Diagnostic Accuracy of Triage Tests to Exclude Pulmonary Embolism

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Key words
Pulmonary embolism, diagnosis, D-dimer, probability, estimate, triage

Summary
We performed a study in 403 prospectively included patients with suspected pulmonary embolism to compare the accuracy of a combination of the SimpliRED D-dimer assay and an intuitive clinical probability estimate with either one alone. Based on a conjoint diagnostic reference standard, including ventilation-perfusion lung scintigraphy and pulmonary angiography, the prevalence of pulmonary embolism was 31%. We demonstrated a high sensitivity (98%, 95% CI 95-100) and negative predictive value (94%, 95% CI 79-99) for the combination of the two tests. These figures were more favorable than for either test alone. The specificity of the combination was lower (11%, 95% CI 9-12) and consequently the proportion of patients in whom further diagnostic tests would have been avoided was only 8%. We conclude that the combined use of the SimpliRED test and the clinical probability estimate attains a higher sensitivity than either test alone. However, there remains a risk of false negatives and the exclusion efficiency is limited.

Introduction
It has been well documented that of all patients with clinically suspected pulmonary embolism only one third has the disease confirmed by objective diagnostic tests (1, 2). The conventional objective diagnostic work-up includes ventilation-perfusion lung scintigraphy as the initial step, followed by pulmonary angiography in case of a non-diagnostic lung scan. However, this work-up has as drawbacks the non-diagnostic lung scan and consequently the proportion of patients in whom further diagnostic tests would have been avoided was only 8%. We conclude that the combined use of the SimpliRED test and the clinical probability estimate attains a higher sensitivity than either test alone. However, there remains a risk of false negatives and the exclusion efficiency is limited.

Triage Tests
A limited number of trained investigators performed the SimpliRED D-dimer assay (Agen Biomedical Ltd, Brisbane, Australia) prior to or within 24 hours of the start of heparin therapy and before other diagnostic investigations. The method for the performance of this rapid D-dimer test has been described elsewhere (13). Briefly, this test is a whole blood agglutination assay, which employs a conjugate of two monoclonal antibodies resulting in a bispe-
cific antibody raised against the human D-dimer epitope (DD-3B6/22) and red blood cells (RAT-1C3/86). Capillary blood (2 × 10 µl) was obtained by fingerstick. The test result is abnormal when agglutination of red cells becomes visible on the test slide within two minutes, reflecting a D-dimer concentration of 0.20 mg/l or above.

The clinical probability estimates of pulmonary embolism were performed as described in a previous report of our study (14). After a medical history, physical examination and routine tests (such as, arterial bloodgas analysis, electrocardiogram and chest X-ray) were performed, and prior to lung scintigraphy, the treating physician was asked to mark a clinical probability estimate of pulmonary embolism on a visual analog scale of 0 to 100 percent. Many different residents who worked under supervision of staff physicians at the various departments where patients were seen gave the clinical probability estimates. The estimates were given on the basis of their intuition without the use of a standardized algorithm. The respective physicians had not received formal training in the performance of the clinical probability estimate and were neither involved in the coordination nor in the analysis of the study. They were aware that no therapeutic management decisions were attached to their estimates. For the purpose of the present study, we dichotomized the estimates afterwards into less than 20% (i.e. low clinical probability) or greater than or equal to 20%. This cut-off point was chosen on the basis of previous literature (2, 15).

In order to avoid potential diagnostic suspicion bias in our study, D-dimer tests and clinical probability estimates were performed independently of each other.

Reference Test

The reference diagnostic test to confirm or refute the diagnosis of pulmonary embolism was ventilation-perfusion lung scintigraphy or pulmonary angiography. Pulmonary embolism was considered to be present in case of a high probability lung scan or abnormal angiography and absent if the lung scan or angiography was normal. Lung scans were obtained within 24 h of study inclusion, after the administration of 100 MBq of 99mTc-Technetium-labelled macro-aggregates of albumin. If segmental or larger perfusion defects were seen, ventilation lung scintigraphy was added using 133XeKrypton gas. The lung scans were classified according to previously described criteria as normal, high probability or non-diagnostic (1). A panel of experienced nuclear medicine physicians interpreted all lung scans by using a lung segment reference chart and reached final classifications by consensus (16). Pulmonary angiographies were performed and interpreted using standard methods in all patients with a non-diagnostic lung scan (17, 18). The angiographies were interpreted independently by two radiologists and in case of disagreement, the independent interpretation of a third was decisive. All reference diagnostic tests were interpreted without knowledge of the D-dimer test results and the clinical probability estimates. The maximum allowed interval between these tests was 24 h, albeit they were mostly performed in one day.

Data Analysis

Patients in whom a definite conclusion regarding the presence or absence of pulmonary embolism was reached according to the conjoint diagnostic reference standard, and both a D-dimer test result and a clinical probability estimate were available, were included in the final analysis. The outcome of the combination of the two tests, further referred to as ‘the combination’, was designated negative (i.e. to exclude pulmonary embolism) in case of a normal D-dimer test result and a low clinical probability estimate (< 20%). All other combinations of test results were designated positive. The sensitivity, specificity, negative predictive value and corresponding exact 95% confidence intervals (CI) were calculated. In addition, the exclusion efficiency, i.e. the proportion of all included patients with a negative outcome of the combination, was calculated. The accuracy indices were compared using Chi-square tests and if necessary Fisher’s exact tests. Two-tailed p-values of less than 0.05 were considered to indicate statistical significance.

Results

From May 1997 through March 1998, a total of 1162 patients with clinically suspected pulmonary embolism were screened for eligibility. Of these patients, 179 were excluded on the basis of the predefined criteria. Of the 983 eligible patients, 627 (64%) agreed to participate in the study. A reference diagnosis regarding the presence or absence of pulmonary embolism was not reached in 110 of these patients because of clear evidence for an alternative diagnosis, medical reasons, technical failure or premature withdrawal of informed consent. In 114 other patients the clinical probability estimate was not obtained before the lung scan result was known and/or the SimpliRED D-dimer assay was not performed due to logistic reasons. This left a total of 403 patients for final analysis. Their baseline clinical characteristics were similar to those of the 224 patients who were not included in the analysis (Table 1). However, the latter patients were more often in-patients, had more co-morbid conditions and more symptoms of deep vein thrombosis.

Of the 403 study patients, 125 (31%) were classified as having pulmonary embolism on the basis of 105 high probability lung scans and 20 abnormal angiographies. The diagnosis of pulmonary embolism was refuted in the remaining patients on the basis of 186 normal lung scans and 92 normal angiographies.

Of the 125 patients with proven pulmonary embolism, 123 had a positive outcome of the combination (sensitivity 98%, 95% CI 95-100).

<table>
<thead>
<tr>
<th></th>
<th>Study patients</th>
<th>Excluded patients</th>
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</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>173 (43%)</td>
<td>97 (43%)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>52 (18)</td>
<td>55 (19)</td>
</tr>
<tr>
<td>Out-patients</td>
<td>329 (82%)</td>
<td>161 (72%)</td>
</tr>
<tr>
<td>Median duration of symptoms, days (quartiles)</td>
<td>3 (1, 9)</td>
<td>3 (1, 10)</td>
</tr>
<tr>
<td>Previous history of VTE</td>
<td>59 (15%)</td>
<td>39 (17%)</td>
</tr>
<tr>
<td>Family history of VTE</td>
<td>80 (20%)</td>
<td>42 (19%)</td>
</tr>
<tr>
<td>Risk-period*</td>
<td>143 (35%)</td>
<td>106 (47%)</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>40 (10%)</td>
<td>31 (14%)</td>
</tr>
<tr>
<td>Symptoms of DVT</td>
<td>19 (5%)</td>
<td>24 (11%)</td>
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</tbody>
</table>

Table 1 Baseline clinical characteristics of the 403 study patients and the 224 patients who were excluded from the final analysis

VTE = venous thromboembolism

* = period of immobilization, surgery or trauma in period of 3 months before presentation

DVT = deep vein thrombosis
The combination had a negative outcome in 31 of the 278 patients without pulmonary embolism (specificity 11%, 95% CI 9-12). Of all 33 patients with a negative outcome of the combination (exclusion efficiency 8%), 2 had pulmonary embolism (negative predictive value 94%, 95% CI 79-99). These two patients were outpatients without co-morbid conditions or risk factors for venous thromboembolism, did not receive anticoagulant therapy prior to the performance of the SimpliRED test and had a short duration of symptoms before presentation (less than 24 h; 3 days). The first patient presented with high fever (39.7°C), a heart rate of 101 beats/min, dyspnea, non-pleuritic retrosternal chest pain and without concurrent symptoms of deep vein thrombosis. The treating physician considered pneumonia with pleural fluid more likely than pulmonary embolism. The second patient suffered only from non-pleuritic retrosternal chest pain and an alternative diagnosis was not considered.

Table 2 illustrates that the sensitivity of the combination was significantly higher as compared to the separate sensitivities of the SimpliRED test (p < 0.001) and the clinical probability estimate (p = 0.02). Its specificity was lower than either test alone (p < 0.001 and p = 0.07, respectively). The combination showed a higher negative predictive value than the SimpliRED test and clinical probability estimate separately, albeit statistically significant differences were not reached (p = 0.54 and p = 0.12, respectively). The exclusion efficiency of the combination was less than either test alone.

### Discussion

This study in a large cohort of consecutive patients with clinically suspected pulmonary embolism demonstrated a high sensitivity and negative predictive value for the combined use of the SimpliRED test and a clinical probability estimate of pulmonary embolism. These figures were more favorable than for either test alone. The resultant specificity of this combination was lower and, consequently, the exclusion efficiency (i.e. the proportion of the study population with a negative outcome) was less. The clinical utility of the combination for the diagnostic work-up of patients with suspected pulmonary embolism is thus limited.

Our results for the combination are discordant with those of two earlier studies in which the SimpliRED test was combined with structured clinical models to exclude pulmonary embolism (11, 12). These studies demonstrated that the combined use of these triage tests attained a higher sensitivity than either test alone. However, the reported pulmonary embolism rates in patients in whom pulmonary embolism was considered absent (false negatives) were lower (1.0 to 2.7%) than observed in our study (6%). Moreover, the exclusion efficiency was substantially higher in the other studies (29 to 46%) than in the present cohort.

What are the potential explanations for these discordant results? Firstly, the reference test in our study was either lung scintigraphy or pulmonary angiography, while the two earlier studies used clinical follow-up as a reference test for a part of their patients (11, 12). We acknowledge that clinical follow-up provides a useful measure to evaluate the safety of treatment decisions made on basis of the outcome of diagnostic tests for pulmonary embolism. However, clinical follow-up may fail to identify smaller pulmonary emboli because of a perceived low tendency for recurrence and immediate mortality when left untreated (19). As previously described such a differential classification could have led to an overestimation of the sensitivity and negative predictive value of the combination in these two studies (20). Secondly, the lower prevalence of pulmonary embolism (17%) in these studies, compared to the present study (31%), could also indicate that the spectrum of patients included was different. This may provide another plausible explanation for the discordant results, as the discriminatory performance of a diagnostic test can vary among patients with a different spectrum of disease (21, 22). Finally, another possible explanation could be that we used an intuitive assessment of the clinical pretest probability of pulmonary embolism instead of structured clinical models. However, we have recently shown that a physician’s judgment alone and these structured clinical models performed comparable in categorizing the pretest probability of pulmonary embolism (14).

Three methodological issues of the present study should be addressed. The first issue is that a proportion of the patients was not included in the final analysis. This could potentially have introduced selection bias in our results. However, most of the baseline clinical characteristics of the final study population were similar to those of the patients who were not analyzed (Table 1). The excluded patients were more often in-patients with consequently more co-morbidity. Therefore, our study results may be more applicable to out-patients than to in-patients generally seen with clinically suspected pulmonary embolism. The second issue is that the treating physicians were aware that no decisions about treatment were attached to their clinical probability estimates of pulmonary embolism. This could have resulted in less well-considered estimates and thereby a loss of predictive value of the triage test combination. The final issue is that a formal training of the treating physicians in estimating the clinical pretest probability was not undertaken prior to the start of the study. Moreover, it can not be excluded that these physicians had a varying experience in the management of patients with suspected pulmonary embolism. Although this could have influenced the accuracy of the probability estimates, one can also argue that this approaches the clinical reality. Nonetheless, until the true impact of experience on the accuracy of the probability estimates has been established, one should be cautious when physicians with less experience estimate the clinical pretest probability of pulmonary embolism.

If we had decided not to treat patients with a negative outcome of the combination, anticoagulant treatment would still have been inappropriately withheld in a small, but unacceptable, proportion (6%) of the patients. Moreover, the clinical utility in terms of reducing the need for further diagnostic testing seems limited due to the low specificity. We realize that conclusions regarding the safety of using the combination to exclude pulmonary embolism should eventually be based on prospect-
tive management studies with assessment of the thromboembolic risk during strict follow-up. It is important to notice that the two patients with pulmonary embolism who were apparently missed by the combination had a relatively short duration of symptoms before they entered the study. This may have caused false normal D-dimer results in these patients, since the fibrinolytic activation may not yet have sufficiently increased the D-dimer levels above the cut-off point for an abnormal test result (23). Although these two patients were incorrectly assigned a low clinical probability estimate of pulmonary embolism, their clinical presentation would also have resulted in a low pretest probability according to the earlier described structured clinical models (11, 12). As the number of patients with a false negative outcome of the combination was small, adequate conclusions whether certain patient characteristics are indeed associated with an increased risk for false negative outcomes could not be drawn.

In conclusion, the combined use of the SimpliRED D-dimer assay and the clinical probability estimate attains a higher sensitivity than either test alone in patients suspected of pulmonary embolism. However, there remains a risk of false negatives and the exclusion efficiency is limited. Further investigations focusing on the recognition of patients in whom the outcome of a triage test may be false negative are needed.

Appendix

The following investigators, all in The Netherlands, were part of the ANTELOPE-Study Group:

B. J. Sanson, J. G. Lijmer, M. H. Prins, H. R. Büller (Academic Medical Center, Amsterdam); W. de Monym, M. V. Huisman, P. M. T. Pattynuma (Leiden University Medical Center, Leiden); M. J. L. van Strijen, G. J. Kieft (Leyenburg Hospital, The Hague); M. R. Mac Gillavry, F. Turkstra, D. P. M. Brandjes (Slotervaart Hospital, Amsterdam); P. J. Hagen, O. S. Hoekstra, P. E. Postmus (University Hospital Vrije Universiteit, Amsterdam); I. J. C. Hartmann, P. F. G. M. van Waes, J. D. Banga (University Medical Center, Utrecht).

References


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