Pulmonary embolism: advances in diagnosis and prognosis
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Chapter 5b

Knowledge of the D-dimer test result influences clinical probability assessment of pulmonary embolism

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Submitted for publication
ABSTRACT

Background
In patients with suspected pulmonary embolism (PE), an unlikely or non-high probability assessment combined with a normal D-dimer test can safely exclude the diagnosis. We, therefore, studied the influence of early D-dimer knowledge on clinical probability assessment.

Methods
A questionnaire was sent to 150 randomly selected pulmonologists and internists in the Netherlands, presenting six hypothetical case-descriptions of patients with suspected PE. Physicians were randomized to receive one of three versions. The version contained a normal, an abnormal or no D-dimer result with each case-description. Each version contained two cases with an abnormal D-dimer result, two cases with a normal D-dimer result and two cases with no D-dimer result.

Results
A total of 71 physicians (47%) returned the questionnaire; the three versions were equally represented. Compared to the control cases in which no D-dimer was given, knowledge of an abnormal D-dimer resulted in more “likely” clinical scores using the Wells’ rule (absolute increase in “likely” of 25-37%, p=0.005, 0.111 and 0.144), while knowledge of a normal D-dimer resulted in more “unlikely” scores (absolute increase in “unlikely” of 27-44%, p=0.001 and 0.070). D-dimer knowledge did not influence the probability assessment when the clinical suspicion was very high.

Conclusion
Knowledge of the D-dimer test influences the physician in how the clinical probability for PE is scored. This will have direct clinical consequences, such as unnecessary imaging testing or inappropriate exclusion of the diagnosis. Physicians should therefore make sure that they examine the patient before they take notice of the D-dimer test result.
INTRODUCTION

Pulmonary embolism (PE) is a frequently occurring and possibly fatal disease, which can be difficult to diagnose due to a wide variation of non-specific signs and symptoms. However, with the introduction of clinical decision rules (CDRs) and the D-dimer test much has changed in the diagnostic work-up of patients with suspected PE. The combination allows a safe exclusion of the diagnosis in a significant proportion of patients without the need for imaging tests (1-3). Current guidelines recommend the assessment of clinical probability in each patient with suspected PE before any further objective testing is ordered (4-7). Then, in case of an “unlikely” or “non-high” clinical probability, the subsequent step is D-dimer testing. An “unlikely” or “non-high” clinical probability combined with a normal D-dimer test result safely excludes the diagnosis.

The D-dimer test is a popular assay for the exclusion of PE, but should not be used as a screening test due to its low specificity (8,9). Also, although the negative predictive value of some D-dimer assays is very high, the test should not be used as a stand alone (7); in patients with a “likely” clinical probability for PE, the false negative rate of the D-dimer test can be as high as 10% (9). Therefore, patients with a “likely” or “high” clinical probability for PE need to undergo CT testing, irrespective of the D-dimer outcome.

Although the advised diagnostic strategies for the workup of suspected PE appear efficient and easy to apply, recent studies on the current clinical practice of physicians showed that physicians have a varied diagnostic approach to PE, which is often not in line with current guidelines (10-12). In the emergency room setting, the D-dimer test is often ordered before the physician has examined the patient (13). The Wells rule, a widely accepted CDR, contains a subjective element with an important contribution to the overall score (“alternative diagnosis less likely than PE”), which may be interpreted differently if the physician is aware of the D-dimer result (14). Indeed, a recent study showed that the knowledge of an abnormal D-dimer test result leads to a higher CDR score compared to no knowledge of the D-dimer test result (12). In the case of an abnormal D-dimer test this could lead to unnecessary diagnostic imaging, as physicians may be triggered to suspect PE by a non-specific abnormal D-dimer test (15). Whether a normal D-dimer result may also influence physicians in how they score the CDR is unknown, but would also have an important clinical consequence. Theoretically, it could result in a lower CDR score, leading to inappropriate exclusion of the diagnosis.

To evaluate the effect of either a normal or an abnormal D-dimer outcome on the scoring of the Wells CDR we performed a questionnaire based study.

METHODS

A questionnaire was designed, containing six hypothetical patient cases with a clinical suspicion of pulmonary embolism. The clinical probability varied from unlikely to likely. For each patient
case, three versions of the case were prepared: one with an abnormal D-dimer result, one with a normal D-dimer result and one in which no D-dimer result was given. Each version contained two cases with an abnormal D-dimer result, two cases with a normal D-dimer result and two cases in which no D-dimer result was given. (See Appendix for the cases and the different versions.)

A random sample of pulmonologists or internists was selected from an online database with practicing physicians of various hospitals in the Netherlands. The sample was randomly divided in three groups and each version of the questionnaire was sent to a different group. The physicians were not informed that different versions of the questionnaire were made; they were informed that a study was being performed to “test the reproducibility of a clinical decision rule”. The Wells rule was added to the questionnaire, illustrating the seven items of the rule and the cut-off point for “likely” and “unlikely” (Table 1)(14)

The variation of the clinical decision rule score in the six cases was analyzed using descriptive statistics. Per case, the proportion of physicians that scored a clinical decision rule above 4 was calculated and the results were compared between the three versions of the questionnaire (i.e. with a low, a high or without a D-dimer result) using Chi$^2$ or Fisher’s exact test. Statistical analyses were applied using SPSS version 16.0.

RESULTS

The questionnaire was sent to 150 pulmonologists and internists in October 2009; a reminder was sent to those who had not responded after two months. In total, 71 (47%) completed questionnaires were returned. The practice characteristics of the physicians are shown in Table 1. There was an equal response among the physicians receiving the three different versions of the questionnaire: 21, 23 and 27 questionnaires were returned of versions 1, 2, and 3, respectively. The questionnaire was more often returned by internists than by pulmonologists: 60% vs. 35%, respectively (p=0.005). There was no difference in responders versus non-responders regarding the type of hospital they worked in.

The scoring of the CDR varied per physician and per case (Figure 1). For cases 1 and 3, most physicians in the control group (in which no D-dimer value was given) agreed on an unlikely clinical probability (81% and 92%, respectively). In cases 2 and 6, an equal number of physicians in the control group scored the cases as unlikely and likely (52% and 48% scored case 2 as unlikely and likely, respectively; 50% and 50% scored case 6 as unlikely and likely, respectively), while in cases 4 and 5, most physicians in the control group agreed on a likely clinical probability (96% and 87%, respectively).

Compared to the control group, in which no D-dimer result was given to the physicians, the cases were scored differently when either an abnormal or normal D-dimer was given in the case description (Figure 1 and Table 2). When physicians were aware of an abnormal D-dimer result, a shift towards more “likely” scores was observed compared to the control group. This
Table 1. Practice characteristics of the responders.

<table>
<thead>
<tr>
<th></th>
<th>Version of Questionnaire</th>
<th></th>
<th></th>
<th></th>
<th>Chi²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Version 1</td>
<td>Version 2</td>
<td>Version 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders, n (%)</td>
<td>21 (30)</td>
<td>23 (32)</td>
<td>27 (38)</td>
<td></td>
<td>0.674</td>
</tr>
<tr>
<td>Specialists</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.064</td>
</tr>
<tr>
<td>Pulmonologists, n (%)</td>
<td>11 (52)</td>
<td>11 (48)</td>
<td>6 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internists, n (%)</td>
<td>10 (48)</td>
<td>12 (52)</td>
<td>21 (78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.875</td>
</tr>
<tr>
<td>Tertiary</td>
<td>2 (10)</td>
<td>4 (17)</td>
<td>3 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary, teaching, n (%)</td>
<td>10 (48)</td>
<td>9 (39)</td>
<td>14 (52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary, non-teaching, n (%)</td>
<td>9 (43)</td>
<td>10 (43)</td>
<td>10 (37)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

was most obvious in the cases scored as “unlikely” by the control group (cases 1 and 3) and in one of the cases in which “likely” and “unlikely” were scored equally (case 2). The number of physicians scoring the case as “likely” increased from 19% to 44% (p=0.111) in case 1 and from 8% to 45% (p=0.005) in case 3 (Table 2). This shift was also present in case 2, in which 48% of the physicians unaware of the D-dimer result scored the case as “likely”, compared to 71% of the physicians with knowledge of an abnormal D-dimer (p=0.144). Cumulatively, 51% of the physicians scored the case as “likely” in the control group, compared to 67% of the physicians who were made aware of an abnormal D-dimer result (p=0.006, Table 2).

When physicians were aware of a normal D-dimer result, a shift towards more “unlikely” was observed compared to the control group. This shift was most obvious in the two cases which the control group-physicians had scored as being “unlikely” and “likely” equally (cases 2 and 6). The number of physicians scoring the case as “unlikely” increased from 52% to 96% (p=0.001) in case 2 and from 50% to 77% (p=0.070) in case 6 (Table 2). Cumulatively, 49% of the physicians scored the case as “unlikely” in the control group, versus 60% of the physicians who were aware of an abnormal D-dimer result (p=0.06, Table 2).

In the cases in which the control group agreed on a “likely” clinical probability, the classification of the clinical probability was influenced by the knowledge of neither an abnormal nor a normal D-dimer (Table 2).

DISCUSSION

These results show that having knowledge of the D-dimer test results influences the physician in the scoring of the clinical probability for PE, even if a semi-quantitative CDR is employed. The knowledge of an abnormal D-dimer result makes the physician more likely to score the patient as having a “likely” clinical probability, while the knowledge of a normal (low) D-dimer test result makes the physician more likely to score the patient as having a “unlikely” clinical probability.
Figure 1. Distribution of the clinical decision rule score for the six hypothetical cases. The left column depicts the outcome when a normal (low) D-dimer was given in the case description; the middle column depicts the outcome when no D-dimer result was given (control group) and the right column depicts the outcome when an abnormal (high) D-dimer was given in the case description. The dotted line in all graphs represents the cut-off for “unlikely” or “likely” clinical probability of pulmonary embolism.
Table 2. Clinical probability assessment of the patient cases according to the Wells clinical decision rule.

<table>
<thead>
<tr>
<th></th>
<th>Normal D-dimer (%)</th>
<th>No D-dimer (%)</th>
<th>Abnormal D-dimer (%)</th>
<th>Chi²*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td></td>
<td></td>
<td></td>
<td>0.049**</td>
</tr>
<tr>
<td></td>
<td>Unlikely</td>
<td>85</td>
<td>81</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Likely</td>
<td>15</td>
<td>19</td>
<td>44</td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
<td></td>
<td>0.001**</td>
</tr>
<tr>
<td></td>
<td>Unlikely</td>
<td>96</td>
<td>52</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Likely</td>
<td>4</td>
<td>48</td>
<td>71</td>
</tr>
<tr>
<td>Case 3</td>
<td></td>
<td></td>
<td></td>
<td>0.008**</td>
</tr>
<tr>
<td></td>
<td>Unlikely</td>
<td>83</td>
<td>92</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Likely</td>
<td>17</td>
<td>8</td>
<td>45</td>
</tr>
<tr>
<td>Case 4</td>
<td></td>
<td></td>
<td></td>
<td>0.236</td>
</tr>
<tr>
<td></td>
<td>Unlikely</td>
<td>0</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Likely</td>
<td>100</td>
<td>96</td>
<td>88</td>
</tr>
<tr>
<td>Case 5</td>
<td></td>
<td></td>
<td></td>
<td>0.257</td>
</tr>
<tr>
<td></td>
<td>Unlikely</td>
<td>0</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Likely</td>
<td>100</td>
<td>87</td>
<td>92</td>
</tr>
<tr>
<td>Case 6</td>
<td></td>
<td></td>
<td></td>
<td>0.070</td>
</tr>
<tr>
<td></td>
<td>Unlikely</td>
<td>77</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Likely</td>
<td>23</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td></td>
<td>Unlikely, % (n)</td>
<td>60 (84)</td>
<td>49 (69)</td>
<td>33 (46)</td>
</tr>
<tr>
<td></td>
<td>Likely, % (n)</td>
<td>40 (55)</td>
<td>51 (71)</td>
<td>67 (93)</td>
</tr>
</tbody>
</table>

Results are stratified for the three versions of the cases, in which a normal, an abnormal or no D-dimer was given. * p-values as calculated for the comparison of the three groups. ** Statistically significant.

Knowledge of the D-dimer result influences clinical probability assessment

results in more patients being scored as having an “unlikely” clinical probability. If the case is very suspect for PE by itself, knowledge of a normal D-dimer result does not influence the clinical probability categorization.

This switch in categorization of the probability is likely to have some direct clinical consequences. The D-dimer test has a low specificity and can be abnormal in numerous situations (16). In emergency departments, D-dimer tests may be ordered in any patient with shortness of breath or chest pain, before the patient is seen (13,15,17). The presence of an abnormal D-dimer test result will lead to a larger group of patients suspected of having PE and this could lead to unnecessary further imaging testing. Moreover, the observation that
awareness of a normal D-dimer makes physicians more likely to score the CDR as “unlikely” could lead to inappropriate exclusion of the diagnosis. As explained above, despite the high negative predictive value of the D-dimer assays, there is a chance up to 10% of a false negative result in patients with a “likely” clinical probability (9). Patients, in whom the physician is influenced to score an “unlikely” probability, due to the awareness of a normal D-dimer, might miss out on imaging tests which they possibly would have received had the physician not been aware of the D-dimer test.

Our results are in line with a previous study, which investigated the influence of an abnormal D-dimer on the scoring of the CDR (12). In this study, abnormal D-dimer results were added to the description of two out of five hypothetical cases, in one of the two available versions. In the present study, besides abnormal D-dimer results, also normal D-dimer results were added to the case-descriptions, resulting in three different versions and a direct comparison of no D-dimer, normal D-dimer and abnormal D-dimer. Furthermore, in contrast to the previous study, different D-dimer results were added to hypothetical cases of varying clinical probability, not only to cases of moderate clinical probability.

The study design of this survey carries some limitations, i.e. bias due to a possible influence of the data by non-responders and the hypothetical character of the questionnaire. More internists returned the questionnaire compared to pulmonologist, for reasons which are unknown. It is unlikely this difference will have biased the results, since pulmonologists and internists use the CDR and D-dimer test in a similar fashion, as a previous study in the Netherlands showed (12). The response rate was comparable to response rates of other questionnaires sent to physicians (11,12), but lower than we had hoped for based on other studies (12,18,19), despite the fact that a reminder was sent to the non-responders. Even though the sample size is limited, differences between the various groups were clearly present. We therefore expect that a higher response would amplify the current findings. Regarding the hypothetical character of the questionnaire, we realize that physicians may act differently in clinical practice from what they report in the questionnaire. However, the physicians were randomly selected, they were unaware of the true objective of the study and the questionnaires were randomly sent to the physicians. We therefore believe our results are a good reflection on the clinical probability assessment for pulmonary embolism.

In conclusion, the knowledge of the D-dimer test result influences the physician in how the clinical probability for PE is scored. This likely has direct clinical consequences, such as unnecessary imaging testing and inappropriate exclusion of the diagnosis. Physicians should therefore make sure that they examine the patient before they take notice of the D-dimer result, in line with the current guidelines, in order to improve patient care (4-7,10).
REFERENCE LIST

### APPENDIX

**Table. Wells clinical decision rule**

<table>
<thead>
<tr>
<th>Items</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats per minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization or surgery in the previous four weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemothysis</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy (treatment or palliative care in the past six months)</td>
<td>1</td>
</tr>
<tr>
<td>An alternative diagnosis is less likely than PE</td>
<td>3</td>
</tr>
</tbody>
</table>

**Clinical probability**

| PE Unlikely                                            | ≤4    |
| PE Likely                                              | >4    |

DVT, deep vein thrombosis; PE, pulmonary embolism.

**Case 1**

A 53-year old Indian man explains he had a severe flu last week, but now he increasingly suffers from shortness of breath and coughing. His medical history reveals diabetes mellitus and a mild hypertension. Furthermore, he had a deep vein thrombosis of his left leg nine years ago after knee surgery. Upon physical examination you find a heart rate (HR) of 110 beats per minute (bpm), his blood pressure (BP) is 145/90 mmHg, his respiratory rate is 20/minute and his body temperature is 37.8°C. Auscultation of the lungs is normal. The chest X-ray shows no abnormalities (unfortunately, a lateral image was not performed). The lab shows a mild leucocytosis of 12,6 x 10^9/L (…version).

Version 1 “____________________”
Version 2 “and the D-dimer result is 1278 µg/L”
Version 3 “and the D-dimer result is 426 µg/L”

**Case 2**

A 20-year old woman suffers from progressive pain when breathing since ten days. She smokes around 15 cigarettes a day. She uses no medication. She has a dry cough, which has worsened since the last week. Otherwise, she has no complaines. The HR is 101 bpm and the BP is 134/84 mmHg. She has no fever. Blood examination shows no leucocytosis (…version). The chest X-ray is normal.

Version 1 “and the D-dimer result is 960 µg/L.”
Version 2 “and the D-dimer result is 232 µg/L.”
Version 3 “_______________________”
**Case 3**
A man, 82 years old, with known COPD suffers from progressive shortness of breath since four days. He coughs more than usual, now also coughing up phlegm. Furthermore, because of a fall while doing groceries last week, he now has a painful right knee for which resting is advised. Until seven years ago, he was a vigorous smoker. T 36.8°C, BP 115/68 mmHg, HR 72 bpm. Auscultation of the lungs is normal. Some pleural effusion may be seen on the left pleural cavity on the chest X-ray. (...

**Version 1** “The D-dimer result is 1550 µg/L”
**Version 2** “The D-dimer result is 403 µg/L”
**Version 3** “_________________________”

**Case 4**
A 34-year old woman complains of pain on the left thorax since two days, worse when breathing. There is no cough. She has always been healthy, although last week she hurt her left knee while exercising, for which she needed to rest. She had bed rest for one day and then daily increased her activities a little. Her left leg is still swollen, with a tense and painful calf. Half a year ago she started taking oral contraceptives. Her BP is 140/92 mmHg; her HR is 88 bpm. The chest X-ray shows no abnormalities and neither does the EKG. (...

**Version 1** “The D-dimer result is 350 µg/L”
**Version 2** “_________________________”
**Version 3** “The D-dimer result is 1240 µg/L.”

**Case 5**
A 76-year old woman complains of progressive shortness of breath, painful breathing and coughing, expectorating yellow phlegm and sometimes a little bit of blood. Her medical history reveals breast cancer six years ago, pulmonary embolism three years ago, and hypertension. Four weeks earlier she had hip surgery. Upon physical examination, you see a short-winded women (respiratory rate 22 per minute), with a HR of 108 bpm and a blood pressure of 134/88 mmHg. The body temperature is 38.0°C. (...

**Version 1** “The D-dimer result is 390 µg/L.”
**Version 2** “_________________________.”
**Version 3** “The D-dimer result is 2680 µg/L.”

**Case 6**
A 45-year old man, suffering from a brain tumor, is admitted on the neurology department. One month earlier he developed aspiration pneumonia after an insult, from which he is now slowly recovering. The nurse calls to tell you the patient’s saturation has dropped to 89% with one liter O₂. He reports no complains and says did not choke himself. He has substantial obesity with a body mass index of 34 kg/m².
One year ago he developed a deep vein thrombosis of his right leg three weeks after surgery. Until 1.5 years ago, he was healthy. Upon physical examination you see a short-winded man, body temperature 38.2°C, HR 92 bpm, BP 132/86 mmHg. Examination of heart and lungs reveals no abnormalities; his calves are supple. The chest X-ray shows some remains of the
aspiration pneumonia basally, but also a clear improvement is seen with respect to a week earlier. (...version)

Version 1 “_________________________”
Version 2 “The D-dimer result is 1834 µg/L.”
Version 3 “The D-dimer result is 270 µg/L.”