Combined use of clinical pre-test probability and D-dimer test in the diagnosis of preoperative deep venous thrombosis in colorectal cancer patients

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Summary
The preoperative prevalence of deep venous thrombosis (DVT) in patients with colorectal cancer may be as high as 8%. In order to minimize the risk of pulmonary embolism, it is important to rule out preoperative DVT. A large study has confirmed that a negative D-dimer test in combination with a low clinical pre-test probability (PTP) can be safely used to rule out the tentative diagnosis of DVT in cancer patients. However, the accuracy in colorectal cancer patients is uncertain. This study assessed the diagnostic accuracy of a quantitative D-dimer assay in combination with the PTP score in ruling out preoperative DVT in colorectal cancer patients admitted for surgery. Preoperative D-dimer test and compression ultrasonography for DVT were performed in 193 consecutive patients with newly diagnosed colorectal cancer. Diagnostic accuracy indices of the D-dimer test were assessed according to the PTP score. The negative predictive value, positive predictive value, sensitivity, and specificity were 99% (95% confidence interval [CI], 95–100%), 17% (95% CI, 9–26), 93% (95% CI, 68–100%) and 61% (95% CI, 53–68%), respectively. In conclusion, the combined use of pre-test probability and D-dimer test may be useful in ruling out preoperative DVT in colorectal cancer patients admitted for surgery.

Keywords
Colorectal cancer, D-dimer, diagnostic accuracy, preoperative, venous thromboembolism

Introduction
The postoperative prevalence of deep venous thrombosis (DVT) among colorectal cancer patients receiving standard thromboprophylaxis may be as high as 20% (1). We have recently shown that 20 – 58% of the thrombi are present prior to surgery, thus suggesting that a large number of patients may undergo abdominal surgery with DVT present (2). Pulmonary embolism (PE) is a serious and potentially fatal complication of DVT, and it is the second most common cause of death in cancer patients (3–6). In order to minimize the risk of PE, it is crucially important to rule out preoperative DVT. Performing preoperative compression ultrasonography (CUS) in all colorectal cancer patients admitted for surgery would be a safe but rather uneconomical and also inconvenient approach. A large study has confirmed that measuring of plasma D-dimer, a degradation product of cross-linked fibrin, combined with the assessment of the clinical pre-test probability (PTP) of thrombosis, can be safely used to exclude the tentative diagnosis of DVT in cancer patients, without resorting to ultrasound imaging (7). However, the accuracy of plasma D-dimer combined with PTP in ruling out preoperative DVT within the group of colorectal cancer patients is unknown. The aim of this study was to assess the diagnostic accuracy of a quantitative D-dimer assay combined with the PTP score in ruling out preoperative DVT in colorectal cancer patients admitted for surgery.
Materials and methods

Patients
Between October 2003 and November 2005, patients with colorectal cancer admitted for intended curative surgery were considered for inclusion in the study. Exclusion criteria were: previous (within three years) or concomitant cancer of any origin, known congenital thrombophilia, venous or arterial thromboembolic event within three months, inflammatory bowel disease, connective tissue disease, severe acute infectious disease, mental disorder, stroke or neurosurgery within six months, pregnancy, ongoing anticoagulant treatment, endocarditis, active peptic ulcer, and severe untreated hypertension.

A total of 314 patients were evaluated as possible study participants. Fifty-four patients did fulfill one or more of the exclusion criteria, thus leaving 260 patients eligible. Fifty-eight of these patients did not enter the study, 46 who refused to give informed consent, ten owing to logistic difficulties, one who had acute surgery and one owing to technical problems with the ultrasound equipment. Of the remaining 202 patients, nine were excluded after operation, eight in whom non-malignant disease was found and one who had pancreatic cancer involving the transverse colon. This left 193 patients for analysis. Prior to diagnostic testing, clinical data were prospectively sampled by one of the authors (MTS) in order to assess the PTP of preoperative DVT according to the clinical model developed by Wells (Table 1) (8). Patients with a score of less than two were considered unlikely to have DVT, and patients with a score of two or more were considered likely to have DVT. All patients received standard thromboprophylaxis with tinzaparin 3.500 IU s.c. once a day, starting two hours prior to the operation, and graded compression stockings for a period of at least the first post-operative week or until they were fully mobilized.

Diagnosis of DVT
CUS, including the femoral, popliteal and calf veins, was performed according to standard procedures (grey scale, B-mode, color Doppler) within 48 h before surgery using a high-end ultrasound scanner (Logiq 9; GE Medical Systems, Milwaukee, WI, USA). In patients with rectal cancer admitted for preoperative radiotherapy, ultrasonography was performed within 48 h of starting radiotherapy. All examinations were performed by one of two experienced sonographers. The sonographers were neither aware of the results of the D-dimer analysis, nor of the Wells’ score assigned to each patient. In case of DVT, it was classified as either proximal or distal, symptomatic or asymptomatic. When preoperative DVT was diagnosed, antithrombotic therapy with low molecular weight heparin was commenced and the operation was delayed, according to an individual risk analysis. Postoperative long-term secondary prophylaxis was commenced in all patients with preoperative proximal (symptomatic and asymptomatic) and symptomatic distal DVT.

D-dimer assay
At the day of the preoperative CUS, we obtained blood samples for D-dimer analysis. The blood samples were obtained according to the European Concerted Action on Thrombosis (ECAT) procedures (9), and analyzed immediately as a routine sample at the Department of Clinical Biochemistry, Aalborg Hospital. The samples were analysed by the Auto Dimer® assay (Biopool® International, Umeå, Sweden), which is the standard assay at Aalborg Hospital. The Auto Dimer is a quantitative latex test for cross-linked fibrin degradation products. All samples were handled according to instructions from the manufacturer, and analysed using the BCS™ Coagulation Analyser (Dade Behring, Marburg, Germany). The technologist who analysed the samples was not aware of the result of the CUS.

Validation of the analytical performance of the Auto Dimer assay has previously been performed at our institution by one of the authors (TBL) (10).

Statistical analysis
In order to determine the optimal cut-off level of D-dimer in the diagnosis of DVT, a non-parametric receiver operating characteristic (ROC) plot was constructed. Patients with positive D-dimers test or PTP scores of two or more were classified as “test positive”, and patients with negative D-dimer tests and PTP scores less than two were classified as “test negative”. The results were expressed as negative predictive values (NPV), positive predictive values (PPV), sensitivity and specificity. No results of the plasma D-dimer analyses were considered as outliers. The data were analysed using Stata™ 9.1 (StataCorp LP, College Station, TX, USA). This study followed the guidelines recommended for reporting of studies of diagnostic accuracy of medical tests (11).

Ethics
Oral and written informed consent was obtained from all patients. The study has been approved by the ethics committee of the Counties of Northern Jutland and Viborg (jr. no. 2–16–4–0001–03).

Table 1: Clinical model for predicting the pre-test probability of deep-vein thrombosis (8). A score of two or higher indicates that the probability of deep venous thrombosis is likely; a score of less than two indicates that the probability of deep-vein thrombosis is unlikely. In patients with symptoms in both legs, the more symptomatic leg is used.

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling at least 3 cm larger than on the asymptomatic side (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting oedema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricose)</td>
<td>1</td>
</tr>
<tr>
<td>Previously documented deep venous thrombosis</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely as deep venous thrombosis</td>
<td>-2</td>
</tr>
</tbody>
</table>
Results

The characteristics of the study population are outlined in Table 2 according to the result of the combined test of plasma D-dimer level and PTP score. The diagnostic accuracy of the Auto Dimer assay in the diagnosis of overall preoperative DVT was 0.61 (expressed as the area under the ROC-curve [Fig. 1]). The combined test of D-dimer and PTP score showed NPVs of 99% (95–100%), 100% (97–100%), and 99% (95–100%) in the diagnosis of overall, proximal and distal DVT, respectively, at a cut-off level of 0.5 mg/l. The PPVs, sensitivities and specificities are outlined in Table 3. According to our recent paper, a diagnosis of preoperative DVT was established in 15 patients (8%) (2). The DVT was classified as proximal in 10 patients (Table 2). Nine patients with DVT reported leg pain, swelling of the entire leg, calf swelling or erythema at admission and were consequently classified as symptomatic. However, none of the patients sought medical attention for symptoms of DVT before admission.

Discussion

This prospective study found a NPV of 99% (95–100%) and a sensitivity of 93% (68–100%) of the combined use of pre-test probability and D-dimer test in the diagnosis of overall preoperative DVT. The combined test failed to detect one distal asymptomatic DVT, which reduced the sensitivity in the diagnosis of overall DVT to 93%. However, of clinical importance, the NPV and sensitivity of the combined test was 100% (97–100%) and 100% (69–100%), respectively, in the diagnosis of proximal DVT.

When applying a diagnostic test, the exact strategy for its use will depend on the requested outcome and the perceived clinical cost of false positive and false negative results. In a patient with venous thrombosis, immediate intervention is needed and it is crucial not to miss a case. In this case a test of high sensitivity is desirable, but it is important to stress that the NPV of the test will vary depending upon the prevalence of venous thrombosis in the

Table 2: Characteristics of the study population according to the combined test of D-dimer and PTP score.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DD$_{\text{neg}}$ &amp; PTP &lt; 2</th>
<th>DD$_{\text{neg}}$ &amp; PTP ≥ 2</th>
<th>DD$_{\text{pos}}$ &amp; PTP&lt;2</th>
<th>DD$_{\text{pos}}$ &amp; PTP ≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (% ) of patients</td>
<td>109 (57)</td>
<td>29 (15)</td>
<td>35 (18)</td>
<td>20 (10)</td>
</tr>
<tr>
<td>Proximal DVT present, No. (DVT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptomatic, No.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>3 (3)</td>
<td>2 (0)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Distal DVT present, No. (DVT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptomatic, No.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (0)</td>
<td>2 (0)</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>DVT absent, No.</td>
<td>108</td>
<td>24</td>
<td>33</td>
<td>13</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>65 (33 – 84)</td>
<td>73 (39 – 94)</td>
<td>71 (48 – 92)</td>
<td>79 (63 – 90)</td>
</tr>
<tr>
<td>Gender, female/male, No. (%)</td>
<td>36/73 (33/67)</td>
<td>15/14 (52/48)</td>
<td>14/21 (40/60)</td>
<td>11/9 (55/45)</td>
</tr>
<tr>
<td>Cancer, colon/rectal, No. (%)</td>
<td>48/61 (44/56)</td>
<td>19/10 (66/34)</td>
<td>21/14 (60/40)</td>
<td>17/3 (85/15)</td>
</tr>
<tr>
<td>Dukes’ stage, A-C/D, No. (%)</td>
<td>93/16 (85/15)</td>
<td>23/6 (79/21)</td>
<td>29/6 (83/17)</td>
<td>15/5 (75/25)</td>
</tr>
</tbody>
</table>

Note: DD, D-dimer; PTP, pre-test probability; DVT, deep venous thrombosis.

Figure 1: Non-parametric receiver operating characteristic (ROC) plot of preoperative plasma D-dimer in the diagnosis of overall preoperative DVT in patients with colorectal cancer admitted for intended curative surgery.
study population. The clinical setting in the present study is very different from previous studies of the performance of D-dimer in combination with Wells' PTP score in ruling out DVT in cancer patients, because the patients are not admitted due to clinical suspicion of DVT but instead due to the diagnosis of cancer. As the preoperative DVT prevalence in the study population was as high as eight percent (2), we have, however, implied the Wells' score as a screening tool to this group of patients.

As D-dimer concentrations can be raised in cancer patients, thus reducing the specificity and PPV due to an increased number of false-positive results (12), the aim of D-dimer measuring is to safely rule out DVT as opposed to ruling in DVT. Due to the fact that D-dimer is perceived to be of less value in cancer patients, large prospective studies have examined the diagnostic accuracy of D-dimer in cancer patients with suspected DVT. These studies suggest that D-dimer may be useful in the exclusion of DVT without resorting to imaging (7, 13). However, a retrospective analysis of three prospective studies suggests a significantly lower negative predictive value of D-dimer in cancer patients than in non-cancer patients, largely due to a higher prevalence of venous thrombosis in the cancer group (14).

Our study has its strengths and limitations. The prospective recording of data and consecutive sampling of patients have reduced the risk of selection and information bias. Furthermore, the risk of reviewer bias was minimized through blinding. The criterion standard test was applied to all patients and thereby minimises the risk of verification bias. The fact that all of the patients suffered from colorectal cancer has increased the internal validity of the results.

Whereas CUS has become the most widely accepted test for the diagnosis of patients with clinically suspected DVT, the accuracy of CUS as a screening tool among high-risk patients without symptoms of DVT is a matter of ongoing debate. However, considering that CUS has supplanted contrast venography in clinical practice almost completely in many countries, the PREVENT-investigators chose CUS when assessing the efficacy of dalteparin for the prevention of VTE in acutely ill medical patients, in concordance with contemporary medical practice (15). CUS has now become the routine procedure at the Department of Radiology at Aalborg Hospital after an in-house examination of the performance of CUS versus phlebography in patients with clinically suspected DVT (personal communication with Dr. A. Hedemann Nielsen, Department of Radiology, Aalborg Hospital, Denmark). Therefore, the present study reflects a general scenario to the clinicians.

The external validity of the results is compromised by the lack of standardization of D-dimer assays. A standardization has not been possible, primarily due to heterogeneity of the fibrin degradation products, lack of specificity of antibodies used in the assays, variability of calibrators and differences of format of the assay systems (16). Furthermore, the D-dimer test was applied on a homogeneous patient material which increased test performance by noise reduction, but it makes a general application of the results difficult.

Studies have provided strong evidence for a poor outcome in cancer associated with VTE, although it seems unlikely that complications of VTE can account entirely for the increased mortality among patients with cancer and VTE (17). However, considering that most of the pulmonary emboli originate from lower limb veins (18), procoagulant exposures may increase the clot burden and the rates of postoperative PE in those patients with preoperative DVT, as general anaesthesia and abdominal surgery followed by bed rest. Hence, we hypothesize that it is possible to improve the outcome of colorectal cancer patients, if surgery is postponed and anticoagulant treatment is commenced in patients with preoperative proximal (symptomatic and asymptomatic) and symptomatic distal DVT.

The study patients did not seek medical attention despite the symptoms of DVT, most likely due to the distress and the implications for daily life caused by the cancer diagnosis. Therefore, the safety of the proposed strategy in a daily clinical non-study setup depends upon a very systematic use of the Wells' score combined with D-dimer testing, which encourages more focus on the important issue of cancer associated VTE.

In conclusion, this prospective study showed that the combined use of pre-test probability and D-dimer test may be useful in ruling out preoperative DVT in colorectal cancer patients admitted for surgery. However, more studies are warranted to confirm the safety of this strategy.

**Acknowledgements**

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**Abbreviations**

DVT, deep venous thrombosis; CI, confidence interval; PE, pulmonary embolism; CUS, compression ultrasonography; ECAT, The European Action on Thrombosis; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.
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