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Correlation between plasma D-Dimer levels and Clinicopathological Characteristics of Cervical Cancer

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Abstract: To investigate the Correlation between plasma D-Dimer levels and Clinicopathological Characteristics of Cervical Cancer. because Plasma D-Dimer levels were determined using immunoturbidimetry in the three groups of cervical cancer, IN and healthy persons, because and detect the distinction among them. To analyzed the relationship among plasma D-Dimer levels and the invasion, metastasize of cervical cancer further. Plasma D-Dimer levels of the group of cervical cancer had significantly higher than those of CIN and healthy control groups ($\chi2=13.5436$, $P < 0.005$;$\chi2=15.7082$, $P < 0.005$,respectively),and then plasma D-Dimer levels had not statistically significant differences compared CIN with healthy control group($\chi2=0.0016$, $P>0.05$). Plasma D-Dimer levels was positively rank-correlated with tumor diameter, lymph node metastasis, numbers and proportion of metastatic nodes($P<0.05$),but no correlation with clinical stage, histological grades, infiltrative depth of muscle, tumor embolus of vessel, latero-uterus infiltration and encroachment of corpus uteri($P>0.05$). Plasma D-Dimer levels were much higher in patients with cervical cancer than those of nontumors, which was distinctively associated with tumor diameter, lymphnode metastasis ($P<0.05$). It is suggested that plasma D-Dimer levels could be play an important role in the invasion and transfer process of cervical cancer.

1. Introduction

Global cervical cancer is the second most common malignancy among women, recent progress in the treatment of late recurrence transfer cases and slow, invasive tumor cells to tumor recurrence and distant metastasis in situ malignant biological behavior is crucial, such as at the molecular level of the invasion and metastasis and prognosis of malignant tumor research become a hot spot in the research of oncology field. D-dimer (DD) is a specific product of the degradation of cross-linked

fibrin in plasmin. The increased level of DD indicates the enhancement of secondary fibrinolytic activity in vivo, and it is a sensitive marker of hypercoagulable state and hyperfibrinolytic activity. Recent studies have shown [1-2] that elevated plasma DD levels in patients with a variety of malignant solid tumors are associated with tumor metastasis, progression and poor prognosis. The relationship and role of DD in the invasion and metastasis of cervical cancer are rarely reported at home and abroad. This study aims to preliminarily explore the correlation between the two and provide a new targeted therapy direction for the prevention and treatment of cervical cancer progression.

2. Materials and Methods

2.1. The research Object

Patients with primary cervical cancer who were hospitalized in Handan Central Hospital from January 2014 to November 2015 were selected. The inclusion criteria were as follows: (1) None of them had received surgical treatment, chemoradiotherapy before the experiment, and all of them were confirmed by pathology; ② Other malignant tumors were excluded; ③ Exclude heart, brain, liver, kidney, thyroid and other important organ diseases and diabetes; (4) Excluding diseases of the blood system and thrombotic diseases, did not use any drugs that affect platelet and coagulation function, such as anticoagulation, thrombolytic and antiplatelet drugs; ⑤ No infectious diseases in the past one month; ⑥ nearly half a year did not take contraceptives and other sex hormone drugs; ⑦ Complete clinicopathological data. A total of 70 patients with cervical cancer were enrolled in the study. Sixty-two patients with cervical intraepithelial neoplasia treated in our hospital during the same period and 80 healthy subjects were selected as the control group. The age of cervical cancer patients ranged from 27 to 74 years, with an average age of 51.67 years. Patients with cervical intraepithelial neoplasia ranged in age from 21 to 71 years (mean, 45.42 years). The health check-up participants ranged from 24 to 71 years old, with an average age of 42.85 years. All pathological sections were reviewed by two senior pathologists. According to the International Federation of Obstetrics and Gynecology (FIGO 2009) clinical staging criteria for cervical cancer, 38 cases were stage ⅰ, 24 cases were stage ⅱ, 7 cases were stage ⅲ, and 1 case was stage ⅳ. High, medium and low differentiation (G1, G2 and G3) were observed in 8 cases, 43 cases and 19 cases, respectively. There were 64 cases of squamous cell carcinoma, 4 cases of adenocarcinoma and 2 cases of small cell carcinoma. The total number of lymph nodes dissected in each case was >10, and the number of positive lymph nodes was 0-6. The age of the three groups were tested for normality and homogeneity of variance analysis, and the results showed that the age data of the three groups were normally distributed, and the difference was not statistically significant (P>0.05), which was comparable.

2.2. Instruments and Reagents

The CA-7000 automatic coagulation analyzer was purchased from Sysmex, and the assay reagent was purchased from Beckman (Immunoturbidimetry).

2.3. Experimental Methods

2ml fasting venous blood was collected from the three groups in the morning and placed in

sodium citrate anticoagulant tube, mixed for 5-10min, centrifuged at 3000r/min for 10min, and serum was separated for detection. The testing process is carried out in strict accordance with the kit operating instructions. The normal reference range for D-dimer is <0.55mg/L.

2.4. Statistical Method

SPSS 21.0 software was used for statistical analysis. Kolmogorov-smirnov and Levene tests were used to perform normality test (P<0.05) and homogeneity of variance analysis (P<0.05) for D-dimer data of the three groups, which showed that the data were not normally distributed and the variance was not homogeneity. Therefore, the non-parametric test (Kruskal-Wallis H test) was used for the comparison of multiple samples, and the Nemenyi test was used for the pairwise comparison of multiple independent samples. Spearman rank correlation test was used for correlation analysis.

3. The Results

(1)The values of DD in cervical cancer, cervical intraepithelial neoplasia and healthy control group were tested for normality and ANOVA. The results showed that the values of DD in the three groups were all P=0.000, indicating that the data were not normally distributed. The homogeneity test of variance showed that P<0.05, indicating that the three groups of data were not homogeneous. Therefore, non-parametric test was used for the experimental data. Measurement data with non-normal distribution were expressed as median (M), 25th percentile and 75th percentile (P25, P75).

(2) The expression of DD in cervical cancer, cervical intraepithelial neoplasia and healthy control group was statistically significant ($\chi2$=19.548, P< 0.05). See table 1.

(3)The results of pairwise comparison of DD values among the three experimental groups showed that the cervical cancer group was statistically significant compared with the cervical intraepithelial neoplasia group and the healthy control group ($\chi2$=13.5436, P<0.005; $\chi2$=15.7082, P<0.005). The DD values of cervical cancer group were higher than those of cervical intraepithelial neoplasia group and healthy control group. There was no significant difference in DD between the cervical intraepithelial neoplasia group and the healthy control group ($\chi2$=0.0016, P> 0.05). Are shown in table 2.

(4)Results of correlation analysis between DD and clinicopathological features of cervical cancer: the value of DD was positively correlated with tumor diameter, lymph node metastasis, number and proportion of metastasis (P< 0.05), but not related to clinical stage, histological grade, depth of invasion, paracyclastic invasion, vascular tumor thrombin, intrauterine invasion (P> 0.05). See table 3.

Table 1. The result of D-Dimer levels of the serum in the three groups

Group	Number	D-Dimer		χ^2	P
		M(P_{25},P_{75})	rank mean		
CC	70	0.310(0.198,0.490)	133.01	19.548	0.000
CIN	62	0.190(0.138,0.323)	93.67		
HP	80	0.205(0.113,0.315)	93.25		

P< 0.05 was statistically significant; The unit of DD measurement in the table is "mg/L".

P< 0.05 was considered statistically significant;The unit of the DD is" mg/L".

Table 2. The result of comparison between the experimental groups

Group	χ^2	P
CC VS CIN	13.5436	< 0.005
CIN VS HP	0.0016	0.995
CC VS HP	15.7082	< 0.005

P<0.05Statistically significant
P< 0.05 was considered statistically significant

Table 3. The result of correlative analysis between Clinicopathological Characteristics and D-Dimer

Clinicopathological Characteristic	r_s	P
clinical stage	0.214	0.076
histological grades	0.066	0.585
infiltrative depth of muscle	0.232	0.053
tumor diameter	0.373	0.001
lymph node metastasis	0.327	0.006
numbers of metastatic nodes	0.364	0.001
proportion of metastatic nodes	0.345	0.003
latero-uterus infiltration	0.205	0.089
tumor embolus of vessel	0.071	0.560
encroachment of corpus uteri	0.009	0.938

Rs is rank correlation coefficient, P< 0.05 was statistically significant
rs was rank correlation coefficients;P< 0.05 was considered statistically significant

4. Discuss

DD is a specific degradation product of fibrin monomer cross-linked by activator XIIIa and hydrolyzed by plasmin. As long as there is active thrombosis and fibrinolytic activity in the blood vessels, DD will increase, reflecting the body's hypercoagulable state and secondary fibrinolytic activity. Patients with malignant tumors are often accompanied by abnormal coagulation function. High levels of DD are not only indicative of hypercoagulability in vivo, but also closely related to the invasion ability of tumor cells. Recent studies have shown that DD levels are significantly increased in esophageal cancer [3], lung cancer [4], ovarian cancer [5], non-Hodgkin's lymphoma [6] and other tumors, and are significantly correlated with invasion and metastasis and poor prognosis.

In this study, there were statistically significant differences in DD values among the three experimental groups ($\chi 2=19.548$, P< 0.05). Pairwise comparison of DD in cervical cancer group was significantly higher than that in cervical intraepithelial neoplasia group and healthy control group (P< 0.05), similar to the study results of Yu Xiaojie et al. [7], but there was no significant difference between the cervical intraepithelial neoplasia group and the healthy control group (P> 0.05). The invasion and metastasis of malignant tumors are accomplished through the expansion and growth of the primary lesion, neovascularization and lymphangiogenesis, extracellular matrix degradation, and the movement, adhesion and localization of tumor cells in the vasculature. Most of the tumor cells that enter the circulatory system are killed by the body's immune system in the process of transport, but a few tumor cells with high metastatic potential survive by forming tumor thrombus. Circulating tumor cells release various procoagulant substances, activate platelets and coagulation cascades, and fibrin is formed. Under the action of thrombin, hyperfibrinolysis is secondary through the internal activation pathway, and plasma DD is increased. Fibrin and platelets and interaction between tumor cells in the circulation of blood platelet - tumor cells and fibrin "[1] tumor emboli survive, while fibrous protein to form a protective layer in the surface of tumor cells, isolation tumor antigen, and lead to tumor cell immune escape, make tumor cell adhesion, fixed value of vascular endothelial and distant metastasis. It is speculated that the circulating tumor cells of patients with cervical cancer form microscopic tumor thrombectomy under the coating of platelets and fibrin. Through the above mechanism and in coordination with other carcinogenic factors, it plays an important role in the malignant biological behavior of cervical cancer invasion and metastasis. Elevated plasma DD indicates active hematogenous metastasis of cervical malignant tumor cells, and the tumor has a faster growth rate [8]. There was no significant difference in plasma DD between the cervical intraepithelial neoplasia group and the healthy control group. CIN lesions were located above the basement membrane of the cervical epithelial tissue, and the tumor cells did not enter the blood, which had no effect on the blood coagulation system, so there was no significant change in plasma DD. It is suggested that DD level has no application value in the diagnosis of cervical intraepithelial neoplasia.

Lymphatic metastasis is an important metastasis route of cervical cancer and an independent predictor of the prognosis of cervical cancer [9]. This study showed that plasma DD level was significantly positively correlated with tumor diameter, pelvic lymph node metastasis, the number and proportion of metastasis (P< 0.05), indicating that the larger the cervical tumor diameter, pelvic lymph node metastasis, the more number and proportion of lymph node metastasis, the higher the plasma DD level, but not related to clinical stage, histological grade, depth of invasion, vascular invasion and uterine invasion (P> 0.05). Hu Yi et al. [10] detected and analyzed the plasma DD level of 166 cases of cervical squamous cell carcinoma, and the group with pelvic lymph node metastasis was higher than the group without metastasis, which supported the results of

this study. A study on esophageal cancer [11] also showed that plasma DD was closely related to TNM stage and lymph node metastasis. It has been reported in the literature [1,4] that the increased plasma DD level is significantly correlated with the poor prognosis of lung cancer and other malignant tumors. Clinical studies have confirmed that anticoagulant therapy is more beneficial to control tumor metastasis and improve the survival of patients with non-small cell lung cancer [12]. Studies have shown that both lymph node metastasis and plasma DD level have predictive value for the prognosis of cervical cancer. However, the specific mechanism through which they play a role and whether plasma DD can be used as a reliable prognostic predictor of cervical cancer need to be further studied with a larger sample size. The results of plasma DD for different clinical stages may be related to the sample size or sample sampling error, which needs to be further verified in later studies. The larger the cervical tumor diameter, the larger the tumor volume, the more serious the tissue destruction. A large number of tissue factors are released into the blood to activate the exogenous coagulation pathway. The tumor cells also release a large number of procoagulant factors to further activate the coagulation cascade.

In conclusion, the plasma DD level of cervical cancer was significantly increased, and increased with tumor diameter, lymph node metastasis, and the number and proportion of lymph node metastases. It is speculated that plasma DD level has certain clinical value in the diagnosis and prognosis prediction of cervical cancer. Previous studies [13] have shown that low molecular weight heparin calcium combined with chemotherapy has obvious survival advantage in the treatment of non-small cell lung cancer. Detection of plasma DD level in newly diagnosed cervical cancer patients provides a new direction for making treatment decisions and predicting prognosis.

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Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Conflict of Interest

The author states that this article has no conflict of interest.

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