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Systematic review and meta-analysis of strategies for the diagnosis of suspected pulmonary embolism

Pierre-Marie Roy, Isabelle Colombet, Pierre Durieux, Gilles Chatellier, Hervé Sors, Guy Meyer

Abstract

Objectives To assess the likelihood ratios of diagnostic strategies for pulmonary embolism and to determine their clinical application according to pretest probability.


Study selection Studies that evaluated diagnostic tests for confirmation or exclusion of pulmonary embolism.

Data extracted Positive likelihood ratios for strategies that confirmed a diagnosis of pulmonary embolism and negative likelihood ratios for diagnostic strategies that excluded a diagnosis of pulmonary embolism.

Data synthesis 48 of 1012 articles were included. Positive likelihood ratios for diagnostic tests were: high probability ventilation perfusion lung scan 18.3 (95% confidence interval 10.3 to 32.5), spiral computed tomography 24.1 (12.4 to 46.7), and ultrasonography of leg veins 16.2 (5.6 to 46.7). In patients with a moderate or high pretest probability, these findings were associated with a post-test probability of pulmonary embolism greater than 85%. Negative likelihood ratios were: normal or near normal appearance on lung scan 0.05 (0.03 to 0.10), a negative result on spiral computed tomography along with a negative result on ultrasonography 0.04 (0.03 to 0.06), and a d-dimer concentration <500 μg/l measured by quantitative enzyme linked immunosorbent assay 0.08 (0.04 to 0.18). In patients with a low or moderate pretest probability, these findings were associated with a post-test probability of pulmonary embolism below 5%. Spiral computed tomography alone, a low probability ventilation perfusion lung scan, magnetic resonance angiography, a quantitative latex d-dimer test, and haemagglutination d-dimers had higher negative likelihood ratios and can therefore only exclude pulmonary embolism in patients with a low pretest probability.

Conclusions The accuracy of tests for suspected pulmonary embolism varies greatly, but it is possible to estimate the range of pretest probabilities over which each test or strategy can confirm or rule out pulmonary embolism.

Introduction

Clinical signs and symptoms of pulmonary embolism allow the clinician to determine the pretest probability of someone having the condition (the clinical probability) but are insufficient to diagnose or rule it out. Laboratory tests and imaging are thus required in all patients with suspected pulmonary embolism. A large number of diagnostic tests and strategies have been evaluated for pulmonary embolism, but their diagnostic value has varied.

We carried out a systematic review to assess the likelihood ratios of the diagnostic tests used for suspected pulmonary embolism. We also estimated the range of pretest probabilities over which each test can accurately confirm or exclude pulmonary embolism.

Materials and methods

We searched Medline, Embase, and Pascal Biomed for studies published from January 1990 to September 2005 (see bmj.com for search terms). We also carried out a manual search of published articles.

Two reviewers (PMR, GM) independently selected potentially relevant studies. Studies were included if they evaluated tests or strategies aimed at confirming or excluding pulmonary embolism and they met the following criteria: the reference method was pulmonary angiography for confirmation strategies and clinical follow-up or pulmonary angiography for exclusion strategies; the study was prospective; participants were recruited consecutively; and the test being evaluated and the reference test were interpreted independently.

Each study was graded according to the reference method and the patients' characteristics (see table A on bmj.com). For studies with multiple publications, we used the most recent publication.

Data extraction

Two investigators (PMR, GM) independently abstracted data on the characteristics of the study and patients; type of reference standard; and the number of
true positive, true negative, false positive, and false negative test results.

When we used follow-up as the reference method, we considered all the patients with a negative test result to have a false negative result if they developed deep vein thrombosis or pulmonary embolism during the three month follow-up period. We classified deaths believed to be caused by pulmonary embolism as thromboembolic events.

Statistical analysis
We calculated the positive likelihood ratio for confirmation strategies and the negative likelihood ratio for exclusion strategies. We used the adjusted Wald method to calculate 95% confidence intervals. Summary estimates of the likelihood ratios were calculated as a weighted average, and we calculated the confidence intervals using the DerSimonian and Laird random effects method. Homogeneity tests were carried out across the studies. We used Cochran’s Q heterogeneity statistic and the quantity I² to determine the percentage of total variation across the studies due to heterogeneity rather than to chance. When I² was more than 0%, we explored possible reasons for heterogeneity, using subgroup analysis based on the three categories for study quality (see table A on bmj.com).

Clinical practice perspectives
We considered that a confirmation strategy was accurate enough to diagnose pulmonary embolism when the post-test probability was above 85%, and that an exclusion strategy was accurate enough to exclude pulmonary embolism when the post-test probability was below 5%. We used Bayes’s theorem to calculate the probability of pulmonary embolism, conditioned by the likelihood ratio as a function of the pretest probability.

Results
We identified 48 of 1012 potentially eligible articles, totalling 11 004 patients with suspected pulmonary embolism (see references w1-w48 on bmj.com). The condition was confirmed in 3329 patients (prevalence 30%). See tables B-D on bmj.com for characteristics of the studies.

Figures
Figure 1 summarises the pooled positive likelihood ratios of confirmation diagnostic strategies (also see table 1 on bmj.com).

Two studies evaluated lung scintigraphy; one assessed the performances of ventilation and perfusion lung scans. Miniati et al studied the value of a perfusion lung scan without ventilation. We were unable to pool the results of these studies.

We found significant heterogeneity among the five studies on magnetic resonance angiography. We excluded this from the calculation of summary negative likelihood ratios.

Exclusion diagnostic strategies
Figure 2 summarise the exclusion diagnostic strategies and their pooled negative likelihood ratios (also see table 2 on bmj.com).

Nine studies analysed the value of a negative result on spiral computed tomography for excluding pulmonary embolism; however, one used a specific definition for negative results. We detected significant heterogeneity in the study group, but not in the two grade A studies.

We found heterogeneity in the group of ultrasonography studies. Of the six studies we considered in patients with a non-diagnostic ventilation and perfusion lung scan and one in patients selected on the basis of clinical probability and D-dimer testing; Wells et al studied the negative diagnostic value of serial ultrasonography after a non-diagnostic ventilation and perfusion lung scan.

Table 2 on bmj.com and figure 3 summarise the studies that evaluated D-dimers for the exclusion of pulmonary embolism (see also table D on bmj.com). In the analysis we included 12 studies that evaluated three different quantitative D-dimer enzyme linked immunosorbent assays, including two classic microplate methods and one rapid quantitative method. One study used a different cut-off threshold. We excluded this from the calculation of summary negative likelihood ratios. We detected significant heterogeneity in the group but no heterogeneity in the grade B or grade C studies.
Studies that used seven different quantitative \( \text{D-dimer} \) latex agglutination assays met our inclusion criteria. Two studies evaluated several latex \( \text{D-dimer} \) tests in the same patients. We therefore excluded them from the calculation of summary negative likelihood ratios. Three studies could be pooled. Two studies that evaluated a semiquantitative agglutination latex assay had significant heterogeneity. A whole blood agglutination \( \text{D-dimer} \) assay was evaluated in three studies, with no significant heterogeneity.

Clinical practice perspectives
For each strategy we calculated the post-test probability as a function of the pretest probability (see figures 4 and 5 on bmj.com). For each diagnostic strategy we express the accuracy of diagnostic decisions as a function of the pretest probability (fig 4).

Relation to pretest probability
Confirmation of pulmonary embolism
Patients with a high pretest probability; and one of the following tests result: positive result with spiral computed tomography, ultrasonography, echocardiography, or magnetic resonance angiography; or a high probability ventilation perfusion lung scan have a post-test probability of over 85\%, allowing pulmonary embolism to be accurately diagnosed. Patients with a moderate pretest probability require additional imaging after a positive echocardiography result. In patients with a low pretest probability, the post-test probability was below 85\% for all tests and therefore further investigations would be needed to confirm pulmonary embolism (fig 4).

Exclusion of pulmonary embolism
In patients with a low clinical probability; negative test results for \( \text{D-dimers} \) or with spiral computed tomography or magnetic resonance angiography; or a normal or low probability lung scan was associated with a post-test probability of below 5\%. In this situation, additional testing would not be needed to rule out pulmonary embolism. Conversely, patients with a negative echocardiography result and a normal venous ultrasonography result would require additional testing to rule out pulmonary embolism, even when the clinical probability was low. In patients with a moderate pretest probability, a negative quantitative \( \text{n-dimer enzyme linked immunosorbent assay} \) result, a normal or near normal lung scan, or a combination of normal spiral computed tomography results and normal venous ultrasonography results accurately exclude pulmonary embolism. In patients with a high pretest probability, the residual post-test probability remained above 5\% for all diagnostic tests (fig 4). In these patients, additional testing would be required to confidently exclude pulmonary embolism.

Discussion
Large differences exist in the accuracy of diagnostic tests used to confirm or rule out pulmonary embolism. Ventilation perfusion lung scanning, spiral computed tomography, ultrasonography, echocardiography, and magnetic resonance angiography have all been used to confirm or rule out pulmonary embolism. The accuracy of these tests varies widely, with some studies reporting high accuracy and others reporting lower accuracy. This variability is likely due to differences in patient population, diagnostic criteria, and diagnostic accuracy of the tests used.
clinical probability of pulmonary embolism they provide a post-test probability greater than 85%. A normal or near normal ventilation perfusion lung scan result, a combination of spiral computed tomography and ultrasonography, and quantitative d-dimer enzyme linked immunosorbent assay results had negative likelihood ratios below 0.10 and can exclude pulmonary embolism in patients with a low or moderate pretest probability. Spiral computed tomography alone, a low probability ventilation perfusion lung scan, magnetic resonance angiography, the latex Tinaquant d-dimer test, and the haemagglutination d-dimer test have higher negative likelihood ratios and can exclude pulmonary embolism only in patients with a low clinical probability. Echocardiography and ultrasonography seem unable to exclude pulmonary embolism.

Pulmonary angiography is the reference method for the diagnosis of pulmonary embolism, but it has the limitations of being an invasive procedure with associated risks and physicians are reluctant to carry it out in all patients. Clinical follow-up of untreated patients with negative test results is considered a valuable alternative to this method, as the number of symptomatic thromboembolic events during a three month follow-up period without anticoagulant treatment reflects the number of false negative tests. Nevertheless, inclusion of follow-up studies in our analysis is associated with some drawbacks. Blinding is not maintained and some false negative test results may be undetected. In addition, in most of these studies a positive angiogram was not used to confirm the diagnosis of pulmonary embolism, and the rate of false positive test results may have been miscalculated. However, the criteria used to confirm pulmonary embolism (positive results with computed tomography or ultrasonography, high probability ventilation perfusion lung scan) are widely accepted.

We expressed test performance as likelihood ratios. According to Bayes's theorem, the likelihood ratio indicates the extent of change in the odds of disease after a test result. Likelihood ratios can be calculated irrespective of the format of the test result.

Some of our findings are limited by the low number of studies meeting our quality criteria.
Systematic comparison of four sources of drug information regarding adjustment of dose for renal function

Liat Vidal, Maya Shavit, Abigail Fraser, Mical Paul, Leonard Leibovici

Abstract

Objective To compare advice on dosage adjustment for renal impairment provided by four commonly used secondary pharmacotherapeutic sources.

Design Systematic comparison of the definitions of renal impairment, recommendations for dosage adjustment, and the evidence in support of these recommendations in four information sources.


Review methods Two reviewers independently extracted data on recommendations for dosage adjustment for impaired renal function of 100 drugs often used in our hospital.

Results The four sources differed in their recommendations for adjustments of dosage and dosing interval. They vary in their definitions of renal impairment; some are qualitative and remain unclear. All sources provide only a general description; the methods on which the advice is based and references for original data are rarely presented.

What is already known on this topic

The accuracy of diagnostic tests for suspected pulmonary embolism varies largely between studies, and the appropriate clinical setting for their use is unclear.

What this study adds

When the clinical probability is moderate or high, pulmonary embolism is confirmed by a high probability lung scan and a positive result on spiral computed tomography or venous ultrasonography.

When clinical probability is low, these results require confirmation by pulmonary angiography.

In patients with a low or moderate clinical probability, the condition can be excluded by a negative quantitative d-dimer test result, a normal or near normal lung scan, or normal findings on spiral computed tomogram and venous ultrasonography.

As proposed by Kearon, we assumed that the diagnosis of pulmonary embolism was accurate when the post-test probability was above 85% and that pulmonary embolism could be safely ruled out when the rate of false negative/true negative test results was below 5%. As a general rule, the results suggest that discordance between clinical probability and the diagnostic test result requires additional studies.

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