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Original Article

Usefulness of D-dimer Assay to Confirm the Course of Overt Venous Thromboembolism (VTE) in Cancer Patients

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Venous thromboembolism (VTE) is a serious complication in patients with cancer. In this population, the presence of thrombi is often assessed at cancer diagnosis by measuring D-dimer levels, which have high sensitivity but low specificity for identifying VTE at this clinical time point. However, the usefulness of D-dimer measurement during anticoagulation therapy has not been fully established, despite its widespread use. In this retrospective observational study, we investigated whether D-dimer measurement during anticoagulation therapy in cancer patients could predict overt VTE at follow-up. The study included patients who underwent D-dimer testing and contrast-enhanced computed tomography between 30 and 100 days after initiation of anticoagulation therapy. Eighty-two patients were included: 60 with cancer and 22 without. The diagnostic performance of D-dimer for overt VTE was as follows: sensitivity, 85.7%; specificity, 87.2%; positive predictive value, 78.3%; and negative predictive value, 89.2%. These findings suggest that D-dimer measurement at follow-up has high sensitivity and specificity for overt VTE in cancer patients and may aid in assessing thrombotic status. Clinically, if anticoagulation therapy is continued until D-dimer levels become negative, the absence of overt VTE could be inferred without additional invasive testing.

Key words: D-dimer, venous thromboembolism, cancer

Venous thromboembolism (VTE) is a common and serious complication in patients with cancer [1]. It is the second leading cause of death in patients with cancer undergoing outpatient chemotherapy, and its diagnosis and treatment are expected to become increasingly important as cancer incidence rises, survival improves, and therapies associated with elevated thrombotic risk are used more widely [2]. In the diagnosis of VTE, a D-dimer assay is widely used, as are the Wells score and medical imaging.

Since D-dimer is released when a thrombus dissolves, an elevated D-dimer level indicates the presence of one or more thrombi [3]. However, D-dimer levels are also known to increase with cancer, age, inflammation, trauma, and surgery [4]. For this reason, D-dimer testing has high sensitivity but low specificity for diagnosing thrombosis. However, because of its high negative predictive value, a low D-dimer level is often used to exclude thrombosis [4-6]. In addition, an elevated

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D-dimer level one month after discontinuation of anticoagulation therapy is frequently associated with recurrent VTE, supporting the need for continued anticoagulation in such cases [7-9]. On the other hand, the clinical value of D-dimer measurement during anticoagulation therapy is less well established, despite its widespread use in patients with VTE, including those with cancer. In cancer patients, D-dimer specificity for diagnosing VTE is particularly low because malignancy itself can elevate D-dimer levels [10].

In the present study, we therefore investigated whether D-dimer measurement during anticoagulation therapy in cancer patients could predict overt VTE at follow-up, despite the low D-dimer specificity in this population. The same investigation was also conducted in noncancer patients.

Methods

Subjects and design. This was a retrospective observational study of patients diagnosed with overt VTE by contrast-enhanced computed tomography (CT) and treated with anticoagulation therapy between January 2016 and June 2019. The present study included patients who underwent D-dimer assays and CT scans between 30 and 100 days after the initiation of anticoagulation therapy. The subjects were divided into two groups: a cancer patient group and noncancer patient group. Each group was further divided into a D-dimer-negative group and a D-dimer-positive group (Fig. 1). D-dimer was measured via the latex immunoturbidimetric assay, and a D-dimer level of 1.0 μg/ml or higher was considered positive. Cancer patients were defined as those with a prior diagnosis of cancer, whereas noncancer patients were defined as those with no known cancer and no obvious cancer lesions on contrast-enhanced CT scans of the chest to pelvis. This study was conducted in accordance with the principles of the Declaration of Helsinki and local regulations. The study protocol was reviewed and approved by the Ethics Committee of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital (approval no. 1908-038). In this study, written informed consent was not required due to the retrospective nature of the research. Participants were informed about the study and given the opportunity to opt out if they did not wish to be included.

Diagnosis of overt VTE. In this study, overt VTE was defined as a thrombus floating in the vessel on contrast-enhanced CT, with contrast medium surrounding it and extending continuously along the vessel's long axis. A thrombus adherent to the vessel wall and lacking surrounding contrast medium (mural thrombus) was considered an organized thrombus and classified as negative for overt VTE.

Risk factors for VTE. Patient information related to VTE risk factors was collected from all patients [11]. We confirmed this information based on the medical records. Pregnancies were defined as current or past month. Collagen disease was defined as having a diagnosis in a medical institution. Bedridden was defined as difficulty walking independently.

Statistical analysis. Continuous variables were expressed as the means ± standard deviations or medians (interquartile ranges), and binary variables were expressed as quantities (%). The Mann–Whitney *U* test was used for continuous variables, and Fisher's exact test was used for binary variables. The sensitivity and specificity of D-dimer at follow-up in patients with overt

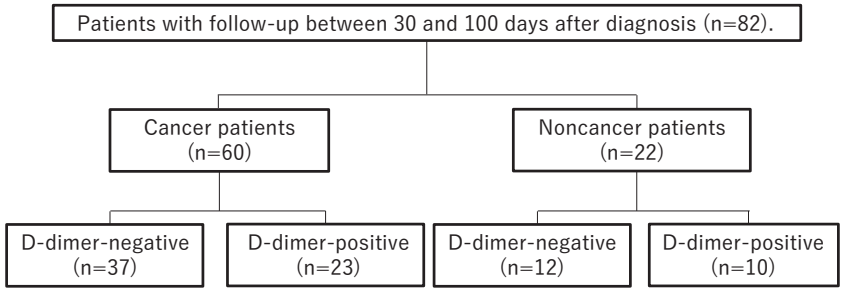

Fig. 1 Flowchart of patient selection. A D-dimer level of 1.0 μg/ml or higher was considered positive. D-Dimer levels were measured at follow-up.
CT, computed tomography; VTE, venous thromboembolism.

VTE were examined. The statistical analysis software R version 4.3.1 was used.

Results

Patient backgrounds. A total of 82 patients were included in the study: 60 with cancer and 22 without. Patient characteristics are shown in Table 1. Noncancer patients were significantly older and included a higher proportion of bedridden patients. D-dimer measurement at follow-up revealed that 23 of the 60 cancer patients and 10 of the 22 noncancer patients were D-dimer positive (Fig. 1). The D-dimer levels at the time of diagnosis and at follow-up are shown in Fig. 2 and 3. The patient background of each group is shown in Tables 2 and 3. Among cancer patients, the D-dimer-positive group had a smaller proportion of males. The number of patients with overt VTE was greater in the D-dimer-positive group than in the D-dimer-negative group, and the time from the date of diagnosis of overt VTE to follow-up imaging was significantly shorter in the D-dimer positive group. There was no difference in the distribution of VTE-provoking risk factors among noncancer patients. Table 4 provides additional details on the presence of metastasis and the types of cancer among the cancer patients. In the present study, lung cancer was more frequently observed in the D-dimer positive group.

Table 1 Patient characteristics

	Cancer n = 60	Noncancer n = 22	*P*-value
Male	24	8	0.80
Age, year	63 ± 11	68 ± 14	0.042
BMI, kg/m^2	21.7 ± 4.0	23.9 ± 9.7	0.091
Surgery within 1 month	19	11	0.20
Pregnancy	0	2	0.070
Bedridden	1	6	0.0012
Collagen disease	0	1	0.27
Steroid use	1	3	0.057
History of VTE	3	1	

BMI, body mass index; VTE, venous thromboembolism.

Thrombi distributions at follow-up. At follow-up, no new thrombi distributions were identified in sites other than those present at diagnosis.

Diagnostic performance of D-dimer for overt VTE. The diagnostic performance of D-dimer for overt VTE is shown in Fig. 4 and 5. In cancer patients, the sensitivity was 85.7%, the specificity was 87.2%, the positive predictive value was 78.3%, and the negative predictive value was 89.2% (Fig. 4). In the noncancer patient group, the sensitivity was 87.5%, the specificity was

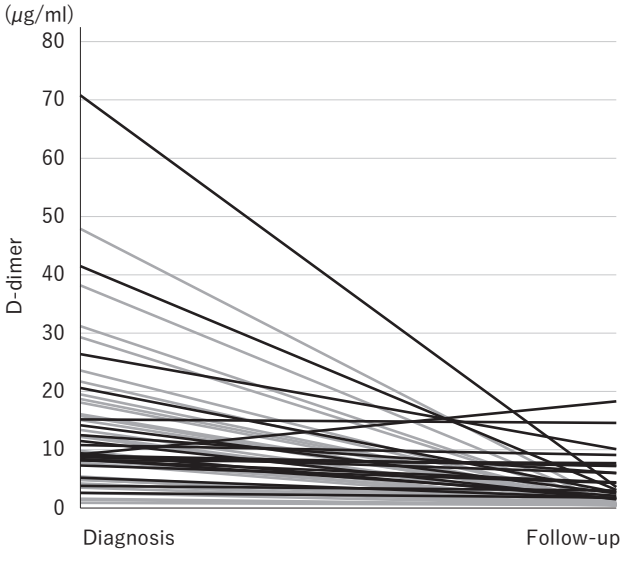

Fig. 2 D-dimer levels at the time of diagnosis and at follow-up in the cancer group. The D-dimer positive group at follow-up is shown in black, and the negative group in gray.

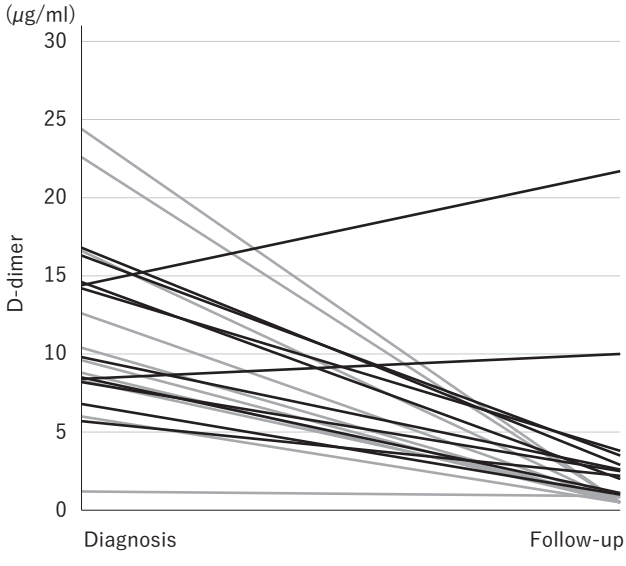

Fig. 3 D-dimer levels at the time of diagnosis and at follow-up in the noncancer group. The D-dimer positive group at follow-up is shown in black, and the negative group in gray.

Table 2 Background of cancer patients

	D-dimer-negative n=37	D-dimer-positive n=23	*P*-value
Male	18 (48.6)	6 (26.1)	0.11
Age, year	64 ± 11	63 ± 11	0.90
BMI, kg/m^2	21.9 ± 4.0	21.5 ± 4.0	0.80
Chemotherapy	14 (37.8)	8 (34.8)	
Surgery within 1 month	14 (37.8)	5 (21.7)	0.26
Pregnancy	0 (0)	0 (0)	
Bedridden	1 (2.7)	0 (0)	
Collagen disease	0 (0)	0 (0)	
Steroid use	1 (2.7)	0 (0)	
History of VTE	1 (2.7)	2 (8.7)	0.55
Overt VTE	3 (8.1)	18 (78.3)	<0.001
D-dimer at follow-up, μg/ml	0.5 (0.5～0.6)	3.6 (2.3～7.3)	<0.001
Until image follow-up elapsed time, days	73.0 ± 20.6	52.7 ± 20.6	<0.001

BMI, body mass index; VTE, venous thromboembolism.

Table 3 Background of noncancer patients

	D-dimer-negative n=12	D-dimer-positive n=10	*P*-value
Male	3 (25)	5 (50)	0.38
Age, year	63 ± 17	71 ± 11	0.24
BMI, kg/m^2	23.1 ± 3.5	25.6 ± 12.5	0.87
Surgery within 1 month	6 (50)	5 (50)	
Pregnancy	2 (16.7)	0 (0)	0.48
Bedridden	2 (16.7)	4 (40)	0.35
Collagen disease	1 (8.3)	0 (0)	
Steroid use	1 (8.3)	2 (20)	0.57
History of VTE	1 (8.3)	0 (0)	
Overt VTE	1 (8.3)	7 (70)	0.0062
D-dimer at follow-up, μg/ml	0.5 (0.5～0.5)	2.75 (2.2～4.2)	<0.001
Until image follow-up elapsed time, days	85.0 ± 11.2	62.5 ± 21.9	0.011

BMI, body mass index; VTE, venous thromboembolism.

Table 4 Presence of metastasis and types of cancer among cancer patients

	D-dimer-negative n=37	D-dimer-positive n=23	*P*-value
Metastasis	14 (37.8)	6 (26.1)	0.41
Types of cancer			
Head and Neck	5 (13.5)	0	0.15
Lung	4 (10.8)	9 (39.1)	0.021
Thymic	1 (2.7)	0	
Esophageal	5 (13.5)	1 (4.3)	0.39
Pancreatic	1 (2.7)	1 (4.3)	
Colorectal	1 (2.7)	2 (8.7)	0.55
Peritoneal	2 (5.4)	0	0.52
Genitourinary	1 (2.7)	0	
Uterine and ovarian	8 (21.6)	5 (21.7)	
Hematologic	2 (5.4)	3 (13.0)	0.36
Skin	2 (5.4)	1 (4.3)	
Unknown primary origin	5 (13.5)	1 (4.3)	0.39

78.6%, the positive predictive value was 70.0%, and the negative predictive value was 91.7% (Fig. 5). In addition, the ROC curve revealed an area under the curve (AUC) of 0.750 for patients with cancer (Fig. 6).

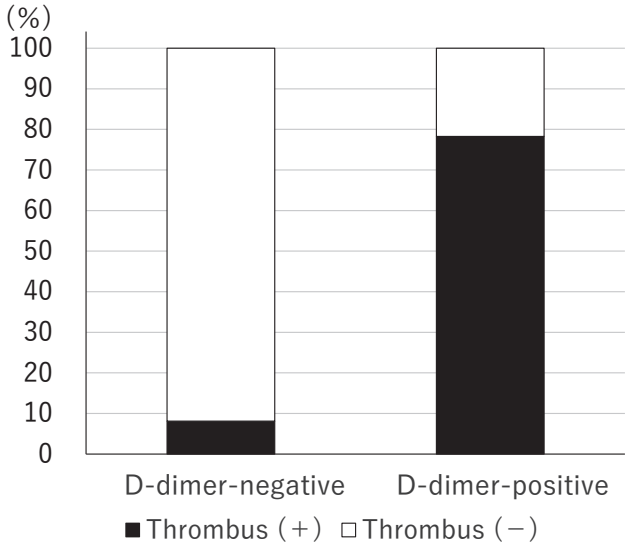

Fig. 4 Ratio of residual thrombus at follow-up in the cancer group. The negative predictive value was 89.2%, the positive predictive value was 78.3%, the sensitivity was 85.7%, and the specificity was 87.2%.

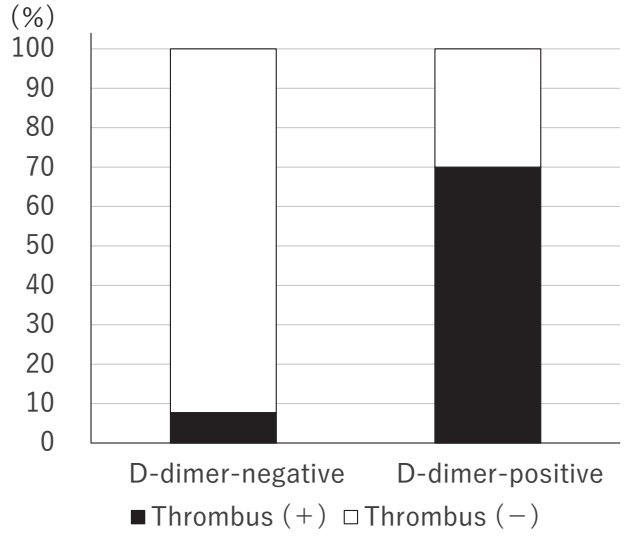

Fig. 5 Ratio of residual thrombus at follow-up in the noncancer group. The negative predictive value was 91.7%, the positive predictive value was 70.0%, the sensitivity was 87.5%, and the specificity was 78.6%.

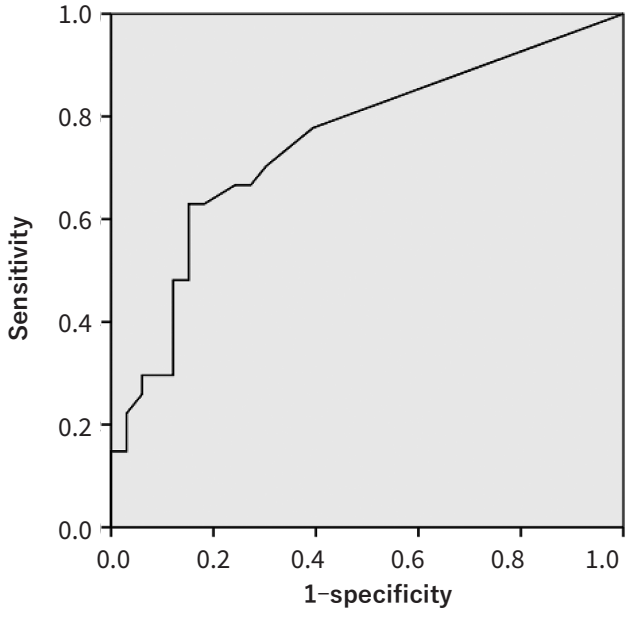

Fig. 6 The area under the ROC curve (AUC) for D-dimer at follow-up in cancer patients was 0.750.

Discussion

The results of this study suggest that D-dimer measurement at follow-up has high sensitivity and high specificity for predicting VTE in both cancer and noncancer patients. The time from diagnosis to follow-up imaging was shorter in the D-dimer-positive group than in the D-dimer-negative group.

Previous studies have shown several clinical uses of D-dimer testing in thrombosis: a) excluding VTE [12], b) predicting a first VTE [13], c) assessing the risk of recurrent VTE [14], and d) determining the optimal duration of anticoagulation therapy [7, 8]. In these studies, D-dimer levels were measured either at the time of diagnosis or after at least 3 months of anticoagulation therapy, and none demonstrated a clinical role for D-dimer measurement during the first 3 months of anticoagulation therapy. The present study is thus the first to show that D-dimer measurement during the first 3 months of anticoagulation may allow confirmation of thrombus status without the need for contrast-enhanced CT scans.

In general, D-dimer measurement at the time of VTE diagnosis has high sensitivity for thrombi but low specificity, and is used to rule out thrombosis [12]. This study revealed that D-dimer at follow-up in cancer

patients has increased specificity, compared with that at diagnosis, as shown in a previous report [15]. The reason for the increased specificity of D-dimer at follow-up may be the absence of microthrombi caused by cancer, age, inflammation, trauma, and surgery due to anticoagulation therapy. Even in the absence of overt thrombi on CT, the presence of microthrombi may increase D-dimer levels, resulting in reduced specificity for identifying overt thrombi at diagnosis. At follow-up, the microthrombi may be dissolved by anticoagulation therapy, which increases the specificity of D-dimer for the treatment of overt thrombi at follow-up. The fact that the follow-up study was conducted in a population with thrombi, unlike at diagnosis, may also have contributed to the increase in specificity.

In this study, the time from diagnosis to follow-up imaging was shorter in the D-dimer-positive group than in the D-dimer-negative group, both among cancer and noncancer patients. It is known that appropriate anticoagulation therapy for VTE results in resolution of the thrombus early in fresh VTE, and most thrombus resolution occurs within 3 months [16]. Therefore, an earlier follow-up time resulted in more positive D-dimer results.

We set the duration of follow-up between 30 and 100 days after anticoagulation therapy. Early in the initiation of anticoagulation, D-dimer levels can increase due to thrombolysis, even if the incidence of thrombus decreases. Therefore, we excluded cases in which D-dimer was confirmed within 30 days because we considered this to be an inappropriate time frame for confirming the presence of a thrombus by D-dimer. We also excluded cases in which follow-up was performed at 100 days or more, since discontinuation of anticoagulation therapy was usually considered by this time point.

We defined a mural thrombus as an organized thrombus and distinguished it from a fresh thrombus. Previous reports have shown that fresh VTE is fixed to the vein wall due to inflammatory changes and then regresses or remains as a partially organized thrombus (residual VT) [16, 17]. It is inconclusive whether residual VT is a risk factor for recurrent VTE [3]. Therefore, we distinguished organized thrombi from fresh thrombi in this study.

Limitations. This was a single-center, retrospective study with a small number of patients. In addition, organized thrombi were classified as non-thrombotic, which may have underestimated the incidence of thrombi, and noncancer patients were not categorized as having provoked or unprovoked VTE.

In conclusion, D-dimer measurement at follow-up between 30 and 100 days after anticoagulation therapy has high sensitivity and specificity for overt VTE in cancer patients and may aid in assessing thrombotic status. If anticoagulation therapy is continued until D-dimer becomes negative in actual clinical practice, it can be assumed that there is no overt VTE without new invasive testing for less than 100 days. D-dimer measurement at follow-up has high sensitivity and specificity for overt VTE in cancer patients and may aid in assessing thrombotic status. Clinically, if the D-dimer level becomes negative within the first 100 days of anticoagulation therapy, clinicians may infer the absence of overt VTE without additional invasive testing.

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