Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts

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Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts

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ABSTRACT

Objectives In older patients, the the D-dimer test for pulmonary embolism has reduced specificity and is therefore less useful. In this study a new, age dependent cut-off value for the test was devised and its usefulness with older patients assessed.

Design Retrospective multicentre cohort study.

Setting General and teaching hospitals in Belgium, France, the Netherlands, and Switzerland.

Patients 5132 consecutive patients with clinically suspected pulmonary embolism.

Intervention Development of a new D-dimer cut-off point in patients aged >50 years in a derivation set (data from two multicentre cohort studies), based on receiver operating characteristics (ROC) curves. This cut-off value was then validated with two independent validation datasets.

Main outcome measures The proportion of patients in the validation cohorts with a negative D-dimer test, the proportion in whom pulmonary embolism could be excluded, and the false negative rates.

Results The new D-dimer cut-off value was defined as (patient’s age×10) μg/l in patients aged >50. In 1331 patients in the derivation set with an "unlikely" score from clinical probability assessment, pulmonary embolism could be excluded in 42% with the new cut-off value versus 36% with the old cut-off value (<500 μg/l). In the two validation sets, the increase in the proportion of patients with a D-dimer below the new cut-off value compared with the old value was 5% and 6%. This absolute increase was largest among patients aged >70 years, ranging from 13% to 16% in the three datasets. The failure rates (all ages) were 0.2% (95% CI 0.1% to 1.0%) in the derivation set and 0.6% (0.3% to 1.3%) and 0.3% (0.1% to 1.1%) in the two validation sets.

Conclusions The age adjusted D-dimer cut-off point, combined with clinical probability, greatly increased the proportion of older patients in whom pulmonary embolism could be safely excluded.

INTRODUCTION

Measurement of D-dimer concentration in the blood is a valuable tool in the diagnostic investigation of patients with suspected pulmonary embolism. A D-dimer measurement below the conventional cut-off point of 500 μg/l combined with a “low/intermediate” or “unlikely” clinical probability can safely rule out the diagnosis in about 30% of patients with suspected pulmonary embolism.1-3 However, the D-dimer concentration increases with age and its specificity for embolism decreases, which makes the test less useful to exclude pulmonary embolism in older patients.4,9 Indeed, the test is able to rule out pulmonary embolism in 60% of patients aged <40 years, but in only 5% of patients aged >80.8

If the D-dimer test is combined with an “unlikely” clinical probability10 to rule out pulmonary embolism, 10% of patients >75 years old versus 32% of patients of all ages do not need further diagnostic testing; the number needed to test for one negative test result is 10.6 and 3.1, respectively.9 Raising the cut-off value to various points between 600 μg/l and 1000 μg/l increased specificity, but this came at the cost of safety, with more false negative test results.11 In this analysis, however, no stratification was made for clinical probability.

By constructing receiver operating characteristics (ROC) curves, we derived a new, age dependent D-dimer cut-off value and analysed its safety and clinical utility, in combination with clinical probability assessment, for the exclusion of pulmonary embolism in two large prospective cohort studies of patients with suspected pulmonary embolism. We then validated the outcome in two other large management studies.

METHODS

Derivation set

We analysed the combined data from two prospective multicentre cohort studies, which included 1721 consecutive outpatient patients with suspected pulmonary embolism.1,2 These outcome studies were designed to evaluate diagnostic strategies for pulmonary embolism, combining clinical probability assessment, D-dimer measurement, lower limb venous compression ultrasonography, and helical computed tomography.

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Briefly, all consecutive patients admitted to the emergency department of four general and teaching hospitals were included if they had a clinical suspicion of pulmonary embolism. The inclusion and exclusion criteria and the results of the two studies have been published previously.1,2

The first study, conducted at Geneva University Hospital, Geneva, and Centre Hospitalier Universitaire Vaudois, Lausanne, both in Switzerland, and at Angers University Hospital, Angers, France, between October 2000 and June 2002, comprised 965 patients.12 The second study, conducted at Geneva University Hospital, Angers University Hospital, and Hôpital Européen Georges Pompidou, Paris, France, between September 2002 and October 2003, comprised 756 patients.1 Both studies were approved by the institutional review boards of each participating institution and written informed consent was obtained from all patients.

All patients underwent a sequential diagnostic investigation, including plasma D-dimer measurement by an enzyme linked immunosorbent assay (rapid ELISA assay, VIDAS D-Dimer Exclusion, Biomerieux, Marcy-l’Etoile, France). For each patient, the Geneva score13 was assessed to assign the patient to a clinical probability category—with possible override by implicit assessment in case the result conflicted with the assessor’s clinical judgment.14 Variables included in the Wells clinical prediction rule for pulmonary embolism10 were also systematically and prospectively collected, allowing calculation of the Wells score.

Pulmonary embolism was ruled out by (a) a D-dimer concentration <500 μg/l, except in patients with a high clinical probability, in the second study; (b) negative results from lower limb venous compression ultrasonography and from helical computed tomography in patients with a low or intermediate clinical probability of pulmonary embolism; or (c) by a normal ventilation-perfusion lung scan or a normal pulmonary angiogram in patients with a high clinical probability or with inconclusive helical computed tomogram. Pulmonary embolism was established by (a) a finding of proximal deep vein thrombosis on lower limb ultrasonography; (b) a positive result from helical computed tomography; or (c) a high probability ventilation-perfusion lung scan or a positive pulmonary angiogram in high clinical probability patients with negative results from both compression ultrasonography and helical computed tomography, and in patients with inconclusive computed tomogram.

Patients were followed up by their family physicians and were interviewed by telephone by one of the study coordinators at the end of three months’ follow-up. The outcome was an estimate of the three month thromboembolic risk in patients in whom pulmonary embolism was considered ruled out by the initial diagnostic investigations and who did not receive anticoagulants during follow-up. Confirmation of venous thromboembolic events during follow-up were established with the usual criteria.1,2,12

Validation set 1

For the first validation set, data from a third prospective multicentre cohort study were used.2 This study evaluated the clinical effectiveness of a simplified algorithm using the dichotomised Wells rule, D-dimer testing, and computed tomography in patients with suspected pulmonary embolism. Briefly, all consecutive inpatients and outpatients with clinically suspected acute pulmonary embolism were eligible for the study, which was conducted between November 2002 and August 2004 in 12 hospitals in the Netherlands. The institutional review boards of all participating hospitals approved the study protocol. The results and the inclusion and exclusion criteria were published previously.2 The study population comprised 3306 patients.

All patients underwent a sequential diagnostic investigation, consisting of clinical probability calculation, a D-dimer test (Tinaquant, Roche Diagnostica, Mannheim, Germany or Vidas D-Dimer Exclusion, Biomerieux) and computed tomography scanning. At admission, the clinical probability of pulmonary embolism was calculated by the treating physician using the Wells score. According to the protocol, a D-dimer test was performed only in patients with a Wells score of ≤4. Pulmonary embolism was ruled out by (a) an unlikely clinical probability (Wells score ≤4) combined with a D-dimer test ≤500 μg/l or (b) a negative helical computed tomogram in patients with a “likely” clinical probability or an abnormal D-dimer test. Pulmonary embolism was established by a positive helical computed tomogram. The follow-up was performed the same way as in the derivation set studies.

Validation set 2

For the second validation set, data from a fourth prospective multicentre study were used.3 This study investigated in a randomised non-inferiority trial whether the addition of venous ultrasonography to multi-detector computed tomography improved the detection of pulmonary embolism. Consecutive outpatients with clinically suspected acute pulmonary embolism were eligible for the study, which was conducted between January 2005 and August 2006 in six hospitals in France, Belgium, and Switzerland. The institutional review boards of all participating hospitals approved the study protocol. The results and inclusion and exclusion criteria were published previously.9 The study population comprised 1812 patients.

All patients underwent a sequential diagnostic investigation, consisting of clinical probability calculation, a D-dimer test (Vidas D-Dimer Exclusion, Biomerieux) and then randomisation to either multi-detector computed tomography alone or compression ultrasonography of the legs followed by computed tomography. At admission, the clinical probability was calculated by the treating physician using the revised Geneva score.15 Pulmonary embolism was ruled out by (a) a non-high clinical probability (revised Geneva score <11) combined with a D-dimer test <500 μg/l or (b) a negative helical computed tomography result in patients with a high revised Geneva score or an
 discusses the age adjusted D-dimer cut-off point was validated only in patients with an “unlikely” or non-high clinical probability score in these two cohorts. We calculated exact 95% confidence intervals using CIA software version 1.0 (Gardner et al. Confidence Interval Analysis (CIA), BMJ Books). All other analyses were performed with SPSS version 15.0 (SPSS, Chicago, IL).

RESULTS

Derivation of the new cut-off value

Of the 1721 patients included in the derivation set, 416 (24.2%) had pulmonary embolism. The D-dimer test was not performed for nine patients from the second study with high clinical probability (all nine had pulmonary embolism diagnosed during initial investigation). Table 1 shows the clinical characteristics of the patients in the derivation cohort.

The figure shows the increase in optimal D-dimer cut-off value by patient age group, obtained from the ROC curves for each group. The cut-off point increased from 512 µg/l in patients <50 years old to 934 µg/l in patients >80 years old. The regression coefficient was 112 (SE 12.03) µg/l increase per decade, or 11.2 µg/l increase per year (r2=0.966). To be conservative and to facilitate clinical usefulness and practicality, we considered a 10 µg/l increase per patient year to be an appropriate new D-dimer coefficient. Starting from the conventional cut-off point of 500 µg/l until the age of 50, for older patients the patient age should be multiplied by 10 to calculate the age adjusted cut-off value.

Derivation set outcome

With the conventional cut-off value, the VIDAS D-dimer test was normal (<500 µg/l) in 512/1712 patients (29.9%), and none had pulmonary embolism during the initial investigation or the three month follow-up (0%, 95% CI 0% to 0.7%). The number of patients needed to test to find one normal D-dimer test result was 3.3. The Wells score could not be computed in 54 of the patients, mainly because information on the likelihood of an alternative diagnosis to that of pulmonary embolism was missing (n=42).

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Table 1 | Baseline characteristics of the derivation and validation cohorts of patients with clinically suspected pulmonary embolism used to produce an age dependent cut-off value for the D-dimer test for pulmonary embolism. Values are numbers (percentages) of patients unless specified otherwise

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Derivation set (n=1721)</th>
<th>Validation set 1 (n=3306)</th>
<th>Validation set 2 (n=1819)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>61 (19)</td>
<td>53 (18)</td>
<td>59 (19)</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>63 (45-76)</td>
<td>51 (39-68)</td>
<td>61 (45-75)</td>
</tr>
<tr>
<td>Female</td>
<td>1016 (59)</td>
<td>1896 (57)</td>
<td>922 (51)</td>
</tr>
<tr>
<td>History of venous thromboembolism</td>
<td>308 (18)</td>
<td>480 (15)</td>
<td>300 (17)</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>164 (10)</td>
<td>474 (14)</td>
<td>127 (7.0)</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>94 (5.5)</td>
<td>46 (1.4)</td>
<td>94 (5.2)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>80 (4.6)</td>
<td>176 (5.3)</td>
<td>83 (4.6)</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/min</td>
<td>362 (21)</td>
<td>867 (26)</td>
<td>369 (20)</td>
</tr>
<tr>
<td>Clinical signs of deep vein thrombosis</td>
<td>246 (14)</td>
<td>190 (5.7)</td>
<td>153 (8.4)</td>
</tr>
</tbody>
</table>

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abnormal D-dimer test result. Pulmonary embolism was established by a positive result from helical computed tomography or compression ultrasonography. The follow-up was performed in the same way as the previous studies.

Data analysis

In the derivation set and validation set 1 the Wells clinical prediction rule for pulmonary embolism was calculated in all patients, and patients were classified according to the dichotomised Wells score as likely or unlikely to have pulmonary embolism. In validation set 2, the revised Geneva score was calculated in all patients and classified as a high or non-high (low or intermediate) score.

To derive a new D-dimer cut-off value, we divided patients aged >50 in the derivation set into 10 year age groups. We constructed receiver operating characteristics (ROC) curves of the D-dimer test for each age group to find the best cut-off value (with a sensitivity of 100% and the highest corresponding specificity). We plotted the D-dimer cut-off level against age group and performed linear regression analysis to obtain the regression coefficient, representing the increase in D-dimer cut-off value per decade. This coefficient was divided by 10 to find the coefficient per year. This coefficient was the multiplication factor for age in the new age-adjusted cut-off value.

We then calculated the proportion of patients with a negative D-dimer test result (as defined by the new cut-off point), the proportion in whom pulmonary embolism could be excluded (based on an “unlikely” Wells score or “non-high” revised Geneva score plus the negative D-dimer test result), and the false negative rates (that is, those patients who had pulmonary embolism in the diagnostic investigation or during follow-up). The number of patients needed to test by D-dimer to rule out one pulmonary embolism was computed as 1 divided by the proportion of patients with a negative D-dimer test result in each age group.16

In the validation sets, D-dimer test results were missing in a large proportion of patients with a “likely” Wells score or high revised Geneva score. Therefore,
patients with an unlikely clinical probability of pulmonary embolism, D-dimer test results were recorded only qualitatively and were therefore missing for this analysis. In another seven patients age was not documented, leaving 2158 patients. Among these, 983 patients had a negative D-dimer test result with the conventional cut-off value, of whom two (0.2%, 95% CI 0.1% to 0.7%) had pulmonary embolism during the diagnostic investigation or three month follow-up. With the age adjusted cut-off value, 1093 patients had a negative D-dimer test result, of whom seven (0.6%, 0.3% to 1.3%) had pulmonary embolism. Table 3 shows the proportion of patients in whom pulmonary embolism could be excluded based on the old and the new cut-off values.

The age adjusted cut-off value resulted in an 11.2% (9.3% to 13.3%) increase in the number of patients with a negative D-dimer test result. The increase in the proportion of patients in whom pulmonary embolism could be ruled out (that is, unlikely clinical probability with a D-dimer level below the cut-off) from using the age adjusted cut-off value was most prominent among patients in the age groups >70 years, with an absolute increase of 14% compared with the conventional cut-off point.

External validation
The concept of using an increasing cut-off value for the D-dimer test according to age was validated in two independent cohorts of patients with suspected pulmonary embolism. The clinical characteristics of the patients in these cohorts were similar to those of the patients in the derivation set (table 1).

Validation set 1
Of the 3306 patients included in validation set 1, 674 (20.4%) had pulmonary embolism. In 41 of the 2206
The clinical usefulness of the new cut-off value increased significantly with age: the proportion of patients in whom pulmonary embolism could be ruled out with the new cut-off value was a third higher in patients older than 50 and almost twice as high in patients older than 70 compared with the conventional cut-off. Increasing the cut-off point to improve clinical utility did not come at the expense of safety: in the derivation and validation sets there was no difference in the false negative rate, and for the total population and for patients aged >50 years the 95% upper confidence limits were well below 3% with the new cut-off value.

**Impact in the clinical setting**

A recent cost effectiveness analysis showed that D-dimer measurement as part of the diagnostic investigation of patients with suspected pulmonary embolism was cost saving until the age of 79 years. After 80 years, the test’s clinical utility was too low to be cost effective, and the costs of strategies with or without D-dimer testing were similar. This analysis was based on the conventional cut-off point of 500 μg/l for ELISA based assays. It can be expected, however, that the test’s cost effectiveness in older patients would increase with the new cut-off value, as the number needed to test was lower with the age adjusted cut-off value compared with the conventional cut-off value in patients >80 years old (3.5 versus 6.6). For a given clinical setting, this means that for every 35 patients aged >80 years old (3.5 versus 6.6). For a given clinical setting, this means that for every 35 patients aged >80 years old (3.5 versus 6.6). For a given clinical setting, this means that for every 35 patients aged >80 years old (3.5 versus 6.6).

**DISCUSSION**

The study shows that an age adjusted cut-off level for the D-dimer test for exclusion of pulmonary embolism doubles the proportion of older patients (>70 years) in whom pulmonary embolism can be safely excluded in comparison with the conventional cut-off value of 500 μg/l. We derived and validated this new cut-off value in three large cohorts of consecutive patients with suspected pulmonary embolism, totalling over 5000 patients. In these three cohorts, the number of older patients in whom pulmonary embolism could be safely ruled out was consistent, between 25% and 30%.

The clinical usefulness of the new cut-off value increased significantly with age: the proportion of patients in whom pulmonary embolism could be ruled out with the new cut-off value was a third higher in patients older than 50 and almost twice as high in patients older than 70 compared with the conventional cut-off. Increasing the cut-off point to improve clinical utility did not come at the expense of safety: in the derivation and validation sets there was no difference in the false negative rate, and for the total population and for patients aged >50 years the 95% upper confidence limits were well below 3% with the new cut-off value.

**Table 4| Proportion of patients in validation set 1 with an unlikely clinical probability of pulmonary embolism* in whom pulmonary embolism could be excluded based on a D-dimer test result below the cut-off value: comparison of different cut-off values stratified by age group**

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>All patients</th>
<th>51-60</th>
<th>61-70</th>
<th>71-80</th>
<th>&gt;80</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (%) of patients below cut-off value</td>
<td>2158</td>
<td>358 (17)</td>
<td>270 (13)</td>
<td>245 (18)</td>
<td>166 (7.7)</td>
</tr>
<tr>
<td>Median (Q2Q3) age (years)</td>
<td>49 (37-66)</td>
<td>55 (52-57)</td>
<td>66 (63-68)</td>
<td>74 (72-77)</td>
<td>84 (82-88)</td>
</tr>
</tbody>
</table>

**Conventional cut-off value†**

<table>
<thead>
<tr>
<th>No (%), 95% CI</th>
<th>4/637 (0.6, 0.2 to 1.6)</th>
<th>3/456 (0.7, 0.2 to 1.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (%) of patients with false negative result</td>
<td>&gt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

**Age adjusted cut-off value†**

<table>
<thead>
<tr>
<th>No (%), 95% CI</th>
<th>2/576 (0.3, 0.1 to 1.3)</th>
<th>0/407 (0, 0 to 0.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (%) of patients with false negative result</td>
<td>&gt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

*Based on Wells clinical decision rule.
††Conventional cut-off value for D-dimer test=500 μg/l, age adjusted cut-off value=(age×10) μg/l (if age >50).
‡Number needed to test to find one normal D-dimer test result.
The combination of D-dimer measurement and clinical probability assessment is valuable for investigation of suspected pulmonary embolism. D-dimer concentrations increase with age, and the specificity of the D-dimer test is decreased in older patients, making the test less useful for excluding pulmonary embolism in such patients. Raising the cut-off value of the D-dimer test for older patients to points between 600 μg/l and 1000 μg/l increases the test’s specificity, but at the cost of safety.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

The combination of D-dimer measurement and clinical probability assessment is valuable for investigation of suspected pulmonary embolism. D-dimer concentrations increase with age, and the specificity of the D-dimer test is decreased in older patients, making the test less useful for excluding pulmonary embolism in such patients. Raising the cut-off value of the D-dimer test for older patients to points between 600 μg/l and 1000 μg/l increases the test’s specificity, but at the cost of safety.

**WHAT THIS STUDY ADDS**

An age-adjusted D-dimer cut-off value combined with clinical probability assessment increased the utility of the D-dimer test for excluding pulmonary embolism among older patients without reducing safety. The new cut-off value has sustained external validation. The next step would be to validate this new cut-off value prospectively before implementation in daily practice.


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