Original Contribution

Kurume Medical Journal, 60, 47-51, 2013

D-dimer Value more than 3.6 μg/ml is Highly Possible Existence Deep Vein Thrombosis

SHINICHI NATA, SHINICHI HIROMATSU, YUSUKE SHINTANI, TOMOKAZU OHNO, HIDETOSHI AKASHI AND HIROYUKI TANAKA

Department of Surgery, Kurume University School of Medicine, Kurume 830-0011, Japan

Received 8 August 2012, accepted 19 August 2013
J-STAGE advance publication 27 January 2014

Edited by TAKASHI OKAMURA

Summary: Objective: The present study aimed to establish whether a more optimal cutoff value for D-dimer testing could definitively rule out acute deep vein thrombosis (DVT).
Methods: Between April 2009 and March 2010, 190 referral patients suspected to have DVT were assessed by the D-dimer assay. Additionally, ultrasonography (US) and computed tomography (CT) imaging were performed to detect thrombosis.
Results: DVT was identified in 47 patients (24%). The average D-dimer level in patients with DVT was 17.6±22.4 μg/ml, and was significantly lower (p=0.035),] at 2.7±4.2 μg/ml, in those without DVT. On the basis of receiver operating curve analysis, the specificity of the D-dimer for diagnosing DVT increased from 40% to 78.3%, and its sensitivity reached 93.8%, when the cutoff value for the assay was set at 3.6 μg/ml.
Conclusions: D-dimer value over 3.6 μg/ml was highly prognostic for DVT.

Key words Acute deep vein thrombosis, D-dimer, pulmonary embolism, venous thromboembolism

INTRODUCTION

Acute deep vein thrombosis (DVT) is a common disease that has potentially serious complications, such as pulmonary embolism (PE) in the acute phase, and post-phlebitis syndrome (PTS) in the chronic phase. Early diagnosis of venous thromboembolism (VTE) and timely initiation of anticoagulant therapy could suppress PE or PTS [1].

Accurate diagnosis of DVT minimizes the risk of thromboembolic complications on the one hand, and allows patients without thrombosis to avoid the risks of anticoagulant therapy on the other. However, ultrasound imaging of the whole body is not a feasible approach for immediate and accurate diagnosis of DVT. In contrast, the D-dimer assay is considered useful for the diagnosis of thrombosis, because a negative test result (a value below a predefined cutoff) rules out the likelihood of this condition [2]. D-dimer is a fibrin degradation product, a small protein fragment present in the blood after a thrombus is degraded by plasmin, named for the 2 crosslinked D fragments of the fibrinogen protein [3]. Testing of D-dimer concentration from blood was introduced in the 1990s, and has become a useful screening tool for patients suspected to have thromboembolic disease. Although the strategies for implementation of this assay appear to be efficient, easy to apply, and safe in clinical research settings, whether the use of this assay can be extrapolated to daily clinical practice is not known.

The cutoff value for the latex D-dimer assay is 1.0 μg/ml; at this value, the sensitivity of the test is high, but its specificity is low. While a negative result practically rules out thrombosis, a positive result may indicate thrombosis, but does not rule out other potential causes, including pregnancy, cancer, infection, in-

Corresponding Author: Shinichi Hiromatsu, Department of Surgery, Kurume University School of Medicine, 67 Asahi-machi, Kurume-shi, Fukuoka-ken 830-0011, Japan. Tel: +81-942-35-3311 Fax: +81-942-35-8967 E-mail address: kaeru@med.kurume-u.ac.jp

Abbreviations: DVT, acute deep vein thrombosis; PTS, post-phlebitis syndrome; VTE, venous thromboembolism.

flammation, recent trauma, extensive burns or bruises, ischemic heart disease, stroke, peripheral artery disease, ruptured aneurysm, aortic dissection, acute arterial thrombosis, or surgery.

Elevated D-dimer does not specifically indicate the presence of DVT because D-dimer can be elevated for various reasons [4]. Therefore, at present additional examinations such as US or CT are necessary for the diagnosis of DVT. With regard to the diagnosis of DVT, US is more useful than computed tomography CT for lower limb veins, whereas CT is more useful than US for intrathoracic and intraperitoneal veins, and both examination methods are often required to make a definitive diagnosis of DVT. US requires 15–20 minutes per person, and CT, in many instances, cannot be implemented quickly in university hospitals. Moreover, administration of a contrast agent is essential for diagnosis with these methods. All of these factors are limitations of these diagnostic methods. Many outpatients have been referred for leg swelling, and therefore, the use of both US and CT would require a considerable amount of time for diagnosis of DVT. For patients with DVT, however, starting on anticoagulant therapy as soon as possible is very important for preventing the formation of a pulmonary embolism (PE); therefore, the time to diagnosis for outpatients should be reduced. In the present study, we measured D-dimer levels for use as a screening test for DVT and performed both US and CT in cases where the levels were abnormal. However, because the cutoff value for the D-dimer is $<$1.0 μg/ml, the negative predictive value is high, whereas the positive predictive value is low; moreover, in many instances, no DVT is present even though the D-dimer level may be abnormal. Therefore, even though the currently recognized D-dimer cut-off value (1.0) is used in screening, additional time is being spent in further tests, such as CT and US, to confirm DVT diagnosis; this interferes with the aim of reaching a prompt definitive diagnosis. To enhance the precision of testing using a D-dimer level, we believe that it is important to raise its cutoff value, thus reducing outpatient testing, and enabling the rapid diagnosis and treatment of DVT. In the present study, we measured D-dimer levels in all patients seeking consultation for leg swelling, performed US and CT, and tried to determine the extent to which the D-dimer cutoff value can be increased and still rule out DVT.

MATERIALS AND METHOD

Patients

Between April 2009 and March 2010, 190 referral patients with suspected DVT, including inpatients and outpatients (67 men and 133 women; mean age: 61.3 years; range 20–94 years), were prospectively evaluated at the Department of Surgery, Kurume University Hospital.

As the D-dimer assay result may be elevated in the absence of DVT in many situations, including pregnancy, malignancy, postoperatively, and in elderly people, individuals in these categories were not considered in this study, but all other referred patients were included, regardless of other concomitant conditions. Further exclusion criteria included a history of DVT, anticoagulant treatment for more than 24 h before referral, and chronic DVT of $>$1 month's duration.

D-dimer assay

For D-dimer testing, a rapid automated quantitative latex-based immuno-agglutination assay was used, which can generate results within 15 min.

A positive test result was defined as a D-dimer level of $>$1.0 μg/ml.

Clinical evaluation

We wanted to prospectively evaluate the cutoff values of the D-dimer assay to indicate the existence of DVT. Thus, regardless of the D-dimer level, all patients were examined to determine whether thrombosis was present, by using multidetector-row CT imaging of the pulmonary artery, inferior vena cava, and pelvic veins, as well as ultrasonography with a of 7.5 MHz transducer for the lower limbs.

CT image interpretation

Two radiologists evaluated CT venography images by consensus. The presence of acute DVT and the degree of luminal occlusion were evaluated on initial CT scans. In acute DVT, a large filling defect in the vein and ipsilateral muscle enlargement was noted. In chronic deep vein thrombosis, the vein was of the normal diameter, but with a filling defect [5]. Thus, when the CT findings were indicative of chronic deep vein thrombosis, patients were classified as "no fresh thrombus."

Ultrasonography of lower limbs

Ultrasonography was performed by one experienced vascular surgeon who was blinded to the result of D-dimer testing. Initially, each patient was examined in the supine position, when the deep veins, from common femoral vein to the proximal segment of Hunter's canal, were evaluated for compressibility. Secondly, each patient was examined in the prone position, when the deep veins, from the popliteal vein to

the calf veins, were evaluated for compressibility.

In patients with no history of DVT, the diagnosis of DVT was established if the vein was non-compressible and when there was no evidence of spontaneous flow on color Doppler imaging. In patients with a history of DVT, the diagnosis of DVT was not established if the non-compressible vein was of normal diameter and there was evidence of some color flow in the lumen.

This protocol was approved by the Ethics Review Board on Medical Research of Kurume University School of Medicine. This study was not supported by any corporate entity.

Statistical analysis

Receiver operating characteristic (ROC) curve analysis, which is a graphical plot of the sensitivity, or true positive rate, vs. the false positive rate for a binary classifier system with variation of its discrimination threshold, was used to assess different cutoff values for the D-dimer assay.

RESULTS

The study group included 112 inpatients (58.9%) and 78 outpatients (41.1%). Fifty-three patients were in a preoperative period and 12 in a postoperative period. The baseline characteristics of the study population are shown in Table 1. The largest number of inpatients had been referred from Gynecology, while 60 patients had malignant disease.

The prevalence of DVT was 24% (47 patients). Of 47 patients with diagnosed DVT on the basis of clinical imaging studies, 24 (51%) were found to have pulmonary embolism (PE); these included both symptomatic and asymptomatic patients.

TABLE 1.
Charactristics of referral patients suspected DVT (Term: April 2009–April 2010)

Patients, N (%)		**Referring Department, N (%)**	
190 patients	mean age; 61.3 years		
male	67 (35.2)	Other hospitals	75 (39.5)
outpatients	102 (53.6)	Gynecology	47 (24.7)
postoperation	12 (6.3)	Cardiovascular Medicine	14 (7.4)
malignancy	60 (31.6)	Neurosurgery	10 (5.3)
trauma	10 (6.3)	Gastrointestinal Surgery	8 (4.2)
hypertension	73 (38.2)	Orthopedics	7 (3.7)
diabetes mellitus	27 (14.1)	Haematology	6 (3.2)
dyslipidemia	33 (17.2)	Critical Care Unit	4 (2.1)
hyperuricemia	10 (5.2)	Gastrointestinal Medicine	4 (2.1)
current smoking	24 (12.6)	Neuropsychiatry	4 (2.1)
atrial fibrillation	5 (2.6)	Others	11 (5.1)

TABLE 2.
Cutoff level of >3.6 μg/ml, sensitivity and NPV is 93.6%

D-dimer (μg/ml)	Sensitivity (%)	Specificity (%)	Positive (N)		Negative (N)	
			True	False	True	False
0.5	100	16.1	47	120	23	0
1.0	100	40.6	47	85	58	0
1.5	100	62.3	47	54	89	0
2.0	100	67.9	47	46	97	0
2.5	100	72.1	47	40	103	0
3.0	95.7	75.6	45	35	108	2
3.5	93.6	77.6	44	32	111	3
4.0	89.5	79.1	43	30	113	5

The mean D-dimer level was significantly higher in patients with DVT than in those without (17.6±22.4 μg/ml vs. 2.7±4.2 μg/ml; $p<0.05$) (Table 2).

We also investigated other cutoff values, via.0.5, 1.0, 1.5, 2.0, 2.5, 3.0 and 3.5 μg/ml. The number of true- and false-positive results and true- and false-negative results for these discriminant values are shown in Table 2.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the D-dimer test were calculated for different cutoff values. The sensitivity and NPV for the diagnosis of DVT reached 100% when using a cutoff value of 0.5–2.5 μg/ml (Fig. 1). ROC curve analysis indicated that the specificity of the D-dimer test for DVT was increased from 40% to78.3%, while its sensitivity was 93.8%, when the cutoff value for the test was set at 3.6 μg/ml (Table 2). The area under the curve was 0.91, which indicated excellent model discrimination (Fig. 2). The Youden index was used to estimate the cutoff value from the receiver operating characteristics (ROC) curve; the cutoff value was found to be 3.6. At values $\geq$ 3.6, there is a strong suspicion of DVT, and therefore, it would be considered necessary to promptly perform imaging to reach a definitive diagnosis. Conversely, at values $<$ 3.6, we believe that US and CT testing can be omitted.

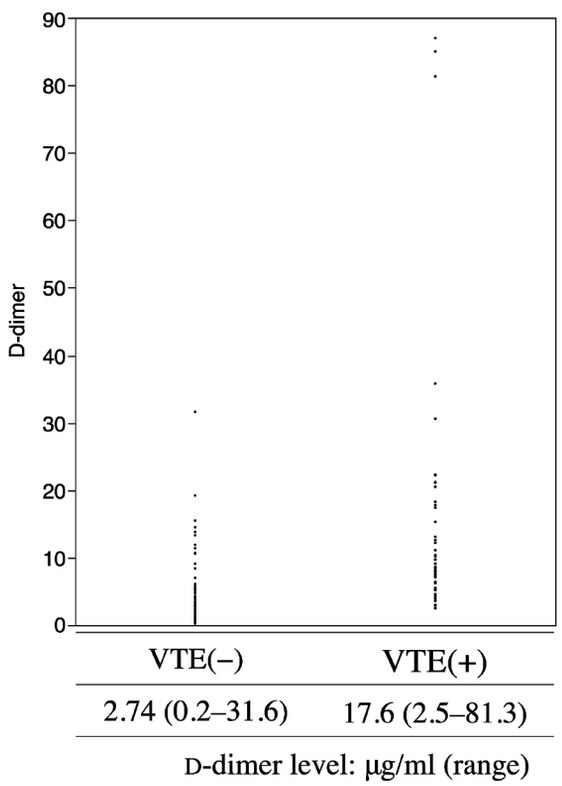

Fig. 1. Positive test result was difinited as a level >1.0 μg/ml, but no patient have DVT $<$ 2.5 μg/ml.

DISCUSSION

Because the D-dimer has been known to increase in various non-thrombotic conditions, further testing, typically by US or CT, are necessary to make a definitive diagnosis. Thus, because of the high sensitivity of D-dimer testing, the main objective of this test is to rule out thromboembolic disease. For this reason, this study investigated whether different cutoff points, other than the standard reference value of 1.0 μg/ml, for the latex agglutination D-dimer assay could reduce the need for venous ultrasound scanning, and thus could rapidly exclude a diagnosis of DVT. On the basis of ROC curve analysis, we found that the specificity of D-dimer testing for DVT was increased from 40% to78.3%, while sensitivity was 93.8%, when the cutoff value of D-dimer was set at 3.6μg/ml.

The relationship between sensitivity and specificity for various D-dimer tests available for venous thromboembolism (VTE) is as follows: latex-based assay (sensitivity: 92–96%; specificity: 46–53%), whole blood assay (sensitivity: 82–86%; specificity: 70–72%), and enzyme-linked immunosorbent assay (ELISA) (sensitivity: 86–96%; specificity: 44–62%) [6]. Thus, the latex-based quantitative assay showed significantly higher sensitivity than that of the other D-dimer methods, and hence, the latex agglutination D-dimer assay was used as the method of choice in this study.

Previously, the use of a specific D-dimer level with a clinical probability score has been reported to be

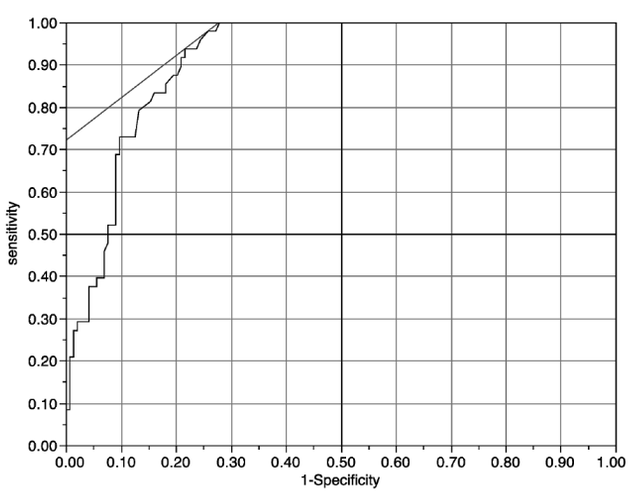

Fig. 2. The area under the curve was 0.91, which indicated that this test excellently discriminates D-dimer levels. The resultant cutoff value estimated using the Youden index was 3.6.

most effective in individuals with a low risk of DVT [7]. The risk factors for DVT in a clinical probability score are active cancer, paralysis, recently bedridden, tenderness of leg, entire leg swelling, calf swelling, pitting edema, and collateral superficial veins. One point is given for every positive finding, and 2 points are subtracted if an alternative diagnosis as likely as DVT is found. The score is calculated as the sum in each patient. A score of 0 indicates low risk, moderate risk is 1 to 2 points, and high risk is 3 or more points [8]. However, even though all referral patients in our study were of more than moderate risk, when the cutoff level of the D-dimer test was set at < 3.6 μg/ml, the assay had a sensitivity of 93.8%.

By using this cutoff, additional tests could have been avoided in 53 patients, who otherwise would have been false positives. Thus, elevation of the cutoff point can reduce the requirement for imaging tests for the exclusion of DVT by over 39%. In future, we intend to optimize the cutoff point for use in different categories of patients, such as those with malignancy, advanced age, post-surgery, etc.

Study limitations

This study involved a small sample size, and the resulting ROC curve was not smooth; therefore, accumulation of a larger amount of data is necessary for further analysis. Moreover, this study did not include any follow-up examinations to confirm the validity of the findings.

Conclusion

In conclusion, DVT is a serious disease causing pulmonary embolism, and hospitalized patients, in particular, have a high incidence of VTE; immediate diagnosis is crucial to facilitate timely commencement of treatment. Because the D-dimer test has a high negative predictive value, it allows exclusion of a diagnosis, but because of its high sensitivity and low specificity, it tends to yield false-positive results. This creates an additional burden in clinical imaging and can result in unnecessary anticoagulant therapy being given in the interim until an accurate diagnosis is obtained. Our study has shown that regardless of the patient's medical background, a D-dimer value greater than 3.6 μg/ml was highly prognostic for DVT.

REFERENCES

1. Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C et al. Evaluation of D-dimer in the diagnosis of suspected deep vein thrombosis. N Engl J Med 2003; 349:1227-1235.
2. Tan M, van Rooden CJ, Westerbeek RE, and Huisman MV. Diagnostic management of clinically suspected acute deep vein thrombosis. Br J Haematol 2009; 146:347-360.
3. Wells PS, Brill-Edwards P, Stevens P, Panju A, Patel A et al. A novel and rapid whole-blood assay for D-dimer in patients with clinically suspected deep vein thrombosis. Circulation 1995; 91:2184-2187.
4. Rigini M. Is it worth diagnosing and treating distal deep vein thrombosis? No. J Thromb Haemost 2007; 5:55-59.
5. Thomas SM, Goodacre SW, Sampsom FC, and van Beek EJ. Diagnotic value of CT for deep vein thrombosis: result of a systematic review and meta-analysis. Clin Radiol 2008; 63:299-304.
6. Di Nisio M, Squizzato A, Rutjes AW, Buller HR, Zwinderman AH et al. Diagnostic accuracy D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Heamost 2007; 5:296-304.
7. Yamaki T, Nozaki M, Sakurai H, Kikuchi Y, Soejima K et al. Combined use of pretest clinical probability score and latex aggutiation D-dimer testing for excluding acute deep vein thrombosis. J Vasc Surg 2009; 50:1099-1105.
8. Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M et al. Values of assessment of pretest probability of deep vein thrombosis in clinical management. *Lancet* 1997; 350:1795-1798.