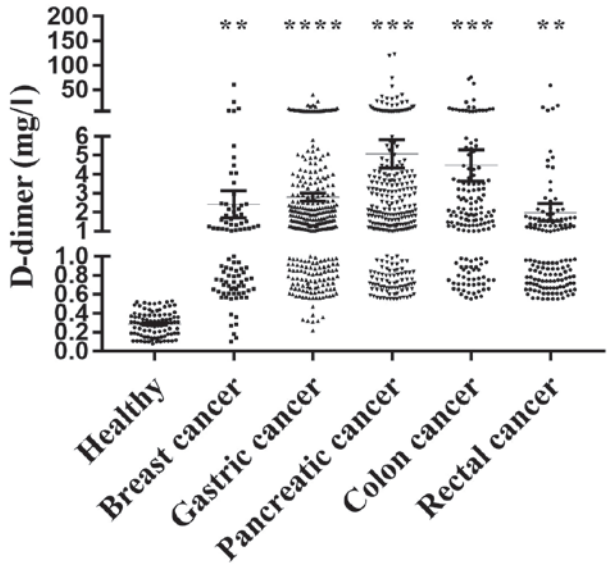

Figure 1. D-dimer levels in healthy volunteers and patients with different cancers. The graph shows the median, quartiles and range of the data. **P<0.01, ***P<0.001 and ****P<0.0001 vs. healthy volunteers.

study was approved by the Ethics Committee of Changzhou No. 2 People's Hospital, and written informed consent from all participants was obtained following full disclosure of the research aims and procedures.

D-dimer level assays. D-dimer expression levels were detected prior to and following treatment in cancer patients. In the healthy controls D-dimer was detected during a fasting (for 8 h prior) physical examination. A total of 3 ml whole blood was drawn from the antecubital vein of each subject and collected in 3.8% sodium citrate vacutainer collection tubes (Greiner Bio-One GmbH, Frickenhausen, Germany). Plasma D-dimer levels were analyzed with an INNOVANCE®D-Dimer Calibrator (Siemens AG, Munich, Germany). All samples were run in duplicate according to manufacturer's recommendations. The D-dimer cross-linkage region has a stereosymmetrical structure, meaning the epitope for the monoclonal antibody occurs twice. D-dimer levels >0.55 mg/l were considered to be elevated, since this was the upper limit of the 90% confidence interval for the average value determined in the healthy volunteers. The D-dimer levels in tumor patients can be affected following surgery (25,26), chemotherapy (27,28) and adjuvant therapy (29). Therefore, the data analyzed herein is the D-dimer expression level of all patients prior to treatment.

Statistical analysis. D-dimer levels were presented as the median and range. Statistically significant differences between healthy volunteers and cancer patients were determined using unpaired Student's t-tests. Cases were divided into two groups, high or low, according to the median D-dimer level as a cutoff. Associations of D-dimer level with clinicopathological characteristics were analyzed by using the χ^2 test. P<0.05 was considered to indicate statistical significance. The statistical analysis and graphing of data were performed with GraphPad Prism version 7.00 (GraphPad Software, Inc., La Jolla, CA, USA).

Table I. Clinical association between D-dimer level and clinicopathological variables of breast cancer patients.

Characteristic	Cases (n=86)	Cases with low and high D-dimer level, n (%)		P-value
		Low	High	
Age, years				1
≥60	46	35 (76.1)	11 (23.9)	
<60	40	31 (77.5)	9 (22.5)	
Metastasis				0.0181
Positive	70	20 (28.6)	50 (71.4)	
Negative	16	10 (62.5)	6 (37.5)	
TNM stage				0.0101
I&II	17	11 (64.7)	6 (35.3)	
III&IV	69	20 (28.9)	49 (71.1)	

For patients with breast cancer, since there were no male patients it was not possible to perform statistics for male vs. female patients. TNM, tumor-node-metastasis.

Results

D-dimer levels are significantly increased in patients with cancer. To investigate the role of D-dimer in the development of cancer, an INNOVANCE®D-Dimer Calibrator was used to analyze the D-dimer levels in patients with breast, gastric, pancreatic, colon and rectal cancers and in healthy controls. The results demonstrated that D-dimer levels were significantly higher in the patients with breast cancer (2.61±0.77 mg/l; n=86; P=0.0022), gastric cancer (2.85±0.21 mg/l; n=317; P<0.0001), pancreatic cancer (5.65±1.39 mg/l; n=37; P=0.0003), colon cancer (4.48±0.83 mg/l; n=153; P=0.0001) and rectal cancer (2.00±0.46 mg/l; n=137; P=0.0028), compared with in healthy volunteers (0.29±0.01 mg/l, n=92; Fig. 1). These results indicated that D-dimer is expressed to a high level and may serve important roles during cancer development.

D-dimer levels are associated with the clinicopathological characteristics of patients with cancer. Additionally, associations of D-dimer level with the clinicopathological characteristics of patients were assessed. Specimens were divided into two groups according to the expression level of D-dimer (≤ or >0.55 mg/l). The data indicated that the D-dimer plasma level differed significantly according to metastasis (P=0.0181) and TNM stage (P=0.0101) in patients with breast cancer (Table I); metastasis (P<0.0001) and TNM stage (P=0.0063) in patients with gastric cancer (Table II); TNM stage (P=0.0395) in patients with pancreatic cancer (Table III); metastasis (P=0.0120), TNM stage (P=0.0039) and sex (P=0.0145) in patients with colon cancer (Table IV); and metastasis (P=0.0104) and TNM stage (P=0.0002) in patients with rectal cancer (Table V). No differences were identified between D-dimer level and other clinical features (Tables I-V). These data suggested that the plasma level of D-dimer may be used as a marker in cancer progression.

Table II. Clinical association between D-dimer level and clinicopathological variables of gastric cancer patients.

Characteristic	Cases (n=317)	Cases with low and high D-dimer level, n (%)		P-value
		Low	High	
Age, years				0.5337
≥60	171	119 (60.0)	52 (40.0)	
<60	146	107 (69.4)	39 (30.6)	
Gender				0.4341
Male	208	145 (69.7)	63 (30.7)	
Female	109	81 (74.3)	28 (25.7)	
Metastasis				<0.0001
Positive	215	117 (54.5)	98 (45.6)	
Negative	102	79 (77.5)	23 (22.5)	
TNM stage				0.0063
I&II	32	26 (84.2)	6 (15.8)	
III&IV	285	174 (61.1)	111 (38.9)	

TNM, tumor-node-metastasis.

Table III. Clinical association between D-dimer level and clinicopathological variables of pancreatic cancer patients.

Characteristic	Cases (n=37)	Cases with low and high D-dimer level, n (%)		P-value
		Low	High	
Age, years				1
≥60	23	10 (43.5)	13 (56.5)	
<60	14	6 (42.9)	8 (57.1)	
Gender				1
Male	22	10 (45.5)	12 (54.5)	
Female	15	6 (40.0)	9 (60.0)	
Metastasis				0.5541
Positive	34	13 (38.2)	21 (61.8)	
Negative	3	2 (66.7)	1 (33.3)	
TNM stage				0.0395
I&II	14	8 (57.1)	6 (42.9)	
III&IV	23	5 (21.7)	18 (78.3)	

TNM, tumor-node-metastasis.

Table IV. Clinical association between D-dimer level and clinicopathological variables of colon cancer patients.

Characteristic	Cases (n=153)	Cases with low and high D-dimer level, n (%)		P-value
		Low	High	
Age, years				0.7127
≥60	113	64 (56.6)	49 (43.4)	
<60	40	21 (52.5)	19 (47.5)	
Gender				0.0145
Male	73	48 (65.8)	25 (34.2)	
Female	80	36 (45.0)	44 (55.0)	
Metastasis				0.0120
Positive	119	51 (42.9)	68 (57.1)	
Negative	34	23 (67.7)	11 (32.3)	
TNM stage				0.0039
I&II	17	15 (88.2)	2 (11.8)	
III&IV	136	70 (51.5)	66 (48.5)	

TNM, tumor-node-metastasis.

Table V. Clinical association between D-dimer level and clinicopathological variables of rectal cancer patients.

Characteristic	Cases (n=137)	Cases with low and high D-dimer level, n (%)		P-value
		Low	High	
Age, years				0.8477
≥60	100	48 (48.0)	52 (52.0)	
<60	37	19 (51.4)	18 (48.6)	
Gender				1
Male	81	40 (49.4)	41 (50.6)	
Female	56	27 (48.2)	29 (51.8)	
Metastasis				0.0104
Positive	109	47 (43.1)	62 (56.9)	
Negative	28	20 (71.4)	8 (28.6)	
TNM stage				0.0002
I&II	44	30 (68.2)	14 (31.8)	
III&IV	93	32 (34.4)	61 (65.6)	

TNM, tumor-node-metastasis.

Discussion

In the present study, it was demonstrated that elevated plasma levels of D-dimer were associated with clinical cancer stages and metastasis in patients with breast, gastric, colon and rectal cancers. It was also identified that D-dimer plasma level was associated with cancer stages in patients with pancreatic cancer and with gender in patients with colon cancer. These findings suggest that D-dimer level has a potential use in predicting the likelihood of metastasis and progression in various cancers.

Distant metastasis is the main cause of poor prognosis and leads to inefficacy in treatments in cancer patients (30). D-dimer is a widely used biomarker for indicating the activation of coagulation and fibrinolysis. It is established that activated

coagulation, which is common in malignancy, plays an important role in cancer metastasis (31). The coagulation/fibrinolytic system is activated in cancer patients and may contribute to cancer progression (14). Thus, tumor-related degradation products of the coagulation and fibrinolytic system have been proposed to predict tumor load and prognosis (14,32). Plasma D-dimer is a pro-coagulation factor that may reflect the presence of micro-metastases or circulating tumor cells, which may be responsible for tumor recurrence (30,33,34). Recent studies have reported a positive association between circulating tumor cells and plasma D-dimer levels in patients with metastatic breast cancer (35,36). Diao *et al* (37) observed that plasma D-dimer levels were markedly increased in gastric cancer patients with distant metastases, particularly in patients with visceral metastases. In fact, they suggested D-dimer to be a promising predictor of clinical stage in the gastric cancer patients (37). Lee *et al* (38) reported that increased plasma D-dimer and fibrinogen degradation product levels were significantly associated with TNM stage in colorectal cancer patients. Furthermore, preoperative plasma D-dimer levels have been associated with larger tumor size and lymph node metastasis in colorectal cancer patients (39). Other recent studies have shown that plasma D-dimer values may predict overall survival and progression free survival in patients with pancreatic cancer (40,41). In accordance with the above studies, the present study confirmed a positive association between D-dimer level and tumorigenesis. It was further identified that D-dimer level was associated with cancer stages but not with metastasis in patients with pancreatic cancer. Among the patients with pancreatic cancer, the majority presented with metastasis (34/37), and fibrinogen and carbohydrate antigen 19-9 (CA19-9) were significantly elevated in the patients with metastatic pancreatic cancer, compared with patients with non-metastatic cancer (data not shown), suggesting that a combination of D-dimer, fibrinogen and CA19-9 may be used for predicting metastasis of pancreatic cancer.

In conclusion, the present retrospective study demonstrated that D-dimer plasma level was significantly higher in patients with cancer and associated with clinical stages and metastasis. The current study was limited in that it only identified the association of D-dimer with tumor stage and metastasis. We will further investigate the sensitivity and specificity of D-dimer as an indicator of tumorigenesis, and the correlation between D-dimer and the survival and prognosis of cancer patients, to clarify whether D-dimer level may be considered as an important factor in the prognosis of cancer patients.

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Availability of data and materials

All data generated or analyzed in this study are included in this published article.

Authors' contributions

PZ, HD and TF designed the study. HZ, YS, ZX and SW performed the experiments and collected and analyzed data. PZ, HD and TF wrote, reviewed and revised the manuscript. All authors read and approved the final version to be published.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou, China, and written informed consent permitting the use of patient samples in the current study was obtained prior to treatment.

Consent for publication

All patients consented to the publication of any relevant data on the basis of anonymization of all personal data.

Competing interests

The authors declare that they have no competing interests.

References

1. Jiang X, Mei X, Wu H and Chen X: D-dimer level is related to the prognosis of patients with small cell lung cancer. Ann Transl Med 5: 394, 2017.
2. Kobayashi T, Kajiki M, Nihashi K and Honda G: Surveillance of the safety and efficacy of recombinant human soluble thrombomodulin in patients with obstetrical disseminated intravascular coagulation. Thromb Res 159: 109-115, 2017.
3. Ahmed S, Siddiqui AK, Iqbal U, Sison CP, Shahid RK, Sheth M, Patel DV and Russo LA: Effect of low-dose warfarin on D-dimer levels during sickle cell vaso-occlusive crisis: A brief report. Eur J Haematol 72: 213-216, 2004.
4. Lowe GD, Haverkate F, Thompson SG, Turner RM, Bertina RM, Turpie AG and Mannucci PM: Prediction of deep vein thrombosis after elective hip replacement surgery by preoperative clinical and haemostatic variables: The ECAT DVT Study. European Concerted Action on Thrombosis. Thromb Haemost 81: 879-886, 1999.
5. Kwietniak M, Al-Amawi T, Błaszkowski T, Sulżyc-Bielicka V and Kładny J: The usefulness of D-dimer in diagnosis and prediction of venous thromboembolism in patients with abdominal malignancy. Pol Przegl Chir 89: 27-30, 2017.
6. Zhang H, Qiu B, Zhang Y, Cao Y, Zhang X, Wu Z, Wang S and Mei L: The Value of Pre-Infarction Angina and Plasma D-Dimer in Predicting No-Reflow After Primary Percutaneous Coronary Intervention in ST-Segment Elevation Acute Myocardial Infarction Patients. Med Sci Monit 24: 4528-4535, 2018.
7. Horowitz NA, Blevins EA, Miller WM, Perry AR, Talmage KE, Mullins ES, Flick MJ, Queiroz KC, Shi K, Spek CA, *et al*: Thrombomodulin is a determinant of metastasis through a mechanism linked to the thrombin binding domain but not the lectin-like domain. Blood 118: 2889-2895, 2011.
8. Im JH, Fu W, Wang H, Bhatia SK, Hammer DA, Kowalska MA and Muschel RJ: Coagulation facilitates tumor cell spreading in the pulmonary vasculature during early metastatic colony formation. Cancer Res 64: 8613-8619, 2004.
9. Huang W and Kim HR: Dynamic regulation of platelet-derived growth factor D (PDGF-D) activity and extracellular spatial distribution by matriptase-mediated proteolysis. J Biol Chem 290: 9162-9170, 2015.

10. Hamzah AB, Choo YM, Hassali MA, Saleem F and Verma AK: Disseminated Intravascular Coagulation and Excessive Fibrinolysis (DIC XFL) Syndrome in Prostate Cancer: A Rare Complicated Disorder. J Clin Diagn Res 11: XD01-XD02, 2017.
11. Hong SK, Ko DW, Park J, Kim IS, Doo SH, Yoon CY, Park H, Lee WK, Kim DS, Jeong SJ, *et al*: Alteration of Antithrombin III and D-dimer Levels in Clinically Localized Prostate Cancer. Korean J Urol 51: 25-29, 2010.
12. Khoury JD, Adcock DM, Chan F, Symanowski JT, Tiefenbacher S, Goodman O, Paz L, Ma Y, Ward DC, Vogelzang NJ, *et al*: Increases in quantitative D-dimer levels correlate with progressive disease better than circulating tumor cell counts in patients with refractory prostate cancer. Am J Clin Pathol 134: 964-969, 2010.
13. Luo YL, Chi PD, Zheng X, Zhang L, Wang XP and Chen H: Preoperative D-dimers as an independent prognostic marker in cervical carcinoma. Tumour Biol 36: 8903-8911, 2015.
14. Satoh T, Matsumoto K, Tanaka YO, Akiyama A, Nakao S, Sakurai M, Ochi H, Onuki M, Minaguchi T, Sakurai H, *et al*: Incidence of venous thromboembolism before treatment in cervical cancer and the impact of management on venous thromboembolism after commencement of treatment. Thromb Res 131: e127-e132, 2013.
15. Sun YH, Cui L, Chen J, Wang M, Liu JJ, Liu XX and Huang XE: Analysis of Relationships Between Prethrombotic States and Cervical Cancer. Asian Pac J Cancer Prev 16: 6163-6166, 2015.
16. Feng JF, Yang X, Chen S, Zhao Q and Chen QX: Prognostic Value of Plasma D-dimer in Patients with Resectable Esophageal Squamous Cell Carcinoma in China. J Cancer 7: 1663-1667, 2016.
17. Carlson RW, Allred DC, Anderson BO, Burstein HJ, Carter WB, Edge SB, Erban JK, Farrar WB, Forero A, Giordano SH, *et al*; National Comprehensive Cancer Network: Invasive breast cancer. J Natl Compr Canc Netw 9: 136-222, 2011.
18. Ettinger DS, Akerley W, Bepler G, Blum MG, Chang A, Cheney RT, Chirieac LR, D'Amico TA, Demmy TL, Govindan R, *et al*; National Comprehensive Cancer Network: Thymic malignancies. J Natl Compr Canc Netw 8: 1302-1315, 2010.
19. Romanus D, Weiser MR, Skibber JM, Ter Veer A, Niland JC, Wilson JL, Rajput A, Wong YN, Benson AB III, Shibata S, *et al*: Concordance with NCCN Colorectal Cancer Guidelines and ASCO/NCCN Quality Measures: An NCCN institutional analysis. J Natl Compr Canc Netw 7: 895-904, 2009.
20. Benson AB III, Arnoletti JP, Bekaii-Saab T, Chan E, Chen YJ, Choti MA, Cooper HS, Dilawari RA, Engstrom PF, Enzinger PC, *etal*; National Comprehensive Cancer Network: Colon cancer. J Natl Compr Canc Netw 9: 1238-1290, 2011.
21. Engstrom PF, Arnoletti JP, Benson AB III, Chen YJ, Choti MA, Cooper HS, Covey A, Dilawari RA, Early DS, Enzinger PC, *et al*; National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Rectal cancer. J Natl Compr Canc Netw 7: 838-881, 2009.
22. Ma J and Qiu LG: Guidelines for treatment of myeloma bone disease. Zhonghua Xue Ye Xue Za Zhi 32: 721-723, 2011 (In Chinese).
23. Lymphoma Working Party of Chinese Society of Hematology: Chinese guidelines for the diagnosis and management of chronic lymphocytic leukemia . Zhonghua Xue Ye Xue Za Zhi 32: 498-501, 2011 (In Chinese).
24. Shen ZX; Chinese Society of Hematology; Chinese Medical Association: Chinese guidelines for the diagnosis and treatment of acute promyelocytic leukemia. Zhonghua Xue Ye Xue Za Zhi 32: 885-886, 2011 (In Chinese).
25. Shi A, Huang J, Wang X, Li M, Zhang J, Chen Y and Huang Y: Postoperative D dimer predicts venous thromboembolism in patients undergoing urologic tumor surgery. Urol Oncol 36: 307 e315 307 e321, 2018.
26. Yao Y, Shen H, Zhou Y, Yang Z and Huang H: Efficacy of thoracoscopic surgery in the treatment of lung cancer in the perioperative period and its effects on serum D-dimer. Oncol Lett 15: 4397-4403, 2018.
27. Zhang B, Liu G, Liu X, Zheng S, Dong K and Dong R: Circulating D-dimer level correlates with disease characteristics in hepatoblastoma patients. Medicine (Baltimore) 96: e8798, 2017.
28. Pace A, Mandoj C, Antenucci A, Villani V, Sperduti I, Casini B, Carosi M, Fabi A, Vidiri A, Koudriavtseva T, *et al*: A predictive value of von Willebrand factor for early response to Bevacizumab therapy in recurrent glioma. J Neurooncol 138: 527-535, 2018.
29. Khangarot SS, Gupta N, Goswami B, Hadke NS, Lal P, Gupta N and Khurana N: Correlation of D dimer and factor VIII levels with histopathology in patients with breast carcinoma. Cancer Biomark 7: 305-314, 2010.
30. Thaler J, Ay C, Mackman N, Bertina RM, Kaider A, Marosi C, Key NS, Barcel DA, Scheithauer W, Kornek G, *et al*: Microparticle-associated tissue factor activity, venous thromboembolism and mortality in pancreatic, gastric, colorectal and brain cancer patients. J Thromb Haemost 10: 1363-1370, 2012.
31. Palumbo JS, Talmage KE, Massari JV, La Jeunesse CM, Flick MJ, Kombrinck KW, Jirousková M and Degen JL: Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. Blood 105: 178-185, 2005.
32. Palumbo JS, Kombrinck KW, Drew AF, Grimes TS, Kiser JH, Degen JL and Bugge TH: Fibrinogen is an important determinant of the metastatic potential of circulating tumor cells. Blood 96: 3302-3309, 2000.
33. Batschauer AP, Figueiredo CP, Bueno EC, Ribeiro MA, Dusse LM, Fernandes AP, Gomes KB and Carvalho MG: D-dimer as a possible prognostic marker of operable hormone receptor-negative breast cancer. Ann Oncol 21: 1267-1272, 2010.
34. Blackwell K, Haroon Z, Broadwater G, Berry D, Harris L, Iglehart JD, Dewhirst M and Greenberg C: Plasma D-dimer levels in operable breast cancer patients correlate with clinical stage and axillary lymph node status. J Clin Oncol 18: 600-608, 2000.
35. Cui LN, Li N, Fu S, Zhang X, Wang X and Wang RT: Combination of preoperative D-dimer and mean platelet volume predicts postoperative deep venous thrombosis in breast cancer patients. Cancer Biomark 21: 909-913, 2018.
36. Mego M, Zuo Z, Gao H, Cohen EN, Giordano A, Tin S, Anfossi S, Jackson S, Woodward W, Ueno NT, *et al*: Circulating tumour cells are linked to plasma D-dimer levels in patients with metastatic breast cancer. Thromb Haemost 113: 593-598, 2015.
37. Diao D, Cheng Y, Song Y, Zhang H, Zhou Z and Dang C: D-dimer is an essential accompaniment of circulating tumor cells in gastric cancer. BMC Cancer 17: 56, 2017.
38. Lee S, Huh SJ, Oh SY, Koh MS, Kim SH, Lee JH, Han JY, Choi HJ, Kim SJ and Kim HJ: Clinical significance of coagulation factors in operable colorectal cancer. Oncol Lett 13: 4669-4674, 2017.
39. Stender MT, Larsen TB, Lundbye-Christensen S, Yilmaz MK and Thorlacius-Ussing O: Haemostatis activity in rectal cancer patients exposed to preoperative radiotherapy: A clinical prospective cohort study. Blood Coagul Fibrinolysis 20: 276-282, 2009.
40. Durczynski A, Skulimowski A, Hogendorf P, Szymanski D, Kumor A, Marski K, Juliebø SØ, Poznanska G and Strzelczyk J: The concentration of D-dimers in portal blood positively correlates with overall survival in patients with non-resectable pancreatic cancer. World J Surg Oncol 15: 223, 2017.
41. Cao J, Fu Z, Gao L, Wang X, Cheng S, Wang X and Ren H: Evaluation of serum D-dimer, fibrinogen, and CA19-9 for postoperative monitoring and survival prediction in resectable pancreatic carcinoma. World J Surg Oncol 15: 48, 2017.