Screening for pulmonary embolism with a D-dimer assay: do we still need to assess clinical probability as well?

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SUMMARY

Clinical risk stratification and D-dimer assay can be of use in excluding pulmonary embolism in patients presenting to emergency departments but many D-dimer assays exist and their accuracy varies. We used clinical risk stratification combined with a quantitative latex-agglutination D-dimer assay to screen patients before arranging further imaging if required. Retrospective analysis of a sequential series of 376 patients revealed that no patient with a D-dimer of <275 ng/mL was diagnosed with pulmonary embolism, irrespective of clinical probability. We conclude that a latex-agglutination assay could be used to exclude pulmonary embolism without the necessity for clinical risk stratification. If these findings are borne out by further work, D-dimer strategies to exclude pulmonary embolism could substantially reduce imaging workload.

INTRODUCTION

The annual incidence of pulmonary embolism (PE) in the community is about 30 per 100 000.¹ Patients commonly present to accident and emergency departments with symptoms and signs that could be due to PE, but clinical examination and routine investigation is of limited value for confirmation or exclusion of this diagnosis. The British Thoracic Society guidelines for the investigation and management of suspected acute PE² emphasize the roles of clinical risk stratification and D-dimer assay to exclude PE, followed by further investigation if required. However, there are numerous D-dimer assays on the market and each has its own sensitivity and specificity.^{3,4} Moreover there is a heterogeneity of results with individual assays;^{5,6} no clear consensus exists about what constitutes a positive or negative result, since the numerous macromolecular complexes containing D-dimer epitopes are measured in different ways.⁴ In addition, some non-quantitative assays require subjective interpretation of the test result and are prone to inter-observer variability.⁵ The British Thoracic Society guidelines incorporate the most investigated assays—a whole-blood red cell agglutination assay (SimpliRed™ AGEN Biomedical, Brisbane, Australia), and a rapid enzyme-linked immunosorbent assay (Vidas).

Quantitative latex agglutination D-dimer assays have been shown to be effective in excluding deep venous thrombosis and PE in some patient subgroups.^{3,7,8} Older non-quantitative or semi-quantitative manual latex agglutination

assays are of limited use in excluding PE since they lack sufficient sensitivity.^{4,9,10}

In our institution, junior doctors in the emergency department use a simple clinical risk assessment model to classify patients into low, intermediate or high clinical probability, followed by an automated quantitative latex microsphere agglutination D-dimer assay. Patients are then either discharged or referred for further investigation. To validate the use of this D-dimer assay in day-to-day practice we retrospectively audited its accuracy by relating the results to final clinical diagnosis.

MATERIALS AND METHODS

Patients presenting to the Leeds General Infirmary emergency department with a potential diagnosis of pulmonary embolism were assessed and investigated in the emergency department and on a twelve-bedded observation and investigation facility called the clinical decisions unit (CDU). They were managed according to the care pathway outlined in Figure 1. History, examination findings, risk factors, assessment of likelihood of PE, results of investigations and progress on CDU were recorded on a multidisciplinary document (the 'protocol document'). The protocol documents of all patients with a possible diagnosis of PE passing through the clinical decisions unit between November 2001 and March 2003 were reviewed. A new D-dimer assay (Instrumentation Laboratory quantitative automated latex agglutination immunoassay) had been introduced in November 2001.

Data abstracted from the protocol documents were: assessment of clinical probability of PE (Box 1); D-dimer

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Figure 1 Patient flowchart. A&E=accident and emergency department; CDU=clinical decisions unit

result; imaging results; and discharge diagnosis from CDU (PE/PE excluded). Any missing data were obtained from the pathology and radiology department computers. The emergency department notes and hospital inpatient notes were not reviewed except to obtain test results where these were unavailable from other sources. Long-term outcome was not assessed.

The presence or absence of PE at discharge from CDU was decided on the basis of test results and clinical review of the patient by either a peri-fellowship CDU fellow or an accident and emergency consultant. If there was felt to be any uncertainty about diagnosis, further investigations were ordered. Patients who had discordant symptoms, signs or results were investigated further. The validity of the discharge diagnosis was reviewed on the basis of the test results and clinical information in the protocol documents. Receiver operator characteristic curves were then produced

for the D-dimer result *versus* discharge diagnosis (PE/PE excluded).

RESULTS

412 patients with a potential diagnosis of PE passed through the clinical decisions unit and protocol documents were available for 395 (96%). 19 of these patients were excluded from further analysis as they were inappropriately entered onto the protocol (see Table 1) leaving 376 patients. Of these, 168 (45%) were classified as low clinical probability, 135 (36%) intermediate and 73 (19%) high.

Patients with PE confirmed

PE was diagnosed in 31 patients (8.2%). The criteria for finally assigning a patient a diagnosis of PE are given below (some patients had more than one test):

- CT pulmonary angiogram showing PE (12 patients)
- Ventilation-perfusion (V/Q) scan high probability *and* high clinical probability (4 patients)
- V/Q scan intermediate probability and continuing signs and symptoms on review (2 patients)
- Doppler ultrasound or CT pulmonary angiogram showing deep venous thrombosis and continuing symptoms and signs of PE on review (7 patients).

Patients with PE excluded

PE was excluded in 345 patients (92%). The criteria for final exclusion of PE were as follows:

- CT pulmonary angiogram normal (49 patients)
- V/Q scan normal (147 patients)
- V/Q scan low probability and at least one of ...
 - low clinical probability (12 patients)
 - intermediate clinical probability (21 patients)
 - and pain gone on review (6 patients)
- D-dimer result normal (<275 ng/mL) and at least one of ...
 - clinical probability low (91 patients)
 - clinical probability intermediate and on review pain gone (4 patients)
- Clinical probability low and on review pain gone (4 patients)
- Clear alternative diagnosis becoming apparent whilst on CDU (10 patients).

A single patient had an intermediate probability V/Q scan and a subsequent CT pulmonary angiogram reported non-normal but unlikely to reflect PE. This patient had improved on review and was discharged with PE excluded.

Box 1 Assessment of clinical risk

Low risk	Risk factors
Absence of risk factors for PE, and alternative diagnosis is as likely as or more likely than pulmonary embolism	Malignancy within the last 6 months Pregnancy or puerperium Surgery within the last 6 weeks
High risk	
Presence of one or more risk factor for PE and symptoms or signs suggestive of PE	Fracture of lower limb within the last 6 weeks Plaster of Paris or other immobilization Prolonged bed rest/incapacitation
Intermediate risk	
Not easily falling into either high or low risk categories	Previous proven PE or DVT Thrombophilia Strong family history of PE or DVT

PE=pulmonary embolism; DVT=deep venous thrombosis

Table 1 Patients excluded from study (inappropriate admissions to CDU on PE protocol)

Reason for exclusion	No. of patients
Clear alternative diagnosis on admission	
Chest infection/pneumonia	11
Cardiac chest pain	2
Pneumothorax	1
Gastro-oesophageal reflux	1
Road traffic accident/chest trauma	2
Patients inappropriate for CDU	
Heavily pregnant (limited diagnostic capability)	1
Confusion (dementia)	1

CDU=clinical decisions unit; PE=pulmonary embolism

Incidence of PE by clinical risk

2 patients of 167 (1.2%) with low clinical risk were diagnosed with pulmonary embolism after investigation. Both these patients had D-dimer >700 ng/mL. 11 patients of 133 (8.3%) with intermediate clinical risk were diagnosed with PE. None of these had a normal value (<275 ng/mL) for D-dimer. 17 patients of 71 (23.9%) with high clinical risk were diagnosed with PE. None of these had a normal D-dimer. Figure 2 summarizes the incidence of PE by clinical risk.

DISCUSSION

Our data are consistent with the findings of others that a normal D-dimer result in combination with a clinical assessment of low probability of PE reliably excludes pulmonary embolism.^{7,11} Intriguingly, our study suggests

that the D-dimer may also be of use in excluding PE in intermediate and high clinical probability groups. None of the 28 patients in these groups who were eventually diagnosed with PE had a D-dimer of less than 275 ng/mL. Other investigators have made similar suggestions: Bates *et al.*,³ using a different automated quantitative latex agglutination assay, found that a normal D-dimer (<500 ng/mL) could potentially exclude deep venous thrombosis in high clinical risk groups³ and the Vidas ELISA D-dimer assay has been shown to exclude PE on its own without the need for clinical risk stratification.^{12,13} Nevertheless, current recommendations are that a normal D-dimer alone does not adequately exclude PE.²

329 imaging studies were conducted on the patient group as a whole. Use of a D-dimer cut-off (to exclude PE) of 700 ng/mL for low clinical probability patients and 275 ng/mL for intermediate and high probability patients has the potential to reduce imaging workload by 208 studies (63%).

Our findings emphasize the role of D-dimer as a test of exclusion. Whilst the test has high sensitivity, it has poor specificity and is not reliable for diagnosis. Moreover, the patient population we studied was an outpatient population. The D-dimer is likely to be of less use in an inpatient population where the incidence of PE is higher¹⁴ and the D-dimer is less likely to be normal.^{8,15}

Strengths and weaknesses of the study

It is unlikely that all low clinical probability patients were captured into the study, since certain patients were discharged directly from the emergency department on the basis of a low clinical probability assessment and a

Figure 2 Percentage of patients with pulmonary embolism (PE) overall and by clinical risk

normal D-dimer, without a protocol document being filled out. However, it was a prerequisite that a protocol document be completed before the patient could be transferred to CDU for further investigation and therefore the capture of intermediate and high clinical probability patients, and of low clinical probability patients with a D-dimer > 275 ng/mL, is likely to be near complete. Rarely, a patient may have been admitted directly to inpatient medical teams (bypassing CDU) if the unit was full or if the patient was deemed unsuitable for a specific reason (e.g. confusion, social circumstances precluding rapid discharge, pregnancy or haemodynamic instability).

Our rates of diagnosis of PE overall and by clinical risk group are lower than those reported by other investigators. The published rates of PE overall and for low, intermediate and high clinical risk groups are in the regions of 17–23%, 3–9%, 16–30% and 40–78%, respectively.^{11,12,16} Our low PE rates may reflect differences in study populations, our population having a larger number of patients in whom PE was excluded relative to other studies. This interpretation is supported by the high proportion of 'normal' V/Q results: of 230 V/Q scans performed, 150 (65%) were 'normal', compared with 16–39% in the other studies.^{11,12,16} The only explanation we can offer for this difference is that the threshold for investigation for potential PE was lower in our series than in others. Departmental ethos encouraged a low threshold to avoid inappropriate discharge; moreover, further diagnostic investigation was readily arranged via CDU without the need for referral to an admitting inpatient team. Therefore, despite the low rate of diagnosis of PE, we feel the study should be generalisable to similar populations of patients presenting to emergency departments.

A potential source of bias was the lack of a gold standard test with which to compare the D-dimer result. A CT pulmonary angiogram reliably diagnoses or excludes PE.^{17,18} A normal V/Q scan reliably excludes PE.¹⁸ The likelihood of PE with high, intermediate and low probability V/Q scans depends on the clinical (pretest) probability but a high probability scan in association with high clinical probability is associated with a 96% risk of PE when compared with pulmonary angiography.¹⁹ A low probability scan in association with low clinical probability is associated with a 4% risk of PE.¹⁹ A normal D-dimer with other assays excludes PE,¹² especially when associated with a low clinical probability.¹¹ On this basis, 83.5% (314) of our sample had PE excluded or diagnosed on the basis of established diagnostic criteria.

The other 62 patients had PE excluded or diagnosed after reassessment and/or further imaging as deemed clinically necessary, but definitive diagnosis (on the basis of established diagnostic criteria) was not achieved for these patients, nor was formal follow-up arranged to assess long-term (e.g. three-month) outcome. This lack of definitive diagnosis and absence of formal follow-up could introduce

bias and represents a weakness of the study. Nevertheless, the results are representative of our day-to-day practice, where patients are assessed and investigated as appropriate and not simply for the sake of completeness. In clinical management terms, the diagnostic certainty in these 62 patients was sufficient to allow discharge or admission for treatment. We therefore believe their discharge diagnoses to be acceptably reliable.

Conclusion

Our study suggests that the Instrumentation Laboratories automated quantitative latex microsphere agglutination assay of D-dimer is able to exclude PE at a level of 275 ng/dL without the need for clinical risk assessment. A more rigorous study design is required to confirm this. If these findings are borne out by further work, use of D-dimer could substantially reduce imaging workload.

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