Usefulness of a semiquantitative D-dimer test for the exclusion of deep venous thrombosis in outpatients

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The D-dimer test is used commonly in diagnostic strategies to reduce the need for ultrasonography in patients suspected of having deep venous thrombosis. We studied several clinical and laboratory variables that might limit the accuracy of a semiquantitative D-dimer test.

In this retrospective cohort study, 704 outpatients suspected of having deep venous thrombosis underwent a semiquantitative D-dimer test and ultrasonography. The performance of the D-dimer test was calculated in patients using anticoagulants (n=61), patients with previous thrombosis (n=127), and patients with malignancy (n=47), including 39 patients with more than one of these characteristics. The 508 remaining patients were considered to be the reference group.

A total of 254 patients (36%) had evidence of deep venous thrombosis. The D-dimer test had a sensitivity of 99% (174/176; 95% confidence interval [CI]: 96% to 100%) and a negative predictive value of 98% (98/100; 95% CI: 93% to 100%) in the reference group. The sensitivity of the D-dimer test in patients using oral anticoagulants was 75% (6/8; 95% CI: 35% to 97%; p=0.01 compared with the reference group). Test sensitivity was 96% (51/53; 95% CI: 87% to 100%) in patients with previous thrombosis, and 100% (29/29; 95% CI: 88% to 100%) in patients with cancer. However, 553 (79%) of all patients, including 43 of the cancer patients (91%), had an abnormal D-dimer test.

The semiquantitative D-dimer test in this study has a high sensitivity and negative predictive value in the exclusion of deep venous thrombosis, except perhaps among patients using oral anticoagulants. D-dimer tests in patients with cancer and in patients over 70 years old may not be worthwhile, as the tests are usually positive.
INTRODUCTION

Diagnosing deep venous thrombosis remains a challenge. The current diagnostic strategy usually consists of performing an ultrasonography of the femoral and popliteal veins; this test is repeated within 1 week if the initial examination was negative. It is safe not to anticoagulate patients with repeated normal ultrasonography (1;2). However, only 15% to 28% of patients suspected of having deep venous thrombosis actually have a thrombosis (1-4), and only 1% of patients with an initially normal ultrasonography develop deep venous thrombosis within 1 week (1;2). This has led to a search for a more efficient diagnostic strategy.

Plasma D-dimer levels, which measure the degradation products of cross-linked fibrin, are a valuable diagnostic test for the exclusion of deep venous thrombosis, and it is safe to withhold anticoagulant treatment in patients with a single negative ultrasonography and a negative D-dimer test (2). In addition, the combination of clinical assessment and a normal D-dimer test might also reduce the need for ultrasonography (5-7). There is a wide range, however, in the diagnostic accuracy of D-dimer tests. The first generation of rapid latex agglutination assays, which can be used in an emergency and bedside setting, has considerably lower sensitivity and negative predictive values than do the classic enzyme linked immunosorbent assays (ELISA) (8-10). Newer, fully-automatic, quantitative rapid latex and ELISA tests may be more accurate (8-10), but are more expensive and are not widely available.

A major disadvantage of measuring D-dimer levels is the frequent finding of a positive test; thus ultrasonography is still needed in the majority of patients suspected of having deep venous thrombosis. It might save both time and health care costs to avoid measuring D-dimer levels in patients with a high a priori likelihood of having a positive test. Therefore, we sought to determine the usefulness of a latex D-dimer test in excluding deep venous thrombosis, as well as to define clinical variables (such as use of oral anticoagulants, previous deep venous thrombosis, malignancy, age) or laboratory variables (renal function, complete blood count) that may affect its usefulness in a cohort of 704 outpatients suspected of having deep venous thrombosis.
PATIENTS AND METHODS

Patients and methods
We retrospectively identified 711 consecutive outpatients who had been suspected of having deep venous thrombosis from November 1994 to December 2000. We excluded 3 women who were pregnant and 4 patients who had a history of a previous deep venous thrombosis without documented recanalization. At initial presentation, all 704 remaining patients underwent ultrasonography of the symptomatic leg and a D-dimer test. The ultrasonography was repeated within 1 week if the first examination was negative for deep venous thrombosis. If the ultrasonography was positive for deep venous thrombosis, the patient was treated with anticoagulants. Data from a 6-month follow-up were obtained by visit or telephone contact with the patient or the general practitioner. We recorded patients’ sex, age, use of oral anticoagulants, previous venous thromboembolism, and active malignancy (defined as receiving any treatment for cancer or documented recurrent or metastatic disease). Patients without use of oral anticoagulants, previous venous thromboembolism, or malignancy were assigned as the reference group. We also recorded serum creatinine levels and complete blood counts at the time of presentation. The medical ethics committee of our hospital approved the study protocol.
Ultrasonography, using real-time B-mode with compression, was performed with a 7.5-MHz or a 5.0-MHz transducer. Two areas of the leg were examined: the common femoral vein at the inguinal ligament and the popliteal vein at the knee-joint line traced down to the point of the trifurcation of the calf veins. Veins were scanned in the transverse plane only. Lack of compressibility was the sole criterion for an abnormal result; a vein was considered fully compressible if no residual lumen was seen.
The D-dimer test used was the Minutex® (Biopool, Umeå , Sweden), used as a semiquantitative test by dilutions. We made a range of samples: the undiluted sample and the sample diluted with buffer 1 + 1, 1 + 3, and 1 + 7. The results are reported as negative, 1+, 2+, 3+, or 4+; 1+ or more was considered to be a positive test result. The tests were performed under standard conditions, using a magnifying glass with a lamp, a black background, and positive and negative control plasma samples.
Laboratory measurements of creatinine were performed by routine methods using an Integra 700 analyzer (Roche, Mannheim , Germany).
Complete blood count measurements were performed using Gen S (Beckman Coulter, Fullerton, California).

Statistics
We calculated the sensitivity, specificity, negative predictive value, and positive predictive value, including 95% confidence intervals, for the D-dimer test. The Fisher exact test (two-tailed) was used to compare proportions. The Cochran-Armitage test for trend was used to compare multiple proportions. For the analysis of the association between age and D-dimer levels, only patients without proven deep venous thrombosis (n=450) were included to eliminate bias from the higher prevalence of thrombosis in elderly patients. General linear regression models were used to compare continuous laboratory variables with categorical D-dimer results. SAS software (Cary, North Carolina) and Confidence Interval Analysis (London, United Kingdom) were used for all calculations.
RESULTS

The sample consisted of 704 patients with a mean (± SD) age of 59 ± 17 years. Of the 464 patients with an initial normal ultrasonography, 187 (40%) underwent a second ultrasonography. Deep venous thrombosis was diagnosed in 254 patients (36%), 240 of whom were diagnosed at presentation and 14 during 6-month follow-up (10 by the second ultrasonography within 1 week, 2 at 8 weeks, 1 at 3 months, and 1 at 5 months). All 14 of these patients had a positive D-dimer test at presentation. In the 464 patients with an initial normal ultrasonography, 6-month follow-up data were obtained by visit in 361 patients (78%) and by telephone contact in 103 patients (22%).

Performance of the D-dimer test

The sensitivity and negative predictive value of the D-dimer test were high (≥ 97%), particularly among patients who did not use anticoagulants or have a history of deep venous thrombosis or cancer (the reference group; Table). A deep venous thrombosis was detected by ultrasonograhy in 4 patients with a negative D-dimer test, of whom 2 used oral anticoagulants. Sensitivity was lower among the 61 patients using oral anticoagulants; of the 8 patients with deep venous thrombosis in this group, 2 had a negative D-dimer test. Anticoagulated patients were more likely to have a negative D-dimer test than was the reference group (46% [28/61] vs. 20% [100/508], p<0.001). Sensitivity and negative predictive value did not differ statistically among patients with a previous deep venous thrombosis (n = 127) when compared with the reference group (Table). Both of the 53 patients with thrombosis in this group who had a negative D-dimer test were using oral anticoagulants.

All 29 of the 47 patients with cancer who had a deep venous thrombosis had a positive D-dimer test; however, so did all but 4 of those without venous thrombosis, a specificity of only 22% (Table). Excluding the 7 patients with cancer who used oral anticoagulants did not significantly improve the specificity.

The positive predictive value of the D-dimer test increased with higher D-dimer concentrations (Figure 1). The prevalence of a positive D-dimer test increased with age (p<0.001; Figure 2). This association remained after adjustment for the use of oral anticoagulants, previous venous thromboembolism, cancer, and sex. Of the 156 patients aged ≥70 years, 79% (n =
123) had a positive D-dimer test, compared with 61% (180/294) of younger patients (p=0.0001).
There was a significant inverse correlation between D-dimer level and the hemoglobin concentration (R=-0.17, p=0.01). Of the 704 patients, data on hemoglobin concentration were available in 513 patients. The mean hemoglobin concentration in the 114 patients with a negative D-dimer test was 13.7 ± 1.4 g/dL, compared with 13.0 ± 1.9 g/dL in the 109 patients with a D-dimer level of 4+ (p=0.01). No correlation was found between D-dimer level and the leukocyte count (R=0.06, p=0.7), platelet count (R=0.05, p=0.9), or serum creatinine concentration (R=0.14, p=0.06).
**Table. Performance of the D-dimer Test in Patients Suspected of Deep Venous Thrombosis in Different Subgroups.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Reference Group * (n = 508)</th>
<th>Current Users of Oral Anticoagulants (n = 61)</th>
<th>Previous Venous Thromboembolism (n = 127)</th>
<th>Active Malignancy (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage (Number) or Mean ± SD</td>
<td>Percentage (Number) or Mean ± SD</td>
<td>Percentage (Number) or Mean ± SD</td>
<td>Percentage (Number) or Mean ± SD</td>
</tr>
<tr>
<td>Female sex</td>
<td>62 (437)</td>
<td>48 (29)</td>
<td>66 (84)</td>
<td>26 (12)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 ± 17</td>
<td>66 ± 15</td>
<td>58 ± 18</td>
<td>70 ± 12</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>36 (254)</td>
<td>13 (8)</td>
<td>42 (53)</td>
<td>62 (29)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>98 (250/254)</td>
<td>75 (6/8)</td>
<td>96 (51/53)</td>
<td>100 (29/29)</td>
</tr>
<tr>
<td>Specificity</td>
<td>33 (147/450)</td>
<td>49 (26/53)</td>
<td>45 (33/74)</td>
<td>22 (4/18)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>97 (147/151)</td>
<td>93 (26/28)</td>
<td>94 (33/35)</td>
<td>100 (4/4)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>45 (250/553)</td>
<td>18 (6/33)</td>
<td>55 (51/92)</td>
<td>67 (29/43)</td>
</tr>
<tr>
<td>Negative D-dimer test</td>
<td>21 (151)</td>
<td>46 (28)</td>
<td>28 (35)</td>
<td>9 (4)</td>
</tr>
</tbody>
</table>

* The reference group consists of patients without use of anticoagulants, previous thrombosis, or malignancy. Thirty-nine patients had more than one characteristic: 7 patients used oral anticoagulants and had a malignancy, 6 patients had previous venous thromboembolism and malignancy, and 26 patients used oral anticoagulants because of previous venous thromboembolism.
† Compared with reference group.
Figure 1. The positive predictive value of the D-dimer test according to D-dimer concentrations among outpatients suspected of having deep venous thrombosis.

![Positive Predictive Value of D-dimer Test](image1)

Figure 2. The prevalence of a positive D-dimer test according to age among outpatients suspected of having deep venous thrombosis, who did not have thrombosis after objective testing.

![Prevalence of Positive D-dimer Test by Age](image2)
DISCUSSION

To develop practical guidelines for the use of the D-dimer test in the management of patients suspected of having a deep venous thrombosis, we studied several clinical and laboratory variables that might affect the test's sensitivity or specificity. The rapid latex D-dimer assay that we used had excellent sensitivity and negative predictive value in outpatients, with the possible exception of those who used oral anticoagulants. The previously reported lower sensitivity and negative predictive value of this latex D-dimer assay may be the result of differences in the preanalytic and analytic process (8-10). For example, Janssen et al. performed this test on frozen and stored samples (8). A more common problem with the rapid latex D-dimer test is that its interpretation is influenced by inter- and intraobserver variability. In our laboratory, we used standard conditions and skilled technicians.

Patients using oral anticoagulants had a significantly lower sensitivity when compared with the reference group, although there were only 8 patients with a deep venous thrombosis in this group. This finding may be explained by a reduced capacity for thrombin generation and plasma D-dimer formation in patients taking oral anticoagulants (11;12). This is consistent with the significant increase in D-dimer levels after cessation of anticoagulant therapy (13) and the normalization of elevated D-dimer levels after beginning their use (14). Although larger studies are warranted to confirm our findings, we have decided not to use the D-dimer test to exclude deep venous thrombosis in patients using oral anticoagulants.

We also found that the D-dimer test can be used to exclude renewed thrombotic activity in patients with previous venous thrombosis, since the sensitivity and negative predictive value of the test were not different from the reference group. As an initial screening in patients with a history of deep venous thrombosis, the D-dimer test is probably more reliable than an ultrasonography when renewed thrombotic activity is suspected. Ultrasonography is less sensitive in the case of distal thrombosis (15) and has a high rate of false-positive results due to persisting venous abnormalities (16).

Only 4 of the 47 patients with malignancy had a negative D-dimer test. Elevated D-dimer levels in patients with malignancy might be the result of production of procoagulant proteases by tumor cells, leading to subclinical intravascular coagulation (17). However, local rather than systemic fibrin
formation may be a more likely cause of elevated D-dimer levels (18). In our opinion, the high prevalence of a positive D-dimer test result, along with its low specificity, suggest that the assay may not be useful as a screening test in patients with cancer. We did not, however, confirm the results of a study that reported the low negative predictive value of a D-dimer test in patients with cancer (19).

As has been reported (20-23), D-dimer tests were more likely to be positive with aging, perhaps due to a greater prevalence of comorbid conditions. Of the 156 patients older than 70 years who did not have deep venous thrombosis, almost 80% (n = 123) had a positive D-dimer test, compared with 61% (180/294) of patients younger than 70 years. Therefore, it is questionable whether the D-dimer test is useful in older patients. The cost-effectiveness of the D-dimer test in elderly patients should be determined. In addition, hemoglobin levels were indirectly proportional to D-dimer levels, perhaps because anemia often occurs in chronic inflammatory disorders that also may lead to increased D-dimer levels.

In conclusion, the sensitivity and negative predictive value of this rapid latex D-dimer assay for the exclusion of deep venous thrombosis are high. The D-dimer test has a good performance in patients with previous venous thromboembolism, but we do not recommend its use in patients using oral anticoagulants because of the reduced sensitivity of the test. D-dimer tests in patients with cancer and in patients over 70 years old may not be worthwhile, as the tests are usually positive.
REFERENCES


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Usefulness of the D-dimer


