

# Relationship between plasma D-dimer levels and clinicopathologic parameters in resectable colorectal cancer patients

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**Received:** 2001-10-12 **Accepted:** 2001-11-27

## Abstract

**AIM:** To assess the clinical significance of the D-dimer levels and the relationship between plasma D-dimer levels and clinicopathologic parameters in operable colorectal cancer patients.

**METHODS:** The plasma levels of D-dimer were measured pre- and postoperatively in 35 patients with colorectal cancer, and 30 healthy subjects served as controls by the method of quantitative enzyme-linked immunosorbent assay (ELISA).

**RESULTS:** The mean preoperative plasma levels of D-dimer in the patients with colorectal cancer ( $1.06 \pm 0.24$  mg/L) were significantly higher than those of controls ( $0.33 \pm 0.12$  mg/L,  $P < 0.01$ ). The D-dimer levels were remarkably elevated on the 1st day after operation ( $1.22 \pm 0.55$  mg/L,  $P < 0.01$ ). On the 3rd day the level of D-dimer began to stepwise descend and on the 14th day nearly returned to control level. The preoperative levels of D-dimer were significantly correlated with the lymph node metastasis and Dukes stage but had no association with tumor location and the degree of differentiation. A stepwise increase in the mean D-dimer levels was found with increase of the tumor stage.

**CONCLUSION:** Hypercoagulation and higher fibrinolytic activities occur in patients with colorectal cancer. The operative trauma could enhance the fibrinolysis in the patients with colorectal cancer. The measurement of preoperative D-dimer levels is considered to be useful for predicting lymph node metastasis and stage of colorectal cancer.

Xu G, Zhang YL, Huang W. Relationship between plasma D-dimer levels and clinicopathologic parameters in resectable colorectal cancer patients. *World J Gastroenterol* 2004; 10 (6): 922-923

<http://www.wjgnet.com/1007-9327/10/922.asp>

## INTRODUCTION

Activation of coagulation and fibrinolysis is known to be frequently associated with malignancy, although the mechanism involved has not been fully clarified. The extent of such activation has been reported to correlate with tumor stage and prognosis in some malignancies, including

colorectal cancer<sup>[1-3]</sup>. D-dimer is a stable end-product of fibrin degradation and levels of D-dimer are elevated by enhanced fibrin formation and fibrinolysis. It is a marker of hypercoagulable stage. D-dimer levels are elevated in the plasma of various solid tumor patients<sup>[4,5]</sup>. The present study was to assess the clinical significance of the D-dimer levels and the relationship between plasma D-dimer levels and clinicopathologic findings in pre and post operative patients with colorectal cancer.

## MATERIALS AND METHODS

### Patients

Thirty-five patients with colorectal cancer were investigated. There were 21 males and 14 females, with a median age of 52 years, ranging from 32 to 75 years. Patients with cerebrovascular and diabetes were excluded. Meanwhile, 30 healthy subjects served as controls (17 males and 13 females, median age 56 years, ranging from 33 to 86 years).

### Measurement of plasma D-dimer

Five milliliter of whole blood was drawn from antecubital vein of patients on the day prior to operation and on the 1st, 3rd, 7th, 14th postoperative days, using 3.8g sodium citrate collection tube. All samples were centrifuged within 4 h of veinpuncture, the plasma components were pipetted off and placed in plastic tubes. Centrifuged plasma was stored at  $-80$  °C until assay. Meanwhile 30 samples of healthy subjects served as controls. Plasma D-dimer levels were determined by quantitative enzyme-linked immunosorbent assay (ELISA).

### Statistical analysis

Statistical analysis of mean value of D-dimer levels was made by Student's *t* test and Student Newman-keuls' *s* test.  $P < 0.05$  was considered to be significant.

## RESULTS

### Relationship between plasma D-dimer levels and clinicopathologic parameters

The D-dimer levels of colorectal cancer patients with positive lymph nodes were significantly higher than that of negative lymph nodes ( $0.94 \pm 0.26$  vs  $1.15 \pm 0.12$ ,  $P < 0.01$ , Table 1). A stepwise increase in the mean D-dimer levels was found with the increase of tumor clinical stage. There was no association between D-dimer levels and tumor location or degree of the differentiation.

### Pre- and postoperative plasma D-dimer levels in colorectal cancer patients

The mean plasma levels of D-dimer in the patients with colorectal cancer were significantly higher than that of the controls ( $P < 0.01$ , Table 1). It was also observed that D-dimer levels were remarkably elevated on the 1st day after the operation ( $P < 0.01$ ). On the 3rd day after operation the D-dimer levels began to stepwise descend and on the 14th day almost returned to control ( $P > 0.05$ ).

**Table 1** Relationship between plasma D-dimer levels (mean±SD) and clinicopathology variables

Course (d)	Clinicopathology		n	D-dimer (mg/L)
Preoperation	Location	Colon	14	1.11±0.16
		Rectum	21	1.03±0.25
	Differentiation	Well	13	1.01±0.28
		Moderate	16	1.02±0.31
		Poor	6	1.08±0.14
	Lymph node	Negative	15	0.94±0.26
		Positive	20	1.15±0.12 <sup>a</sup>
	Metastasis	A + B	15	0.94±0.26
		C	15	1.12±0.11 <sup>c</sup>
		D	5	1.29±0.11 <sup>d</sup>
1			35	1.22±0.55 <sup>b</sup>
Postoperation			35	0.82±0.49 <sup>bc</sup>
			30	0.67±0.41 <sup>bf</sup>
			17	0.46±0.17 <sup>f</sup>
Control			30	0.33±0.12

<sup>b</sup>P<0.01 vs control; <sup>a</sup>P<0.05 vs negative; <sup>c</sup>P<0.05, <sup>d</sup>P<0.01 vs Dukes A+B; <sup>e</sup>P<0.05, <sup>f</sup>P<0.01 vs preoperation.

**DISCUSSION**

Both experimental and clinical data have shown that coagulation disorders are common in patients with cancer although clinical symptoms may occur rarely. Recent reports showed hypercoagulable state in cancer patients and the plasma D-dimer levels were increased in these patients<sup>[4,5]</sup>. The process of metastasis involves multiple tumor-host interactions. To survive, metastatic cancer cells must leave the primary tumor, migrate into the lymphovascular system and establish a new blood supply at their metastatic site<sup>[6-8]</sup>. Fibrin remodeling is almost certainly involved in all steps of metastasis and has been proved to play a crucial role in new vessel formation<sup>[9-11]</sup>. Our study showed that the preoperative D-dimer levels were higher and correlated with the tumor lymph node metastasis. It confirmed that unregulated fibrinolytic activities in colorectal cancer and increased levels of fibrinolytic activities in metastasis of colorectal cancer. The reason may be that cancer cells appear to be capable of both thrombin formation and induction of fibrin degradation because cancer cells tend to adhere to, aggregate, necrose, which could induce monocytes and endothelioid cells to release many clotting factors<sup>[12,13]</sup>. Studies suggested that higher D-dimer levels could induce the secretion of interleukin-1, urokinase-type plasminogen activator (u-PA) and plasminogen activator inhibitor-2 in a human promonocytic leukemia cell line. u-PA is the predictive marker in many malignant tumors and may play an important role in the invasive cancer<sup>[14-16]</sup>. The prethrombotic state (depicted by a prolongation of PT and increase of D-dimer) is confirmed to be an aggravating condition in cancers. Studies suggesting an attempt to reverse possible haemostatic abnormalities with the use of anticoagulants have been justified. Thus anticoagulant treatment may have a positive influence on colorectal cancer therapy.

We found that D-dimer levels were remarkably elevated on the 1st day after the operation. On the 3rd day after operation the D-dimer levels began to stepwise descend and on the 14<sup>th</sup> day returned to control. The remarkable increase in D-dimer levels occurring in patients indicated that patients undergoing surgery were at high risks for the occurrence of a thromboembolic event. Thus D-dimer could be used for estimating individual risk of thromboembolism and prophylactic treatment in these patients. Oya *et al* had obtained the same results. In addition,

we found the D-dimer levels of colorectal cancer patients with positive lymph nodes were significantly higher than that of negative lymph nodes. A stepwise increase in the mean D-dimer levels was found with the increase of tumor clinical stage. The measurement of preoperative D-dimer levels is considered to be useful for predicting lymph node metastasis and clinical stage of colorectal cancer.

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