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Original Article

Elevated plasma D-dimer level was correlated with lymphatic metastasis and worse outcome in patients with gastric cancer

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Abstract: *Objectives:* Plasma D-dimer was found to be associated with progression in many kinds of tumors, however, the studies of the roles of D-dimer in the gastric cancer (GC) were rare. The present study aimed to explore the roles of D-dimer in GC. Methods: A total 96 GC patients and 30 healthy peoples were enrolled. The clinical, pathological and survival information were collected. The associations between lymphatic metastasis and plasma D-dimer level was analyzed. The prognostic value of plasma D-dimer level was also investigated. Results: The plasma D-dimer levels of GC patients were higher than those in healthy peoples ($P < 0.005$). The plasma D-dimer level was elevated in 42 patients, while 54 patients were within the normal range. Plasma D-dimer levels (P=0.003) and T stage (P=0.021) were identified as independently relative factors of lymphatic metastasis in GC patients. Multivariate Cox proportional hazard regression model found location (P=0.004), N stage (P=0.012), D-dimer levels (P=0.011) and T stage (P=0.037) were identified as the independent factors of the overall survival. Conclusions: High plasa D-dimer level was associated with lymphatic metastasis and indicated poor survival of GC patients.

Keywords: Gastric cancer, D-dimer, lymphatic metastasis, prognosis

Introduction

D-dimer, which is a stable end product of the degradation of cross-linked Fibrin, results from enhanced fibrin formation and fibrinolysis [1]. D-dimer levels are widely used to detect patients with suspected disseminated intravascular coagulation (DIC), thromboembolic events, and myocardial infarction [2]. Recently, it has been reported that increased D-dimer was correlated with cancers [3]. Researchers had reported that D-dimer can not only affect cellular signaling systems, promote cell proliferation and induce angiogensis, but also stimulate the cellular adhesion of tumor cells to endothelial cells, affect platelets and extra-cellular matrix, and ultimately, induce the growth and spread of tumors [4]. D-dimer had been accepted as a diagnosis and prognosis parameter for cancers [5]. Many studies had reported that D-dimer level was associated with tumor stage, prognosis, lymph node involvement, and overall survival in patients with solid tumors. In gynecologic tumor, D-dimer had been proved to be correlated with CA-125 and the combination of CA-125 and D-dimer to differentiate benign from malignant ovarian tumors was better than single detection of either CA-125 [6]. Chen *et al*. [7] also found high D-dimer level was associated with poor disease-free survival and increased risk of mortality in nasopharyngeal carcinoma patients.

However, there was little studies on the role of D-dimer level in GC, and the association between lymphatic metastasis and D-dimer level remained unknown. Diao *et al*. [8] had demonstrated that D-dimer was an marker in predicting asymptomatic hematogenous metastasis. Liu *et al*. [9] found D-dimer level was increased in GC patients, high D-dimer level can predict poor outcomes in GC patients. In present study, we detected the differences of D-dimer level between GC patients and healthy

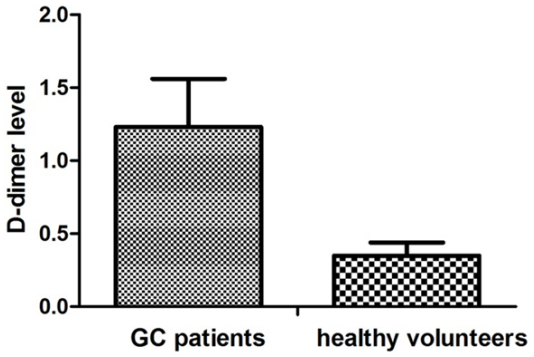

Figure 1. The D-dimer level of GC patients were higher than those of healthy peoples.

Table 1. Clinicopathological characteristics of GC patients

Variables	Cases (%)
Gender	
Male	52 (54.2%)
Female	44 (45.8%)
Age	
≤ 60	62 (64.6%)
> 60	34 (35.4%)
Size of tumor (cm)	
≤ 5	65 (67.7%)
> 5	31 (32.3%)
Location	
Lower 1/3	42 (43.8%)
Middle 1/3	18 (18.8%)
Upper 1/3	36 (37.5%)
Differentiation	
Well/Moderate	19 (19.8%)
Poor	77 (80.2%)
T stage	
T1	10 (10.4%)
T2	7 (7.3%)
T3	10 (10.4%)
T4	69 (71.9%)
N stage	
N0	33 (34.4%)
N1	23 (24.0%)
N2	28 (29.2%)
N3	12 (12.5%)
D-Dimer levels	
High	42 (43.8%)
Normal	54 (56.3%)

peoples. Additionally, we examined the relationships between lymphatic metastasis and plasma D-dimer level. Lastly, we investigated the prognosis value of plasma D-dimer level in GC patients.

Patients and methods

Patients

GC patients at the Tianjin Nankai hospital and Tianjin Cancer hospital from February 2009 to December 2013 were enrolled for this study. The inclusion criteria included the following: (1) histologically proven adenocarcinoma, (2) no history of gastrectomy or other malignancy, (3) availability of complete follow-up data. The exclusion criteria are as follows: (1) patients who underwent palliative surgery and (2) patients who had distant metastasis or peritoneal dissemination that was confirmed during the operation. Based on these criteria, 96 GC patients were enrolled in the present study. Meanwhile, 30 healthy peoples from the physical examination of Tianjin Nankai Hospital were also chosen in this study.

Enzyme-linked fluorescent immunoassays for D-dimer levels

Peripheral venous blood samples were collected prior to surgery for the GC patients and healthy peoples, D-dimer level was measured using an enzyme-linked fluorescent immunoassay method with a mini-Vidas device (BioMerieux SA). D-dimer levels < 0.5 μg/mL were considered normal.

Follow-up

All patients were followed up every 6 months for 2 years, then every year or until death. The overall survival (OS) was defined as time from the date of diagnosis to the date of death or last visit. The clinical-pathological information was reviewed from the database of hospital, and the survival data was collected from clinic visit or family contact.

Statistical analysis

Continuous variables were described using mean ± standard deviation, differences in the different variable were estimated paired-sample t-test. Qualitative correlation analysis was performed by X^2 test. Multivariate correlation analysis was conducted by logistic regression. The survival was compared through the Kaplan-

Table 2. Relationships between lymphatic metastasis and clinicopathological characteristics in GC patients

Variables	The status of lymphatic metastasis		Univariate	Multivariate
	Metastasis	No-metastasis	*p* value	*p* value
Gender			0.419	
Male	36	16		
Female	27	17		
Age			0.137	
≤ 60	44	18		
> 60	19	15		
Size of tumor			0.032	0.074
≤ 5	38	27		
> 5	25	6		
Location			0.051	
Lower 1/3	27	15		
Middle 1/3	16	2		
Upper 1/3	20	16		
Differentiation			0.428	
Well/Moderate	11	8		
Poor	52	25		
T stage			0.001	0.021
T1	1	9		
T2	5	2		
T3	9	1		
T4	48	21		
D-Dimer level			0.005	0.003
High	34	8		
Normal	29	25		

Meier method and log-rank tests. Furthermore, the prognostic role of the D-dimer levels was identified by the multivariate analyses. The statistical analyses were performed using SPSS version 17.0. Significance was defined as *p*-Values < 0.05.

Result

Plasma D-dimer levels

Plasma D-dimer level was measured from peripheral venous blood samples. The D-dimer level of GC patients was higher than those of healthy peoples (1.23 ± 0.33 *vs.* 0.35 ± 0.09, P < 0.05) (**Figure 1**). All the patients were divided into high group (> 0.5 μg/mL) and normal group (≤ 0.5 μg/mL) according to the plasma D-dimer level, and plasma D-dimer levels was elevated in 42 patients, while 52 patients were within the normal range. The other clinicopathological factors of GC patients were shown in **Table 1**.

Association between lymphatic metastasis and clinicalpathological factors

Lymphatic metastasis in different gender, age, size of tumor, location, differentiation, T stage and D-dimer levels were analyzed. The relationships between lymphatic metastasis and various clinicopathological characteristics were shown in **Table 2**. Ultimately, D-dimer level (P= 0.003) and T stage (P= 0.021) were identified as independently relative factors of lymphatic metastasis in GC patients.

Survival outcomes

Univariate analysis showed significant relationships between the OS and size of tumor, location, T stage, N stage and D-dimer levels, but not with gender, age, of tumor and differentiation. Location [hazard ratio (HR)=1.639; P=0.004], T stage (HR=1.546; P=0.037), N stage (HR=1.293; P=0.012) and D-dimer level (HR=1.637; P=0.011) were identified as the independent factors of OS in all GC patients following multivariate analysis (Cox proportional hazards model) (**Table 3**). In clinical, GC patients with normal D-dimer level presented significantly better overall survival than those with high D-dimer level (**Figure 2**).

Discussion

As the fourth most common cancer worldwide, more than 60% GC patients were in the advanced stage at the initial diagnosis [10]. Recent progress in early diagnosis, surgical techniques, perioperative management and chemotherapy had improved patient satisfaction and outcomes; however, the long-term survival rate was still dismal [11]. Thus, exploring

Table 3. Survival analysis of GC patients

Variables	5-YSR (%)	Univariate analysis		Multivariate analysis	
		X^2 value	*p* value	HR value	*p* value
Gender		2.206	0.137		
Male	46.2				
Female	61.4				
Age		0.015	0.903		
≤ 60	51.6				
> 60	52.9				
Size of tumor		9.100	0.003	1.791	0.056
≤ 5	58.0				
> 5	32.3				
Location		8.743	0.013	1.639	0.004
Lower 1/3	71.4				
Middle 1/3	38.9				
Upper 1/3	35.9				
Differentiation		0.541	0.462		
Well/Moderate	63.2				
Poor	50.6				
T stage		9.142	0.027	1.546	0.037
T1	90.0				
T2	71.4				
T3	60.0				
T4	49.3				
N stage		45.558	< 0.001	1.293	0.012
N0	75.8				
N1	47.8				
N2	50.0				
N3	8.3				
D-Dimer level		7.050	0.008	1.637	0.011
High	42.9				
Normal	61.1				

novel and special promising predictive factors were urgent needed to improve the prognosis of GC.

The development of cancer was often accompanied with several complicated changes of homeostatic system [12]. Coagulation abnormalities had been observed in GC patient. D-dimer was a stable final product of fibrin degradation. Fibrin degradation products such as fragments E and D were released into the bloodstream after fibrin clots being digested by plasmin. Finally, D-dimers were formed steady with 2 covalently bound D-domains by factor XIII [13]. D-dimer had been used as a specific marker which reflected the enhanced secondary fibrinolysis in fibrinolytic process. D-dimer had displayed high sensitivity for diagnosis of VTE and its related adverse outcomes [14]. Recent studies had revealed that D-dimer level could be used to determine tumor stage, disease progression, response to treatment, or oncological outcome [15, 16]. In pancreatic cancer, D-dimer had proved to play important roles in tumor spread and distant metastases and showed better correlation with tumor stage and unfavorable prognosis in patients [17]. Takeshi *et al*. [18] found up-regulation of plasma D-dimer level indicated poor oncological outcome in metastasis and total survival rate in musculoskeletal sarcoma patients. In current study, we found plasma D-dimer level of GC patients were higher than those of healthy peoples, which may suggest high D-dimer level may promote the progression of GC. To assess the prognostic value of plasma D-dimer level in GC, we analyzed the expression of proteins in GC patients with GC by using the OS. Kaplan-Meier curves proved that patients with high D-dimer level had poorer OS than those with normal D-dimer level. In addition, D-dimer level was identified to be an independent predictor of survival of GC patients via Multivariate Cox regression analysis. Determination of plasma D-dimer level may help to identify high-risk GC patients.

Many investigators demonstrated that lymphatic metastasis was an independent risk factor for GC and lymph node metastasis was an increasingly important criterion in judging the prognosis of GC [19]. Reducing lymphatic metastasis had promising impacts on the treatment of GC [20]. In our study, lymphatic metastasis in different clinicopathological characteristic was analyzed, and D-dimer level was identified as an independently relative factor of lymphatic metastasis in GC patients. Those results may indicate that D-dimer may affect

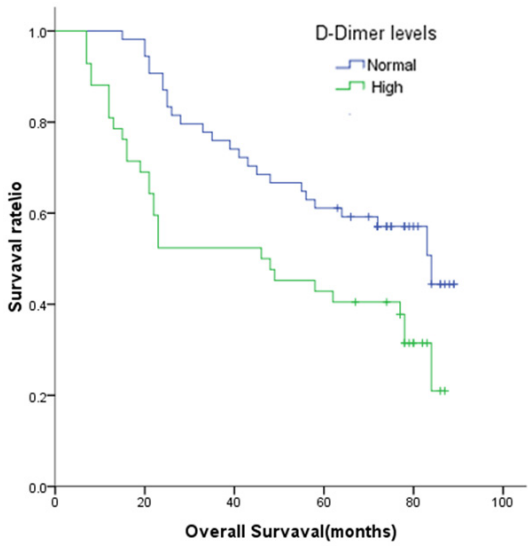

Figure 2. Survival curve for GC patients according to D-Dimer levels (High or Normal).

lymphatic metastasis and relate with lymphangiogenesis of GC, and homeostatic system may relate with lymphatic system in progression of GC.

Our study had some shortcomings such as small size, single-center study and retrospective design, better designed large scale and multicenter studies should be conducted to confirm our results. In conclusion, the higher plasma D-dimer level was associated with lymphatic metastasis. Plasma D-dimer level was an independent prognostic factor, and higher D-dimer level may indicate worse outcome in GC patients.

Disclosure of conflict of interest

None.

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