Management of venous thromboembolism. Etiology, diagnosis, prognosis and treatment

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Citation for published version (APA):

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The clinical usefulness of D-dimer testing in cancer patients with suspected deep venous thrombosis

Marije ten Wolde, Roderik A. Kraaijenhagen, Martin H. Prins, Harry R. Büller

Little is known about the diagnostic value of a D-dimer test in cancer patients with clinically suspected deep venous thrombosis (DVT). We evaluated the clinical utility of a whole blood rapid D-dimer test (SimpliRED®) in cancer patients compared to non-cancer patients. In consecutive patients with suspected lower limb DVT a D-dimer test and ultrasonogram were performed. Cancer status was recorded at presentation. If the D-dimer test and ultrasonogram results were normal, DVT was considered absent. If the D-dimer result was abnormal, ultrasonography was repeated one week later. Anticoagulant therapy was only instituted in those patients with an abnormal ultrasonography result. All patients were followed-up for three months to record subsequent thromboembolic events. The accuracy of the D-dimer test was assessed, and the efficiency and safety of withholding additional ultrasonography in cancer patients with normal results on both D-dimer and ultrasonography was compared with non-cancer patients. A total of 1739 consecutive patients were studied of whom 217 suffered from cancer (12%). The negative predictive value of the D-dimer test was 97% in both cancer and non-cancer patients. In 63 of all 217 cancer patients (29%) the D-dimer and ultrasonography results were normal at referral, the diagnosis of DVT was therefore refuted and anticoagulant treatment was withheld. In these 63 patients one thromboembolic event occurred during follow-up (1.6% [95% CI: 0.04%-8.53%]). The negative predictive value of a whole blood D-dimer test in cancer patients seems as high as in non-cancer patients. In a substantial proportion of cancer patients the diagnosis can likely be refuted at referral, based on a normal D-dimer test and ultrasonogram results. Furthermore, it seems safe to withhold anticoagulant therapy in these patients.
Major improvements in the diagnostic management of patients with suspected deep venous thrombosis (DVT) have been achieved in the last decades. At first, the invasive procedure of venography was replaced by non-invasive tests, such as impedance plethysmography and compression ultrasonography. However, additional tests performed during a two-week period were required to rule out adequately the diagnosis. Subsequently, it was shown for compression ultrasonography, that the number of follow-up tests could be safely reduced to a single follow-up test with a one week interval. Recently, further improvements have been attained by the introduction of the D-dimer test. A D-dimer test represents the level of plasma D-dimers, which are degradation products of cross-linked fibrin. Numerous studies have investigated the accuracy of this test for the diagnosis of DVT. Since the sensitivity of the test is approximately 90% to 95%, and the specificity is only 55%, the test is best suited for ruling out DVT instead of proving the presence of the disease. However, the test cannot be used as a sole test to exclude DVT, since given a sensitivity of around 90% to 95%, still 5% to 10% of DVT’s will be missed. Therefore, the test should be used as an adjunct to other diagnostic methods. Management studies have shown that if a rapid D-dimer test is performed with ultrasonography in patients suspected of having DVT, the diagnosis can be ruled out if both test results are normal. Two large studies have recently demonstrated that, using this strategy, the follow-up ultrasonogram and thus an extra hospital visit can be safely omitted in more than 45% of patients. A follow-up ultrasonogram is necessary to exclude an extending (calf) vein thrombosis only in the remaining patients with an abnormal D-dimer test result at referral.

Although it is well documented that the D-dimer test is useful in the diagnostic work-up of patients with suspected DVT, it is thought that the D-dimer test is of less value in patients with underlying cancer. Since D-dimer levels are likely higher in cancer patients, more of these patients will have an abnormal test result making the test less efficient in this population to exclude DVT at referral. Lee and colleagues found that the D-dimer test is of less value in cancer patients because the negative predictive value (NPV) of the test in these patients is lower than in non-cancer patients, as a consequence of the higher prevalence of deep venous thrombosis among cancer patients. The high prevalence of DVT among cancer patients and the relatively low specificity of the D-dimer test in these patients will result in a decreased NPV. On the other hand, the expected lower NPV could theoretically be counterbalanced by an increased sensitivity. The aim of this paper is to examine the clinical utility of a whole blood D-dimer test in cancer patients suspected of having DVT compared to non-cancer patients suspected of having DVT. We assessed the sensitivity, specificity, and predictive values of the D-dimer test. In addition, the safety and efficiency of withholding repeat ultrasonography in patients with both a normal D-dimer test and ultrasonogram result were evaluated.
Patients and Methods
Consecutive outpatients with clinically suspected DVT of the leg treated from November 1995 to January 1999, were eligible for the study. Patients were referred by their family physician to the thrombosis unit. Patients were excluded if they were pregnant, aged less than 18 years, had experienced a previous episode of DVT in the same leg without documented normalisation, had concurrent signs or symptoms suggestive of pulmonary embolism, had received anticoagulant treatment for more than 24 hours or were unable to return to the study centre for follow-up because of geographical inaccessibility. Cancer status was recorded at presentation. Patients were considered to have active cancer if they were receiving (palliative) treatment for cancer or if they had received treatment for cancer in the past six months.

Study design
Patients were investigated according to the following diagnostic strategy ".. All patients underwent compression ultrasonography of the proximal veins and D-dimer testing at the day of referral. Both tests were performed blinded by two independent investigators, who were both unaware of the cancer status of each patient. If the D-dimer and ultrasonography result turned out to be normal, the patient was considered not to have DVT and no further testing was performed. If the ultrasonography result was normal and the D-dimer test abnormal, ultrasonography was repeated one week later. If this second ultrasonogram result was also normal, DVT was again ruled out. Anticoagulant therapy was only instituted in those patients with an abnormal ultrasonogram result. All patients were followed for three months to record possible subsequent thromboembolic events. All patients were scheduled for a visit after three months and were instructed to contact the study centre immediately if signs or symptoms of venous thromboembolism occurred before this visit. Objective testing was performed in these patients to confirm or refute the disease: ultrasonography and venography in case of suspected DVT, and in case of suspected pulmonary embolism, ventilation-perfusion scintigraphy, followed by angiography if a non diagnostic result was obtained.

For the analysis, patients were divided into two groups: patients with cancer and patients without cancer. In both groups clinical utility was determined by assessing the accuracy indices, venous thromboembolic complication rates and the efficiency of D-dimer testing.

1 Accuracy indices. The sensitivity, specificity and negative and positive predictive values were calculated, using the 3-month follow-up as the reference standard (i.e. DVT was considered absent if no venous thromboembolic event could be detected from referral through 3 month of follow-up and DVT was considered present when venous thrombosis was shown by objective testing).

2 Venous thromboembolic complication rate. The safety of withholding repeat ultrasonography was
The clinical usefulness of D-dimer testing in cancer patients

determined in both patient groups by calculating the number of subsequent venous thromboembolic complications during the 3 month follow-up period (i.e. complication rate).

3 Efficiency. The efficiency of using the D-dimer test as an adjunct to ultrasonography was defined as the proportion of patients in whom additional ultrasonography could be avoided (which is the proportion of patients in whom the diagnosis could be refuted on the day of referral).

Diagnostic tests
A rapid whole blood bedside D-dimer assay (SimpliRED D-dimer assay, Agen Biomedical Ltd., Brisbane, Australia) was used. The test can be performed by using 10 mL of whole blood obtained from a capillary or venipuncture sample. This autologous red cell agglutination assay uses as an active agent a chemical conjugate of a monoclonal antibody specific to human D-dimer (DD-3B6/22) linked to a monoclonal antibody that binds to the surface of human red blood cells (RAT-IC3/86)\(^6\). Agglutination occurs at D-dimer concentrations above 200 mg/l within 2 minutes. The outcomes of the test were categorised as normal or abnormal.

Compression ultrasonography was performed and interpreted as described previously\(^7\). Briefly, the common femoral and the popliteal vein down to the trifurcation of the calf veins were examined. The compressibility of these veins was assessed in the transverse plane. The outcomes were categorised as normal or abnormal (i.e. non-compressible).

Statistical analysis
Sensitivity, specificity, predictive values and venous thromboembolic complication rates in both patients groups were calculated. Their exact 95% confidence intervals were calculated using Confidence Interval Analysis (version 1.0)\(^11\).

Results
During the study period, 1899 consecutive patients with suspected DVT were screened. Of these, 143 (8%) patients were excluded for the following reasons: a previous episode of DVT in the same leg without documented ultrasonographic normalisation (53%), anticoagulant treatment for more than 24 hours (43%), geographic inaccessibility for follow-up (2%) and refusal of informed consent (2%). In 17 patients the D-dimer was not done or performed with knowledge of the ultrasonogram test result and these were excluded from further analysis. Thus, 1739 patients were included in the present analysis. Of these patients, 217 were known to have cancer at presentation (12%). Twenty-one percent of the cancer patients were bedridden or underwent surgery in the past 4 weeks; 54% of
the cancer patients were hospitalised in the past 6 months and the 3-month mortality in the cancer group was 3%. Table 1 summarizes the characteristics of the patients with and without cancer. Both groups were comparable with respect to age, sex and median time since onset of symptoms. However, more cancer patients had been immobilised or had undergone surgery. A recent trauma had occurred in a higher percentage of the patients without cancer.

Table 1. Baseline characteristics of 1739 patients suspected of deep venous thrombosis with and without cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with cancer</th>
<th>Patients without cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>217 (12%)</td>
<td>1522 (88%)</td>
</tr>
<tr>
<td>Mean age, year (range)</td>
<td>65 (22 – 94)</td>
<td>60 (18 – 96)</td>
</tr>
<tr>
<td>Sex, female</td>
<td>144 (66%)</td>
<td>944 (62%)</td>
</tr>
<tr>
<td>Median time since onset of symptoms, days</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Underlying disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Immobility or surgery in past 4 weeks</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>- Recent trauma</td>
<td>7%</td>
<td>16%</td>
</tr>
<tr>
<td>- Positive family history</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>- Previous venous thromboembolism*</td>
<td>7%</td>
<td>12%</td>
</tr>
</tbody>
</table>

* This refers to patients with documented normalised ultrasonogram results of the symptomatic leg

Cancer patients

Of the 217 cancer patients, 64 had a normal D-dimer test result (29%) and 153 an abnormal D-dimer test result. The ultrasonogram result was abnormal in one patient with a normal D-dimer test result, whereas it was abnormal in 79 patients with an abnormal D-dimer test result. Of those 63 patients (29%: 95% confidence interval [CI]: 23%-35%) with both a normal D-dimer and normal ultrasonogram results, one patient developed a thromboembolic event during follow-up. Those patients with an abnormal D-dimer test and a normal ultrasonogram result underwent additional ultrasonography, the results of which were abnormal in three patients. In three of the other patients (with an abnormal D-dimer test and normal serial ultrasonography result), a thromboembolic complication occurred during follow-up. Thus, overall, in 87 cancer patients venous thromboembolism was present (prevalence 40%). Figure 1a shows an overview of the diagnostic strategy arms with the corresponding patients numbers.
Overview of the diagnostic strategy arms of the study. CUS indicates compression ultrasonography; VTE, venous thromboembolism; and DVT, deep venous thrombosis.

**Patients without cancer**

In 782 of the 1522 non-cancer patients, a normal D-dimer test result was obtained (51%). Of these patients, 17 had an abnormal ultrasonogram result. Of the 765 remaining patients with both a normal D-dimer test and normal ultrasound results (50%; 95% CI: 48%-53%), 5 developed a venous thromboembolic event during follow-up. In those patients with an abnormal D-dimer test result, DVT was detected by an abnormal ultrasonogram in 294 patients. The other 446 patients had a normal ultrasonogram result and underwent follow-up ultrasonography one week later, which was abnormal in 14 patients. In the remaining 432 patients (with an abnormal D-dimer test and normal serial ultrasonography result) a thromboembolic event occurred in 8 patients. Hence, venous thromboembolism was present in 338 non-cancer patients (prevalence 22%). Figure 1b outlines the distribution of patients throughout the different strategy arms.
Overview of the diagnostic strategy arms of the study. CUS indicates compression ultrasonography; VTE, venous thromboembolism; and DVT, deep venous thrombosis.

**Accuracy indices**

Of the 87 cancer patients with venous thromboembolism, 2 patients had a false negative D-dimer test result (sensitivity 98%; 95% CI 92%-100%; specificity 48%; 95% CI: 39%-56%). In 22 of the 338 non-cancer patients with venous thromboembolism a false negative D-dimer test result was present (sensitivity 93%; 95% CI 90%-96%; specificity 64%; 95% CI: 62%-67%). Of the 64 cancer patients with a negative D-dimer test result, 62 did not have venous thromboembolism, resulting in a NPV of 97% (95% CI: 89%-100%). Of all 782 non-cancer patients with a normal D-dimer test result, 760 seemed not to have venous thromboembolism (NPV 97%; 95% CI: 96%-98%). Table 2 gives the accuracy indices for both patient categories.
Table 2. Accuracy of the SimpliRED D-dimer test in patients suspected of having deep venous thrombosis with and without cancer

<table>
<thead>
<tr>
<th></th>
<th>Patients with cancer</th>
<th>Patients without cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VTE -</td>
<td>VTE -</td>
</tr>
<tr>
<td>DD-</td>
<td>85</td>
<td>68</td>
</tr>
<tr>
<td>DD -</td>
<td>2</td>
<td>62</td>
</tr>
<tr>
<td>Total</td>
<td>87</td>
<td>130</td>
</tr>
</tbody>
</table>

VTE = Venous thromboembolism, DD = D-dimer

Venous thromboembolic complication rate

In 63 patients of all 217 cancer patients (29%) the D-dimer and ultrasonography results were normal at the day of referral; DVT was considered to be excluded and anticoagulant therapy was withheld. In these 63 patients only one thromboembolic event occurred during follow-up (complication rate 1.6% [95% CI: 0.04-8.5%]). Of those 71 cancer patients who had normal serial ultrasonogram results, 3 thromboembolic events occurred (complication rate 4.2% [95% CI: 0.9%-11.9%]).

The complication rate of withholding repeat ultrasonography in cases of both normal D-dimer and ultrasonogram results in patients without cancer was 0.9% [95% CI: 0.4%-1.9%]. In 8 out of 432 non-cancer patients with normal serial ultrasonography results thromboembolic complications occurred (complication rate 1.9% [95% CI: 0.8%-3.6%]).

Efficiency

The need for additional ultrasonography and therefore an extra hospital visit could be avoided in 63 of all 217 cancer patients. The efficiency of using a D-dimer test as an adjunct to ultrasonography is therefore 29% (95% CI: 23%-35%), compared with 50% (95% CI: 48%-53%) in the non-cancer patients.

Discussion

Our results indicate that the use of the D-dimer test, as measured in this study, does seem useful in cancer patients presenting with suspected DVT. This conclusion is supported in three ways. Firstly, we found that the negative predictive value of a whole blood D-dimer test (SimpliRED D-dimer) in cancer patients is as high as in patients who do not have cancer. Secondly, the low complication rate after withholding anticoagulant therapy indicates that it seems safe to reject the diagnosis in cancer patients with suspected DVT who have both a normal ultrasonogram and a normal D-dimer test.
result. Third, 29% of cancer patients with a clinical suspicion of DVT have a normal D-dimer test in combination with a normal ultrasonogram result (and considering the 95% confidence interval, this proportion is unlikely to be lower than 23%). Therefore, using the D-dimer test, the need for a repeat ultrasonogram can potentially be avoided in approximately 25% of the cancer patients with clinical suspected DVT. However, although the D-dimer test could be used as an exclusionary test to rule out DVT when a normal D-dimer test result is obtained, the test is not helpful in cancer patients (which is not different from non-cancer patients) to prove DVT in case of a positive or abnormal test result, given the low positive predictive value of 56%.

The predictive values of a test are influenced both by the prevalence of the disease in the studied population and the accuracy parameters (i.e. the sensitivity and the specificity of the test itself) 12. A higher prevalence of the disease and also a lower specificity of the test tend to decrease the NPV, whereas a higher sensitivity would tend to increase the NPV. This balancing effect is nicely illustrated by our study results. The prevalence of DVT in cancer patients was almost twice as high as in non-cancer patients and the specificity of the D-dimer test was decreased by 25%, which could have resulted in a lower NPV of the D-dimer test in the cancer group. However, because high D-dimer levels are often present in cancer patients - also in the absence of DVT - it is expected that the D-dimer test will have a higher sensitivity in this subset of patients. Indeed, the sensitivity of the D-dimer test was 98% in cancer patients compared with 93% in non-cancer patients. The decreasing effect of the higher prevalence and the lower specificity on the NPV of the test is therefore compensated by the higher sensitivity of the D-dimer test in cancer patients, resulting in an equally high NPV of 97% for both cancer and non-cancer patients.

It could be argued that the high sensitivity and NPV found in the cancer patients was partly owing to the relatively high percentage of cancer patients who recently underwent surgery, which can also lead to high D-dimer levels. However, when the same analysis was performed after excluding those cancer patients who recently underwent surgery a sensitivity of 97% (95% CI: 89%-100%), a prevalence of DVT of 37% (95% CI: 30%-44%) and a NPV of 97% (95% CI: 89%-100%) were observed. Hence, it is unlikely that the relatively high proportion (21%) of patients who were immobilised or underwent surgery has influenced our findings.

Our results are different from the findings of Lee et al. 13, who observed a significantly lower NPV of 79% in cancer patients compared to a NPV of 97% in non-cancer patients. Using the same D-dimer assay, they reported a sensitivity of 83% in non-cancer patients and a sensitivity of 86% in cancer patients, which are low values compared with the sensitivities in our study but also compared with sensitivities of the SimpliRED D-dimer assay reported in other studies 13-17. The prevalence of DVT in their cancer patients (49%) was higher than in our cancer patients (40%). This high prevalence
might be due to the fact that their patients suspected of having DVT were partly referred from a regional cancer centre. These patients are possibly more sick compared with cancer patients referred from a general practitioner, as was the case in our study. The low sensitivity of their D-dimer test and the high prevalence of DVT probably resulted in the low NPV.

Apart for assessing the NPV of the D-dimer test, we prospectively demonstrated that it appears safe to reject the diagnosis of DVT in patients suspected of having DVT with concomitant cancer when both normal D-dimer test and ultrasonogram results are obtained. Regarding the complication rate of 4.2% (95% CI: 0.9% -11.9%) for serial ultrasonography (the current diagnostic standard) the observed complication rate of 1.6% (95% CI: 0.04%-8.5%) of withholding anticoagulants after normal D-dimer and ultrasonogram results is acceptable in this particular high-risk group of cancer patients. However, ideally more patients need to be studied to increase the confidence of this observation.

Some issues of our study require comment. Although the results of this study indicate the clinically usefulness of D-dimer testing for the diagnosis of DVT, confidence intervals are still too wide to draw definite conclusions. Therefore, and also because our study concerns a post hoc analysis, further investigation is necessary before these results can be implemented in daily practice. Moreover, the available D-dimer assays are not interchangeable. Accuracy variables of different D-dimer assays could vary among different populations and should be tested in each patient population before clinical introduction.

In conclusion, our results indicate that D-dimer testing is helpful in cancer patients. When a D-dimer test is used as an adjunct to ultrasonography, a subsequent ultrasonogram can be avoided in about one quarter of all cancer patients referred for clinically suspected deep venous thrombosis.

Acknowledgements
We are grateful to the following colleagues who have contributed to the study, i.e. Drs. Paolo Prandoni and Franco Piovella from Padua and Pavia, Italy and Dr. Bert Jan Potter van Loon, Sint Lucas Andreas Hospital, Amsterdam, The Netherlands.

References


