RESEARCH ARTICLE

A New D-dimer Cutoff Value to Improve the Exclusion of Deep Vein Thrombosis in Cancer Patients

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Abstract

Objective: To find a more appropriate alternative to D-dimer cutoff value for the diagnosis of deep vein thrombosis (DVT) in cancer patients. Methods: A total of 711 cancer patients with symptoms suspicious of DVT were included in the study. D-dimer levels were assessed using ELISA. All patients were subjected to imaging procedures. Results: Among 711 patients with cancer, 466 (65.5%) were females and 245 (34.5%) were males, with an average age of 57.3± 13.23 years. The mean age in the DVT group was significantly higher than in the non-DVT group ($P<0.05$). The D-dimer levels of the DVT group were significantly higher than those of the non-DVT group ($P<0.05$). The incidence rate of DVT varied significantly according to cancer type ($P<0.05$). Increasing age and lung cancer were significantly correlated with D-dimer levels ($P<0.05$), and a one-year increase in age was associated with a 14.28 ng/ml increase in the D-dimer value. The optimal cutoff point for D-dimer was found to be 981 ng/ml, with a sensitivity of 86.4%, specificity of 79.4%, and accuracy of 82.6%. If the D-dimer cutoff point was set to 981ng/ml, the specificity would increase from 61.8% to 85.5% without loss of sensitivity in patients aged 40 years or younger. In patients aged more than 40 years, the new cutoff almost doubled the specificity with slightly reduced sensitivity. Conclusion: In cancer patients, a new cutoff value of 981 ng/ml effectively improved the exclusion of DVT, especially for patients aged more than 40 years.

Keywords: D-dimer - cutoff - deep vein thrombosis - cancer

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Introduction

Deep vein thrombosis (DVT) refers to the formation of a blood clot in the venous system, predominantly in the legs. DVT is one of the most serious disease, which can be life-threatening if left untreated. It has an annual incidence estimated at 160 per 100 000 (Cardiovascular Disease Educational and Research Trust et al., 2006). It is widely accepted that patients with cancer have a four- to six-fold increased risk of vein thrombosis as compared to those without cancer and they account for approximately 20% of all vein thrombosis events (MacLellan et al., 2012). Moreover, cancer patients with DVT had a 2.2-fold increase in mortality compared with matched patients without DVT (Khorana et al., 2007). Thus, early diagnosis is crucial to proper management and therapeutic intervention for cancer patients with DVT.

Patients with DVT usually have minimal or atypical signs and symptoms including pain, redness, tenderness, swelling, warmth, and distention of surface veins. However, about half of people with DVT have no symptoms at all. The diagnosis of DVT is therefore difficult and not reliable when depending on clinical presentation alone. Other diagnostic tests for evaluation of suspected DVT include D-dimer assays, duplex ultrasound, magnetic resonance venography, contrast-enhanced CT, and, less commonly, contrast venography (Douketis et al., 1995). Generally, the patient with D-dimer above the cutoff value is subjected to imaging procedures. Thus, D-dimer measurement helps patients avoid unnecessary imaging tests.

D-dimer is the primary degradation product of cross-linked fibrin. A positive D-dimer test usually indicates blood clots or thrombosis in the body, which is associated with the severity of DVT. A standard cutoff of 500 ng/ml is used in routine clinical practice, with values above that level considered positive. Recently, several studies suggest that the customary D-dimer cutoff is inappropriate under special conditions, such as the elderly, and pregnancy (Antonelli et al., 2007; Harper et al., 2007; Kovac et al., 2010). However, the optimal D-dimer cutoff in cancer patients has not yet been reported. Is the conventional cutoff value suitable for cancer patients? Is there a more appropriate alternative to D-dimer cutoff value? All these remain to be resolved in the study.

Materials and Methods

A total of 711 cancer patients with symptoms suspicious of DVT, were recruited from the Tianjin Medical University Cancer Institute and Hospital from

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Table 1. Clinical and Biological Characteristics of Patients in DVT and Non-DVT Groups

Variables		N	DVT	Non-DVT	*P*
		711	317	394	0
Age(years)		57.29± 13.23	60.10±11.25	55.03±14.25	
Gender	M	245	106	139	0.63
	F	466	211	255	
BMI (kg/m^2)			27.92±3.08	27.90±3.12	0.94
Smoking	N	407	171	236	0.13
	Y	304	146	158	
D-dimer (ng/ml)		977.34 (1640.90)	2192.26(2900.89)	486.57(588.38)	0
Sites of cancer					
	Soft Tissue	100	27	73	0
	Lung	56	42	14	
	Esophagus	23	14	9	
	Breast	127	83	44	
	Ovary	176	69	107	
	Stomach	57	14	43	
	Colon	46	15	31	
	Thyroid	59	18	41	
	Liver	25	12	13	
	Other	42	23	19	

Table 2. A Multiple Linear Regression Analysis of Patients' Characteristics and D-dimer

Variables	B	SD	t	*P*
Age (years)	14.28	5.93	2.41	0.02
Gender	43.99	196.58	0.22	0.82
BMI (kg/m^2)	14.73	23.77	0.62	0.54
Smoking	167.6	152.71	1.1	0.27
Sites of cancer				
Lung	1121.81	465.54	2.41	0.02
Other				>0.05

January 2012 to December 2012. Inclusion criteria were as follows: (1) Cancer diagnosis based on histopathology; (2) Signs and symptoms of DVT according to the Wells prediction rule (Qaseem et al., 2007). Exclusion criteria were as follows: (1) History of proximal DVT; (2) Use of anticoagulant or heparin therapy prior to administration. Samples of venous blood were obtained within 12h after hospital admission. D-dimer levels were detected using ELISA (VIDAS, BioMerieux, France). All patients were then subjected to ultrasound scanning. If the duplex ultrasound had not provided a clear diagnosis, venography would have been performed. The study was specifically approved by the Hospital's Ethical Committee. All examinations have been performed in accordance with the ethical standards of Helsinki Declaration, and all participants were fully informed about the nature and purpose of the study.

Continuous variables with a normal distribution (age, BMI) were expressed as mean ±standard deviation (Std). The remaining continuous variables with a skewed distribution (D-dimer) were expressed as median (interquartile ranges). The intergroup differences were tested using the Mann-Whitney U test, the $\chi 2$ test, or the Kruskal-Wallis analysis of variance where appropriate. The relationship between patients' characteristics and D-dimer levels were analyzed by multiple linear regression. The Receiver Operating Characteristic (ROC) curve was constructed to evaluate the diagnostic performance and to define the optimal cutoff point of D-dimer. A P-value less than 0.05 was considered statistically significant. Statistical analysis was performed using the PASW Statistics 18 software.

Results

Among 711 patients, 466 (65.5%) were females and 245 (34.5%) were males, with an average age of 57.29± 13.23 years. There was no significant difference in the D-dimer levels between females and males (P=0.51). All cancer patients were divided into two groups according to diagnostic criteria of DVT. The mean age in the DVT group was significantly higher than in the non-DVT group (P<0.05). The D-dimer levels of the DVT group were significantly higher than those of the non-DVT group (P<0.05). The incidence rate of DVT varied significantly according to cancer type (P<0.05). However, no statistical difference was found between DVT and non-DVT groups in other parameters, including gender, body mass index (BMI), and history of smoking. Clinical and biological characteristics of patients are summarizes in Table 1.

A multiple linear regression analysis was carried out to model the relationship between patients' characteristics and D-dimer levels (Table 2). Increasing age and lung cancer were significantly correlated with D-dimer levels (P<0.05), other parameters were not statistically significantly related to D-dimer, including gender, BMI, history of smoking, other sites of cancer.

Statistical analysis indicated that the mean age was significantly higher in the DVT group than in the non-DVT group. The multiple linear regression analysis showed that age was positively correlated with D-dimer levels (P=0.02), and a one year increase in age was associated with a 14.28 ng/ml increase in the D-dimer levels. Figure 1 shows the upward trend of D-dimer levels in different age groups.

In order to determine the best D-dimer threshold that maximized the sum of sensitivity and specificity, the ROC curve of 711 cancer patients was constructed (Figure 2). The optimal cutoff was found to be 981 ng/ml, with

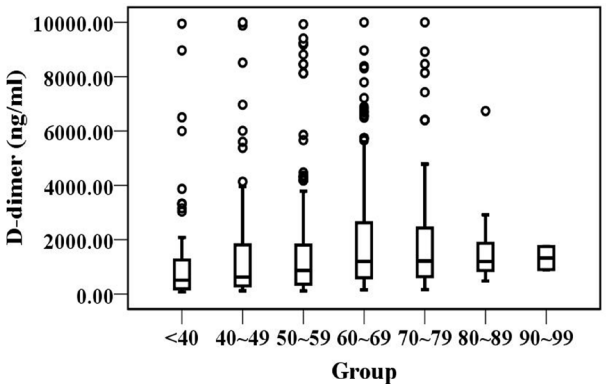

Figure 1. The D-dimer Levels of Patients in Different Age Groups

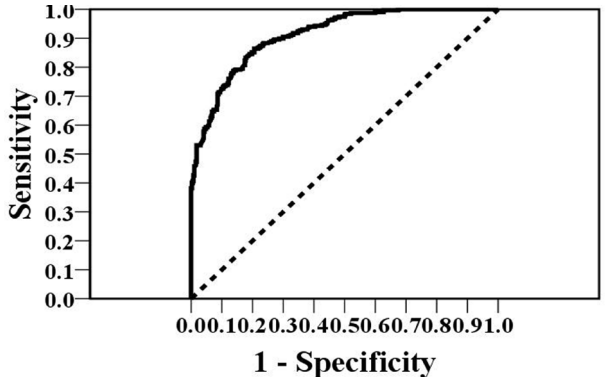

Figure 2. The ROC Curve Analysis of D-dimer Values in Cancer Patients. The area under the curve (AUC) is 0.911 with 95% confidence interval 0.89~0.93

sensitivity of 86.44%, specificity of 79.44%, and accuracy of 82.56% (Table 3).

In our cohort, D-dimer significantly increased with patients' age. Thus, the sensitivity, specificity, positive predictive values, negative predictive values, and accuracy were analyzed in different age groups. If the D-dimer cutoff point was set to 981ng/ml, the specificity would increase from 61.82% to 85.45% without loss of sensitivity in patients aged 40 years or younger. Moreover, the new cutoff was more suitable for cancer patients who were more than 40 years old, and it almost doubled the specificity with slightly reduced sensitivity (Table 4).

Table 3. Comparison of Customary and New D-dimer Cutoff Values

Cutoff (ng/ml)	Sensitivity (%)	Specificity (%)	Positive predictive values (%)	Negative predictive values (%)	Accuracy (%)
>500	97.47	50.76	61.43	92.59	71.59
>981	86.44	79.44	77.18	87.92	82.56

Table 4. The Evaluation of New Cutoff Value in Different Age Groups

Age (years)	Cutoff (ng/ml)	Sensitivity (%)	Specificity (%)	Positive predictive values(%)	Negative predictive values (%)	Accuracy (%)
≤40	>500	94.12	61.82	43.24	97.14	69.44
	>981	94.12	85.45	66.67	97.92	87.50
>40	>500	97.67	48.97	62.88	95.95	71.83
	>981	86.00	84.90	61.90	97.83	86.57

Discussion

Venous thromboembolism (VTE) includes the development of either deep vein thrombosis (DVT) or pulmonary embolism (PE). Symptomatic and asymptomatic VTE can occur in a substantional number of patients with cancer. Almost half of the patients may have additional risk factors for thrombosis (Aleem et al., 2012). The interrelationship between cancer and haemostasis is well illustrated. Cancer-associated DVT has significant clinical and economic consequences, including increased morbidity resulting from hospitalization and anticoagulation use, bleeding complications, increased risk of recurrent DVT and cancer treatment delays (Khorana et al., 2009). From a clinical point of view, a venous thrombotic event may impact the chemotherapy routine and potential therapeutic approaches. Moreover, the hemostatic system itself could contribute to tumor cell survival, disease progression, and metastatic cancer (Kuderer et al., 2009). Thus, all patients with cancer should be assessed for DVT risk on admission.

Chew et al. (2006) retrospectively evaluated the impact of venous thromboembolism on 235,149 cancer patients in the California Cancer Registry and found that the incidence of venous thromboembolism varied with cancer type, and the highest incidence of venous thromboembolism occurred during the first year of follow-up among cases with metastatic-stage pancreatic, stomach, bladder, uterine, renal, and lung cancer. Khorana et al. (2007) conducted a retrospective cohort study which included 1,824,316 hospitalizations. They found that venous thromboembolism was an increasingly frequent complication of hospitalization in cancer patients. Patients with black ethnicity, specific sites of cancer, or those receiving chemotherapy were at a disproportionately higher risk. In their study, 4.1% cancer patients were diagnosed with venous thromboembolism. Sites of cancer with the highest rates of venous thromboembolism included pancreas, kidney, ovary, lung, and stomach. Among hematologic malignancies, myeloma, non-Hodgkin lymphoma, and Hodgkin disease had the highest rates of venous thromboembolism. In our study, sites of cancer with the highest rates of DVT were breast, ovary, lung, soft tissue, thyroid, colon, esophagus, stomach, liver, and other, respectively. Because of the relatively low incidence rates of pancreatic, bladder, uterine, renal, hematologic malignancies in our country, they were classified as "other" group. The relationship of them and DVT should be further studied in larger sample sizes.

D-dimer is a fibrin degradation product, and it is also a marker of DVT. Because DVT is closely related to cancer development and progression, routine blood tests are imperative for cancer patients. Recently, plasma D-dimer could be detected by several diagnostic methods and novel kits. While, many of them reveal a higher sensitivity but a trend towards lower specificity. In order to find the best D-dimer cutoff for clinical practice, the ROC curve of cancer patients was analyzed. The alternative cutoff of 981ng/ml maximized the sum of sensitivity and

specificity. Although the sensitivity of the new cutoff in our study was lower than the value accepted today, it still reached high sensitivity. Moreover, the new cutoff help patients reduce the need for further imaging studies. Raviv et al. (2012) demonstrated that it may be safe and cost effective to use a D-dimer value of 900 ng/ml rather than the customary 500 ng/ml for patients suspected with pulmonary embolism (PE).

It is reported that a D-dimer value below the conventional cutoff (500 ng/ml) combined with clinical probability could rule out the PE in about 30% suspected patients (Perrier et al., 2005; van et al., 2006; Righini et al., 2008). The D-dimer value increases with age. However, the diagnostic specificity decreases with it, which reduce the clinical usefulness in the elderly (Sohne et al., 2006). Righini et al (2000) found that the customary D-dimer test could rule out PE in 60% of patients aged<40 years, but in only 5% of patients aged>80. Douma et al (2012) developed a new D-dimer cut-off point in 2818 consecutive outpatients with suspected DVT. The new cut-off value was defined as (patient's age×10) μg/l in patients aged more than 50 years.

When analyzing the sensitivity and specificity of the new D-dimer cutoff value (981 ng/ml) in different age groups, we found that the specificity would increase from 61.82% to 85.45% without loss of sensitivity in patients aged 40 years or younger. Moreover, the new cutoff was more suitable for patients aged more than 40 years, which almost doubled the specificity and preserved high sensitivity. The new cutoff minimize radiation exposure by eliminating unnecessary scans, thus the slightly reduced sensitivity could be neglected. Similarly, other reports identified that base lines of D-dimer were higher in the elderly (Smith-Bindman et al., 2009; Duriseti et al., 2010; Kabrhel et al., 2010).

In conclusion, a new cutoff of 981ng/ml effectively improved the exclusion of DVT in cancer patients, especially for patients aged more than 40 years.

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