Pulmonary embolism: advances in diagnosis and prognosis
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Chapter 7
Clinical decision rule and D-dimer have lower clinical utility to exclude pulmonary embolism in cancer patients: explanations and potential ameliorations

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Submitted for publication
ABSTRACT

Background
Patients with malignancy frequently present with clinically suspected pulmonary embolism (PE). However, the safe and efficient combination of a clinical decision rule (CDR) and D-dimer test to rule out PE performs less well in patients with malignancy. We examined potential explanations and analysed whether elevating the D-dimer cut-off could improve the clinical utility.

Methods
We used data on consecutive patients with suspected PE included in a multicenter management study. The performance of the Wells CDR and the D-dimer test was compared between patients with and without malignancy and multivariable analysis was used to compare the weights of the CDR variables. Furthermore, we combined the CDR (cut-off ≤4) with different D-dimer cut-off levels for the exclusion of PE.

Results
Of 3,306 patients with suspected PE, 475 (14%) had cancer. The Wells rule variables were less diagnostic in cancer patients. Increasing the D-dimer cut-off level to 700 μg/L for all ages or using an age-dependent cut-off resulted in an increase in the proportion of patients in whom PE could be excluded from 8.4% to 13% and 12%, respectively. The corresponding false-negative rates were 1.6% (95% confidence interval 0.3-8.7%) and 0.0% (0.0-6.3%).

Conclusions
The Wells CDR and D-dimer perform less well in patients with suspected PE if they have cancer. Individual variables in the Wells rule are less diagnostic in cancer patients than in non-cancer patients with suspected PE. A CDR combined with an age-dependent D-dimer cut-off shows a modest improvement of the strategy in cancer patients.
INTRODUCTION

Patients with malignancy have an increased risk of developing venous thromboembolism (VTE) (1). Conversely, a substantial proportion of patients with suspected VTE has active malignancy (2). Pulmonary embolism (PE) is a potentially fatal disease, which can be effectively treated with anticoagulant therapy. However, treatment with anticoagulant medication comes with a risk of bleeding, which is higher among cancer patients (3). Therefore, the main challenge in the diagnostic work-up of patients with suspected PE is to differentiate the patients without from those with the disease.

Several studies have validated a diagnostic strategy based on a clinical decision rule (CDR) and D-dimer test to safely exclude the diagnosis in an effective and non-invasive way (2,4,5). Although considered safe in patients with active malignancy, the standard CDR-D-dimer strategy has a lower exclusion rate in this subgroup of patients (6). Only one in ten patients with malignancy and suspected PE are classified as “unlikely” by the CDR and have a normal D-dimer test result, compared to a third of all patients with suspected PE (6). This means that significantly more patients with active malignancy need additional imaging tests.

One of the explanations for this difference could be a different accuracy of the Wells CDR in cancer patients. The Wells CDR was developed in patients of whom the majority did not have a malignancy. So far it is unclear whether the individual items of the Wells score are similarly diagnostic in cancer patients relative to non-cancer patients. Another explanation for the difference in clinical utility could be the lower specificity of the D-dimer test in patients with cancer, leading to a higher number of false positive D-dimer results (7-9). The low proportion of cancer patients with a normal D-dimer test result raises the question whether a higher diagnostic cut-off would be more suitable and equally safe in cancer patients.

In the study reported in this paper we had two objectives: to compare the performance of D-dimer testing and of the Wells CDR (10) among patients with and without malignancy and to examine whether elevating the D-dimer cut-off would increase the number of patients with a malignancy in whom PE can be safely ruled out.

METHODS

Patients

Data from a large prospective management study were used, which included consecutive in- and outpatients (both from the emergency department and from outpatient clinics) with suspected PE in 12 hospitals in the Netherlands. The study is reported in full elsewhere (2). In short, patients were included between November 2002 and August 2004. Patients were excluded if they had received (low molecular weight) heparin for more than 24 hours, were younger than 18 years of age, were pregnant, had a known hypersensitivity for iodinated contrast fluid or renal failure, had a life expectancy of less than three months, if there was
geographic inability for follow-up or if no informed consent was obtained. The study group comprised 3,306 patients with suspected PE, of whom 475 (14%) had active malignancy at presentation. The Institutional Review Boards of all participating hospitals approved the study protocol and from eligible patients informed consent was obtained.

**Diagnostic work-up**

A sequential diagnostic workup was evaluated; consisting of the dichotomous Wells rule (10), a D-dimer test (either Tinaquant®, Roche Diagnostica, Mannheim, Germany or Vidas D-dimer Exclusion®, Biomerieux, Marcy-l’Etoile, France) and CT scanning. PE was ruled out by an “unlikely” Wells score (≤4) combined with a normal D-dimer test (≤500 μg/L) or a negative spiral CT scan in patients with a likely clinical probability or abnormal D-dimer test. In these patients, anticoagulant medication was withheld and they were followed up for three months for any subsequent signs of VTE. In case of clinically suspected deep vein thrombosis (DVT) or PE, appropriate objective tests (compression ultrasound for suspected DVT, CT for suspected PE) were performed to confirm or refute the diagnosis. In case of death, information was obtained from the general practitioner, from the hospital records or from autopsy.

**Diagnosis of active malignancy**

Cancer status was determined at the time of study inclusion. Patients were classified as having cancer if there was objectively confirmed active cancer, if they were receiving cancer treatment or had received cancer treatment within six months prior to study enrolment, or were receiving palliative care. Solid and haematological malignancies were both included.

**Analysis and statistical methods**

We calculated the proportion of patients with PE, the proportion classified as “PE unlikely” with the Wells score (cut-off ≤4), the proportion with a normal D-dimer (cut-off <500 μg/L) and the performance of this combination both for patients with and without malignancy. To determine the overall performance of the CDR and D-dimer test in both groups the area under the Receiver Operating Characteristic (ROC) curves were calculated for both tests and compared between the two groups.

To explain an anticipated difference in accuracy, we evaluated to what extent the diagnostic value of the variables in the Wells rule differed in patients with and without malignancy. For this purpose, we built a multivariable logistic regression model with the items in the Wells decision rule, using the presence of pulmonary embolism as the outcome variable. We included interaction terms with malignancy to allow for a differential diagnostic weight in patients with malignancy, compared to those without malignancy. We tested these interaction terms for statistical significance. By evaluating the magnitude of the corresponding coefficients, transformed to odds ratios, we could compare the relative weight of these variables for patients without and patients with malignancy.
Next, we explored the possibility of increasing the utility of the Wells-rule – D-dimer combination to exclude PE without compromising its safety. We calculated the proportion of patients classified as “unlikely” with the Wells rule and a low D-dimer with the cut-off set at various levels. We also investigated the performance of a new age-dependent D-dimer cut-off, which varies by age (11). For this cut-off the regular cut-off of 500 μg/L is used for patients ≤50 years, but the D-dimer cut-off is calculated as age x 10μg/L for patients >50 years. For example: for a patient aged 67 years, the cut-off would be 670 μg/L. For each strategy we calculated the false negative rate: i.e. those who had symptomatic and objectively confirmed VTE in the diagnostic workup or during 3-month follow-up. Safety was determined as a false negative rate below 2.0%.

Statistical analyses were performed using SPSS software, version 15.0 (SPSS, Inc., Chicago, Illinois) and GraphPad Software (GraphPad Software, Inc., La Jolla, California). Exact 95% confidence intervals (CI) were calculated using Confidence Interval Analysis (CIA, version 1.0; Gardner MJ).

RESULTS

The baseline characteristics of patients with and without active malignancy were compared (Table 1). Patients with malignancy were older, were more often female and were more often inpatient, compared to patients without malignancy (see Table 1). Overall, suspected pulmonary embolism was more often confirmed in cancer patients than in non-cancer patients: 27% (130/475) versus 19% (544/2831), respectively (p<0.001) (Table 2).

Clinical probability

Significantly fewer patients with active malignancy were classified as ‘unlikely’ with the Wells rule: 232/475 (49%) versus 1942/2831 (69%), p<0.001. There were also fewer patients with a normal D-dimer result in the group with an active malignancy: 47/359 (13%) versus 1032/2419

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients without malignancy N=2831</th>
<th>Patients with malignancy N=475</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>51 (19)</td>
<td>63 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender, n(%)</td>
<td>1646 (58)</td>
<td>250 (53)</td>
<td>0.026</td>
</tr>
<tr>
<td>Outpatients, n (%)</td>
<td>2383 (84)</td>
<td>318 (67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>204 (7.2)</td>
<td>39 (8.3)</td>
<td>0.422</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>291 (10)</td>
<td>50 (11)</td>
<td>0.845</td>
</tr>
<tr>
<td>Recent surgery, n (%)</td>
<td>132 (4.6)</td>
<td>53 (11)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disorder.
Table 2. Proportion of patients with unlikely clinical decision rule (10) and/or normal D-dimer test among patients with and without malignancy and suspected pulmonary embolism.

<table>
<thead>
<tr>
<th>Patients without malignancy</th>
<th>Patients with malignancy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>2831</td>
<td>475</td>
</tr>
<tr>
<td>Patients with PE, n (%)</td>
<td>544 (19)</td>
<td>130 (27)</td>
</tr>
<tr>
<td>Patients with CDR “unlikely”, n (%)</td>
<td>1942 (69)</td>
<td>232 (49)</td>
</tr>
<tr>
<td>Patients with CDR “unlikely” and PE, n (%)</td>
<td>215/1942 (11)</td>
<td>41/232 (18)</td>
</tr>
<tr>
<td>Patients with D-dimer &lt;500 μg/L, n (%)</td>
<td>1032/2432 (42)</td>
<td>47/359 (13)</td>
</tr>
<tr>
<td>“Unlikely” and normal D-dimer, n (%)</td>
<td>942/2831(33)</td>
<td>40/475 (8.4)</td>
</tr>
<tr>
<td>VTE incidence during FU among patients with CDR “unlikely” and normal D-dimer, n (%), 95% CI</td>
<td>2/942 (0.2, 0.1-0.8)</td>
<td>0/40 (0.0, 0.0-8.8)</td>
</tr>
</tbody>
</table>

CDR, clinical decision rule; CI, confidence interval; FU, follow up; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 3. Odds ratios of the Wells rule items observed among patients with and without malignancy.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients without malignancy Odds ratio (95% CI)</th>
<th>Patients with malignancy Odds ratio (95% CI)</th>
<th>p-value for interaction malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical symptoms of DVT (leg swelling, pain with palpation)</td>
<td>5.3 (3.7-7.6)</td>
<td>1.5 (0.7-3.2)</td>
<td>p = 0.005*</td>
</tr>
<tr>
<td>Heart rate &gt;100 bpm</td>
<td>1.9 (1.5-2.4)</td>
<td>1.3 (0.8-2.0)</td>
<td>p = 0.17</td>
</tr>
<tr>
<td>Immobilization (≥3 days) or surgery in the previous four weeks</td>
<td>2.4 (1.9-3.0)</td>
<td>1.3 (0.8-2.0)</td>
<td>p = 0.03*</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
<td>1.9 (1.4-2.5)</td>
<td>1.5 (0.8-2.8)</td>
<td>p = 0.64</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2.0 (1.4-3.0)</td>
<td>1.1 (0.4-2.7)</td>
<td>p = 0.25</td>
</tr>
<tr>
<td>Malignancy</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other diagnosis less likely than pulmonary embolism</td>
<td>3.6 (2.8-4.6)</td>
<td>3.7 (2.2-6.3)</td>
<td>p = 0.33</td>
</tr>
</tbody>
</table>

*Significant difference between patients with and without malignancy.

(42%), p<0.001. As a consequence, there were fewer cancer patients in whom PE could be excluded based on the Wells rule and a normal D-dimer test: 8% (42/475) versus 33% (942/2831), p<0.001.

The discriminatory performance of the CDR was significantly lower among patients with malignancy compared to patients without (as is shown in Figure 1A, where the ROC curves of the Wells CDR for the two groups are depicted). The area under the curve (AUC) was 0.665.
(95% CI: 0.612 to 0.717) for patients with malignancy and 0.743 (95% CI: 0.720 to 0.765) for patients without malignancy, respectively (p=0.004).

The odds ratios of the variables in the Wells rule for patients with and without malignancy were obtained in the multivariate logistic regression analyses (Table 3). The odds ratios of the Wells rule items “clinical symptoms of DVT” and “immobilization or surgery in the previous four weeks” were significantly lower in patients with cancer (p<0.005 and p=0.03, respectively). In patients with malignancy, only the variable “alternative diagnosis less likely than PE”, was highly discriminative for PE. For all other variables, the 95% confidence interval around the odds ratio included 1.

Separate analyses including only outpatients showed similar results (data not shown).

**D-dimer test**

The ROC curves of the D-dimer test for patients classified as “PE unlikely” with the Wells rule were compared for patients both with and without malignancy (Figure 1B). The AUC was 0.803 (95% CI: 0.734 to 0.871) for patients with malignancy, which differed significantly from the AUC for patients without malignancy: 0.875 (95% CI; 0.865 to 0.895, p=0.02). The specificity of the 500 μg/L cutoff is markedly lower in cancer patients. A separate analysis including only outpatients showed similar results (data not shown).

Increasing the D-dimer cut-off level, combined with an unlikely Wells score resulted in an increasing number of patients in whom PE could be excluded (see Table 4). Among the patients with malignancy, the D-dimer cut-off level could safely be increased to 700 μg/L. At this level,
the number of patients in whom PE could be ruled out would increase from 40 (8%) to 61 (13%), whereas the false-negative rate would increase from 0.0% (95% CI: 0.0% to 8.8%) to 1.6% (95% CI: 0.3% to 8.7%). Using higher cut-off levels would increase the false negative rate to more than 2%. With a cut-off of 700 μg/L, the specificity of the CDR – D-dimer combination would increase significantly from 12% (95% CI: 98.9% to 16%) to 18% (95% CI: 14% to 22%, p<0.0001).

Using the age-dependent D-dimer cut-off, the number of cancer patients in whom PE could be excluded would increase to 57 (13%), with a false-negative rate of 0.0% (95% CI: 0.0% to 6.3%). The specificity of the CDR – D-dimer combination would increase to 22% (95% CI: 17% to 27%, p=0.0001).

In the study cohort, two different D-dimer assays were used: the Tinaquant® assay was used in 55% of patients with cancer and the Vidas® test was used in the other 45% of patients. The tests were used in similar proportions of patients without malignancy: in 57% the Tinaquant® assay was used and in 43% the Vidas® test was used. Separate analyses showed no differences in the AUC for the CDR – D-dimer combinations between the two D-dimer groups for patients with and without malignancy (p-values 0.22 and 0.089, respectively). Also, the failure rates were comparable between the two D-dimer groups (p-values ranging from 0.507-1.000 for the various D-dimer cut-off levels).

**DISCUSSION**

This analysis confirms that the clinical utility of the standard CDR – D-dimer combination is significantly lower among patients with compared to those without active malignancy. Fewer cancer patients were categorized as PE “unlikely” with the Wells rule and fewer had a normal D-dimer test. Consequently, the proportion of patients in whom PE can be excluded based on CDR and D-dimer test is lower in patients with malignancy (8% versus 33%).

The difference in clinical utility of the CDR and D-dimer test between cancer patients and patients from a general population was described previously in this population (6). An important initial explanation for the difference is the difference in prevalence of PE between the two groups: in more patients with malignancy the suspected PE was confirmed compared to patients without malignancy: 27% vs. 19%. In addition we now show that the overall discriminatory performances of both the CDR and D-dimer are also significantly weaker in patients with malignancy compared to patients without malignancy, as revealed by the ROC-curves.

For the clinical decision rule, an explanation may be found in the rule itself. The diagnostic values of the individual items in the Wells score were significantly lower in patients with active malignancy. In these patients, only the variable “alternative diagnosis less likely than PE” was significantly discriminative for PE. Interestingly, this subjective variable is at the same time the most often debated item in the decision rule (12). This suggests that ‘gestalt’ or the clinician’s
<table>
<thead>
<tr>
<th>D-dimer cut-off value (μg/L)</th>
<th>Patients without malignancy</th>
<th>Patients with malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients with CDR unlikely and normal D-dimer (% 95%CI)</td>
<td>False negative rate¹ (% 95%CI)</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>942 (33, 32-35)</td>
<td>2 (0.2, 0.1-0.8)</td>
</tr>
<tr>
<td>&lt; 600</td>
<td>1056 (37, 36-49)</td>
<td>11 (1.0, 0.6-1.9)</td>
</tr>
<tr>
<td>&lt; 700</td>
<td>1145 (40, 38-42)</td>
<td>19 (1.7, 1.1-2.6)</td>
</tr>
<tr>
<td>&lt; 800</td>
<td>1222 (43, 41-45)</td>
<td>24 (2.0, 1.3-2.9)</td>
</tr>
<tr>
<td>&lt; 900</td>
<td>1287 (46, 44-47)</td>
<td>38 (3.0, 2.2-4.0)</td>
</tr>
<tr>
<td>&lt; 1000</td>
<td>1327 (47, 45-49)</td>
<td>40 (3.0, 2.2-4.1)</td>
</tr>
<tr>
<td>&lt; 1100</td>
<td>1368 (48, 47-50)</td>
<td>46 (3.4, 2.5-4.5)</td>
</tr>
<tr>
<td>&lt; 1200</td>
<td>1409 (50, 48-52)</td>
<td>51 (3.6, 2.8-4.7)</td>
</tr>
<tr>
<td>&lt; 1300</td>
<td>1449 (51, 49-53)</td>
<td>56 (3.9, 3.0-5.0)</td>
</tr>
<tr>
<td>Age-dependent D-dimer cut-off value</td>
<td>1028 (36, 35-38)</td>
<td>7 (0.7, 0.3-1.4)</td>
</tr>
</tbody>
</table>

¹Qualitative D-dimer results missing in 23 of 2831 patients without malignancy,
²Qualitative D-dimer results missing in 5 of 475 patients with malignancy
implicit judgment is of great value and may be equally effective in the clinical assessment of cancer patients with suspected PE. The other items of the Wells CDR appeared less diagnostic in cancer patients. Perhaps this calls for new clinical probability scores more specific for cancer patients with suspected PE. Items such as chemotherapy and type of malignancy are currently not incorporated in a score, but could be of value in assessing pre-test probability in this subgroup of patients.

The D-dimer test also performed less well in patients with malignancy compared to patients without. Previous studies have shown that especially the false positive rate is increased in cancer patients (7,9). As a second objective of our study, we examined whether elevating the D-dimer cut-off could increase the clinical utility of the CDR – D-dimer combination in excluding PE in patients with malignancy. Adhering to our pre-set safety definition (a false-negative rate below 2%), raising the cut-off to <700 μg/L for patients of all ages or using the age-dependent D-dimer cut-off would result in a modest absolute increase in the proportion of patients in whom PE could be ruled out of 5%, i.e. from 8% to 13%. The upper confidence interval of the false negative rate was somewhat lower when the age-dependent cut-off was used (6.3%), compared to the upper confidence interval with a D-dimer cut-off of <500 μg/L (8.8%) or <700 μg/L (8.7%).

Our findings are in line with previous studies on the performance of the D-dimer test in patients with cancer and suspected PE (9) and also with studies on the performance of the CDR – D-dimer combination in patients with cancer and suspected DVT (13,14). Previously, Righini and colleagues also attempted to increase the D-dimer cut-off in cancer patients (9). In contrast to our analysis, no stratification according to pre-test probability was made, yet increasing the cut-off value progressively to 900 μg/L did not affect the 100% sensitivity and negative predictive value and it resulted in a large increase in specificity (16% to 30%). Although we only included patients classified as “PE unlikely” in our analysis, and therefore expected a lower false negative rate even with a higher cut-offs, we were unable to increase the cut-off to more than 700 μg/L.

It can be argued that the false negative rates in patients in whom PE is excluded with the CDR – D-dimer combination are too high and that the confidence intervals are too wide. In outcome studies, an observed false negative rate of 1% to 2% is usually targeted, with an upper 95% confidence interval limit below 3% (15). This figure is comparable to the false negative rate of VTE found for pulmonary angiography (16). However, even though the combination of a CDR and D-dimer is widely used to exclude PE, also among cancer patients, the estimated false negative rate in clinical outcome studies for this subgroup of patients has never been below the threshold. In order to confirm the safety of the strategy and to narrow the confidence interval, a larger sample of patients is needed. Although we analyzed the largest sample of cancer patients with suspected PE reported to date, the confidence intervals remained wide.

Unfortunately, we had no additional information about the underlying cancer, such as tumour type, stage or given therapy. These factors could all have influenced the D-dimer results (17-
Furthermore, in our analysis two different D-dimer assays were used. Although the two assays are not identical, we are confident that our results are not confounded by the use of two different assays. There was no differential use of the two tests in patients with, versus patients without malignancy. Separate analyses for accuracy, although possibly limited by the number of patients, showed no differences between the two D-dimer assays. Furthermore, previous studies showed good correlation between the two assays (20) and comparable accuracy in outcome studies (21,22). However, as we only used two assays, it is unknown how the new D-dimer cut-off will perform in other D-dimer assays.

One can argue whether developing strategies for specific subgroups of patients is desirable. Doing so will complicate the diagnostic process. In our view, it can only be justified by a large improvement in the diagnostic yield and safety. Based on our findings, we see no advantage in customizing the diagnostic approach for patients with malignancy by elevating the D-dimer cut-off. However, the age-dependent cut-off proved promising for both patients with and without malignancy. Prospective validation in larger patient cohorts is necessary to further study the safety of this age-dependent approach. Cancer patients are usually older compared to patients without malignancy, and a D-dimer cut-off corrected for age is expected to increase the diagnostic performance among cancer patients.

In conclusion, in patients with malignancy and suspected pulmonary embolism the Wells clinical decision rule and the D-dimer test are less diagnostic compared to patients without cancer and have a lower clinical utility. Potential ameliorations for this situation could be a modified clinical probability score more specific for a cancer population and an adjusted cut-off for the D-dimer test. Increasing the cut-off for in cancer patients classified as “PE unlikely” with the CDR would yield a modest increase in clinical utility and seems most promising and safe with an age-dependent approach.

**Authorship and Disclosures**

RAD, GLvS, PWK, PMMB and HRB were involved in the conception and design of the study and in analysis and interpretation of data. MS and FWGL were involved in collection and interpretation of data. RAD, PMMB and GLvS drafted the manuscript. All authors were involved in revision and final approval of the manuscript. RAD and GLvS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors report no conflicts of interest.

**REFERENCE LIST**


