INTERNAL MEDICINE JOURNAL

doi:10.1111/imj.13753

Diagnostic utility of an age-specific cut-off for d-dimer for pulmonary embolism assessment when used with various pulmonary embolism risk scores

Imogen Ackerly,[1] Sharon Klim,[2] James McFarlane[3] and Anne-Maree Kelly[2,4]

[1]Western Health and Joseph Epstein Centre for Emergency Medicine Research at Western Health, Sunshine Hospital, [2]Joseph Epstein Centre for Emergency Medicine Research at Western Health, [3]Department of Emergency Medicine, Footscray Hospital, and [4]Department of Medicine, Melbourne Medical School – Western Precinct, The University of Melbourne, Melbourne, Victoria, Australia

Key words
pulmonary embolism, risk scores, d-dimer, age.

C**orrespondence**
Anne-Maree Kelly, Joseph Epstein Centre for Emergency Medicine Research at Western Health, Sunshine Hospital, Furlong Road, Melbourne, Vic. 3021, Australia.
Email: anne-maree.kelly@wh.org.au

Received 19 June 2017; accepted 29 July 2017.

Abstract

This retrospective cohort study compared the diagnostic utility (sensitivity, specificity and negative predictive value (NPV)) of the age-times-10 adjusted d-dimer cut-off used in combination with the original and simplified Well's pulmonary embolism (PE) scores and the original and simplified revised Geneva scores to identify patients in whom PE is classified as unlikely according to each score. The PE risk scores performed similarly with high sensitivity (97.6, 97.1, 96.9 and 97.1% respectively) and NPV (99.3, 99.3, 99.2 and 99.2% respectively). Each missed only one PE. The age-times-10 age-adjusted d-dimer assay cut-off performed similarly with each of the clinical risk scores tested with high sensitivity and NPV.

Pulmonary embolism (PE) is an important consideration in patients presenting to emergency department (ED) with dyspnoea with or without chest pain due to its significant morbidity and mortality. However, the non-specific and variable clinical presentation of PE creates diagnostic difficulty for clinicians, especially in older patients.[1] Typical signs and symptoms such as dyspnoea and pleuritic chest pain are not as frequently reported in older populations, widening the spectrum of presentations for which PE must be considered.[2] The current recommended diagnostic workup of PE includes the sequential use of risk assessment and diagnostic tests. For patients with non-high clinical probability (as determined by a validated clinical risk score), a d-dimer assay can be used to rule out PE due to the high sensitivity of the test.[3] However, d-dimer assays are not

Funding: None.
Conflict of interest: None.

highly specific for PE and may be elevated for several other reasons, including malignancy, trauma, inflammation or pregnancy.[4] The standard d-dimer cut-off, < 500 μg/L, is able to exclude PE in about 30% of patients without the need for further imaging.[5] Patients with a d-dimer score ≥ 500 μg/L or with high clinical probability require either a computed tomography pulmonary angiography (CTPA) or a ventilation-perfusion lung scan for definitive diagnosis.[6]

There is good evidence that 'normal' d-dimer concentrations physiologically increase with age leading to a lower specificity for PE and more false positives in older patients.[4,7–10] In fact, d-dimer testing is able to rule out PE in 60% of patients aged <40 years but only 5% for patients aged >80 years.[9,10] This results in an increased number of potentially unnecessary and expensive advanced imaging tests in older patients who are also at increased risk of adverse clinical outcomes, such as contrast-induced nephropathy.[2,11]

An age-specific d-dimer cut-off approach has been suggested, aimed at increasing specificity without reducing sensitivity of d-dimer testing in older populations. Several versions of age-specific d-dimer cut-offs have been described with the most studied being age in years × 10 μg/L which has been recommended for use in recent clinical practice guidelines.[12]

There are also several risk scores in common use, among them the original and simplified Well's PE score and the original and simplified revised Geneva score.[6] To our knowledge, clinical accuracy of age-adjusted d-dimer cut-offs has not been tested comparing these clinical risk scores.

The objective of this study was to compare the diagnostic utility (sensitivity, specificity and negative predictive value (NPV)) of the age-times-10 age-adjusted d-dimer cut-off when used with the original and simplified Well's PE score and the original and simplified revised Geneva score to identify patients who are classified as 'PE unlikely' according to each score. Score variables and calculation are shown in Table 1.

This was a retrospective cohort study conducted by medical record review of adult patients having both d-dimer and CTPA for investigation of suspected PE. Eligible patients presented to the ED of one of two community teaching hospital ED in Melbourne between 1 January 2012 and 31 December 2015 and were investigated for suspected PE. Patients were excluded if they did not undergo both d-dimer assay and CTPA, if either result was missing or if they were not being investigated for suspected PE. Data were collected from the electronic patient records system and electronic medical imaging system and coded onto specifically designed and piloted data collection forms (I.A., J.M., S.K.). Data collectors were not blinded to study objectives. Data collected included patient demographics, clinical features, data to calculate original and simplified Well's PE scores and original and modified revised Geneva scores, d-dimer result, CTPA result and final diagnosis. Data definitions were as specified in a pre-designed data dictionary. Patient observations were taken from the first recordings on the emergency observation charts. Where the CTPA result was equivocal, we determined whether PE was present by reference to other investigations, such as ventilation-perfusion lung scan and the opinion of the specialist clinician looking after the patient (A.-M.K.). Inter-rater reliability assessment was performed for 132 cases.

Table 1 PE risk scores

Modified Well's score	Original	Simplified
Clinical signs of DVT	3	1
No alternative diagnosis better explains the illness	3	1
Previous PE or DVT	1.5	1
Heart rate > 100	1.5	1
Surgery or immobilisation within 4 weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	2
Clinical probability		
PE unlikely	≤4	≤1
PE likely	>4	>1
Revised Geneva score		
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Previous PE or DVT	3	1
Heart rate		
75–94	3	1
≥95	5	2
Unilateral limb pain	3	2
Surgery or fracture within 1 month	2	1
Haemoptysis	2	1
Active cancer	2	1
Age > 65 years	1	1
Clinical probability		
PE unlikely	≤5	≤2
PE likely	>5	>2

DVT, deep venous thrombosis; PE, pulmonary embolism.

D-dimer level was measured using the Siemens INNOVANCE D-Dimer assay measured on the Siemens/Sysmex CA-1500 (Siemens/Sysmex, Japan). The age-adjusted cut-off used was 500 μg/L for patients aged 50 and younger and age-times-10 for those aged over 50 years.

The outcome of interest was diagnostic utility (sensitivity, specificity and NPV) for the combination of the defined 'PE unlikely' category of each PE risk score combined and d-dimer below the defined age-adjusted cut-

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Table 2 Score and d-dimer classification as low risk

Criterion	Low-risk definition	Number (%, 95% CI)
Modified Well's score – original	≤4	564 (92%, 90–94%)
Modified Well's score – simplified	≤1	536 (88%, 85–90%)
Revised Geneva score – original	≤5	458 (75%, 71–78%)
Revised Geneva score – simplified	≤2	480 (79%, 75–82%)
D-dimer – conventional cut-off	<500 μg/L	82 (13%, 11–16%)
D-dimer – aged-adjusted cut-off	<age × 10 μg/L	165 (27%, 24–31%)

off. Analysis was by descriptive statistics and diagnostic utility analysis. The study was approved by the institutional ethics panel. Patient consent for data collection was not required.

Six hundred and ten patients met the criteria for inclusion. Median age was 60 years (interquartile range 49–70) and 328 patients were female (53.8%, 95% confidence interval (CI): 49.7–57.8%). Seventy-three patients had a prior history of deep venous thrombosis (DVT)/PE (12% 95% CI: 9.6–14.9%). Overall, the rate of PE was 9.5% (95% CI: 7.4–12.1%). The distribution of classification as low risk by each PE risk score, the conventional d-dimer cut-off and the age-adjusted d-dimer cut-off are shown in Table 2. Of note, an additional 83 d-dimer assay results became classified as low risk by the application of the age adjustment.

The PE risk scores assessed performed similarly (Table 3) with high sensitivity and NPV. Each missed only one PE. This was an 81-year-old woman with a d-dimer of 560 who was found to have sub-segmental PEs and a previously unknown lung mass, thought to be neoplastic but unconfirmed at the time of writing. Inter-rater reliability assessment was performed for 132 cases for which there was 100% agreement for item's study eligibility, age, gender, CTPA and d-dimer results.

Discussion

There is a growing body of evidence that age-adjusted d-dimer cut-offs have acceptable sensitivity for PE and that their use could avoid a significant proportion of CTPA which carry the risk of adverse effects for patients (such as contrast reaction and contrast nephropathy), often cause inconvenience to patients in terms of an extended ED stay and contribute to reduced ED patient flow by requiring an extended ED stay.[2,5,7–10,13–16] Age-adjusted d-dimer cut-offs are intended to be used in conjunction with a clinical risk score to identify a group of patients in whom PE is unlikely and therefore further imaging can be avoided. There are sparse data comparing the performance of age-adjusted d-dimer cut-offs with the various risk scores in common use.

Our findings suggest that the age-times-10 age-adjusted d-dimer cut-off has similar accuracy when used with each of the risk scores tested, with point estimate of sensitivity of approximately 97% and NPV >99%. This sensitivity is similar to that reported for CTPA, both standard and low-dose protocols.[17] We have previously reported that compared to the conventional cut-off, use of the age-times-10 cut-off would avoid 21% of further imaging tests.[18]

The one missed patient with PE was an elderly lady with sub-segmental PE and a previously undiagnosed lung lesion. Controversy remains about the treatment of such cases in the absence of DVT.[12] It is unclear whether identification of the incidental lung lesion was of benefit to the patient as she has so far declined further testing/follow-up.

Our study has some limitations that should be considered when interpreting the results. Data were collected from medical records so are subject to problems with documentation, particularly omitted data.[19] We did not

Table 3 Diagnostic utility of clinical risk scores combined with age adjusted d-dimer values for low risk patients

Risk score	Number of eligible cases	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Negative predictive value (%, 95% CI)	Number of CTPA scans avoided
Modified Well's original 2-level score	564	97.6% (85.5–99.9%)	27.9% (24.2–32.0%)	99.3% (95.7–100%)	78
Simplified modified Well's score	536	97.1% (82.9–99.8%)	28.1% (24.2–32.3%)	99.3% (95.6–100%)	78
Revised Geneva score – original	458	96.9% (82.0–99.8%)	28.6% (24.4–33.2%)	99.2% (94.9–100%)	64
Revised Geneva score – simplified	480	97.1% (83.3–99.9%)	29.0% (24.9–33.5%)	99.2% (95.2–100%)	65

Note: As scores classified a small number of cases differently, the number of cases classified as low-risk varies by score. CI, confidence interval; CTPA, computed tomography pulmonary angiography.

collect data on patients who had a d-dimer but did not go on to advanced imaging, thus very low-risk and some high-risk patients were not included. Limitations of the patient identification systems available meant that we were not able to identify these groups accurately. CTPA reporting was done by a range of general CT radiologists, not specialist pulmonary/thoracic radiologists, so there may be a higher risk of report error than if specialist pulmonary/thoracic radiologists had performed the reporting. However, this reflects the working reality of radiology reporting in most hospitals. The d-dimer test used in this study used fibrinogen equivalent units. Internationally, another unit (the d-dimer unit) is sometimes used which has a different standard cut-off and therefore will have different age-adjusted cut-offs. There is a variety of d-dimer tests available of varying sensitivity. Our findings cannot be assumed to be generalisable to other d-dimer assays, particularly those of lower reported sensitivity.

The age-adjusted d-dimer assay cut-off performed similarly with each of the clinical risk scores tested with high sensitivity and NPV.

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