Application of an age-adjusted D-dimer threshold for exclusion of pulmonary thromboembolism (PTE) in older patients: a retrospective study

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Abstract

The D-dimer assay's ability to exclude pulmonary thromboembolism (PTE) falls with age.[1,2] Douma et al. have proposed an age-adjusted D-dimer threshold ([threshold, µg/l] = [age, years] x 10) for patients aged >50 years with low clinical risk of PTE.[3] We retrospectively applied this threshold to patients who underwent computer tomographic pulmonary angiogram (CTPA) for suspected PTE during a 13 month period at a busy District General Hospital. Of the 423 patients >50 years old who underwent CTPA, 22 (5.2%) had D-dimer concentrations higher than the traditional threshold but lower than the age-adjust threshold, none of whom had evidence of PTE on CTPA. This suggests that use of the age-adjusted D-dimer threshold may reduce necessity for CTPA concept patients aged >50 years.

Keywords

D-dimer, pulmonary thromboembolism, age-adjusted cut-off, threshold, CTPA.

Key Points

- The ability of the D-dimer assay to exclude PTE in the older population is limited by an age-associated rise in D-dimer concentration.
- A new age-adjusted threshold proposed by Douma *et al. ([threshold, µg/l] = [age, years] x 10)* increases the specificity of the D-dimer assay in patients over 50 years of age.[3]
- A majority (in our study 80%) of patients undergoing CTPA are aged >50 years.
- There was no significant difference in the proportion of patients with measured D-dimer levels between the <50 and >50 years age groups, suggesting age does not substantially influence the decision to measure D-dimer concentration.
- This study showed that 5.2% of patients >50 years had D-dimer concentrations below the age-adjusted threshold but above the traditional threshold of interpretation.
- No patient with a D-dimer concentration below the age-adjusted threshold had PTE confirmed by CTPA.
- Further study is required to substantiate whether application of this D-dimer threshold will in clinical practice reduce the rate of CTPA, reduce the necessity for anticoagulation whilst imaging is awaited and expedite discharge, and to quantify its impact on cost and service-provision.

Introduction

Suspected pulmonary thromboembolism (PTE) can present a diagnostic difficulty to the clinician. It is a condition with significant associated morbidity and mortality, but the common presenting symptoms of dyspnoea, pleuritic chest pain and haemoptysis are non-specific with a wide differential diagnosis.[4,5] The judicious use of D-dimer measurement can be a useful tool in clinical practice, enabling the safe exclusion of PTE in patients with a low/intermediate clinical risk of PTE (based on validated clinical risk stratification tools such as the modified Geneva score).[6] D-dimer is a fibrin degradation product, and it has been established that D-dimer concentrations below established thresholds are associated with very low risk of PTE. For D-dimer assays (such as the VIDAS and MDA assays) which quantify D-dimer in terms of fibrinogen equivalent units, this threshold has been taken as a concentration of <500 µg/l. This threshold has been shown to have a high sensitivity of 97–99% for acute PTE.[7,8] The combination of clinical risk assessment and D-dimer assay is able to exclude PTE in ~33% of patients with suspected PTE (assuming a true prevalence of 20%).[4] However, the D-dimer assay offers a notoriously low specificity, and may be elevated due to numerous extraneous factors including malignancy, recent trauma or surgery, inflammatory conditions, and pregnancy.[9] Mean D-dimer concentration has also been shown to rise with age, and thus with increasing age the specificity accorded by application of the traditional 500 µg/l threshold diminishes.[1] Indeed, the D-dimer assay when interpreted with the traditional threshold is able to exclude PTE in 60% of patients aged <40 years but only 5% in those >80 years.[2]

In an effort to counteract the diminished specificity of the assay in older patients, Douma *et al.* have argued that for patients aged >50 years, higher age-adjusted D-dimer thresholds, when combined with clinical risk assessment, could safely exclude PTE.[3] They proposed an age-adjusted threshold of a D-dimer concentration equal to 10-times the patient's age, which they found improved the specificity of the

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D-dimer test without unduly reducing its sensitivity in patients with a low clinical risk of PTE ([threshold, μg/l] = [age, years] x 10).[3] This age-adjusted threshold was derived from the combined data of two prospective multicentre cohort studies, which included 1721 outpatients with suspected PTE from two Swiss and two French hospitals. Those patients aged >50 years were categorised according to age in 10-year brackets, and for each age-bracket the D-dimer threshold that provided 100% sensitivity with the highest possible corresponding specificity was selected using receiver operating characteristic (ROC) curves. From this, the age-adjusted multiplication factor was calculated using linear regression analysis. The resulting threshold ([threshold, μg/l] = [age, years] x 10) was tested in two external validation cohorts, which included 5118 patients. Douma *et al.* found that their age-adjusted threshold doubled the proportion of patients aged >70 years in whom PTE could be safely excluded when compared with the traditional threshold of 500 μg/l.[3]

Objective

To analyse, retrospectively, the effect of applying Douma *et al.'s* age-adjusted threshold to the D-dimer concentration of the patients who underwent CTPA in a 13-month period at Crosshouse Hospital.

Method

A list of all patients who underwent CTPA in a 13-month period between August 2009 and August 2010 was generated by the information technology support staff of the Radiology Department of Crosshouse Hospital, the District General Hospital serving the Kilmarnock area of Scotland. The electronic radiology reporting system was used to access radiologists' reports to determine if PTE was confirmed on CTPA. This system was also used to gather information on patient sex, age and clinical indication for the investigation. The blood results of each of the above patients were accessed using the electronic blood reporting system to determine if a D-dimer test had been undertaken in the week preceding the CTPA. In those patients aged >50 years in whom a D-dimer level was taken, we applied the traditional threshold of 500 μg/l and the age-adjusted threshold ([threshold, μg/l] = [age, years] x 10). The number of patients in whom the age-adjusted D-dimer was negative and the CTPA was negative (true negatives) was calculated from this. The number of patients in whom the age-adjusted D-dimer score was negative and the CTPA was positive (false negatives) was also calculated.

The percentage of patients aged >50 years with a D-dimer concentration below the age-adjusted threshold but above the traditional threshold was taken as an indication of the potential for age-adjusted D-dimer interpretation to reduce CTPA requirements.

Results

In the 13-month period, 528 patients underwent CTPA scanning at Crosshouse Hospital. The characteristics of the patients undergoing CTPA are shown in Table 1.

The percentage of patients with confirmed PTE on CTPA was 18%, which is consistent with the reported mean (range) prevalence of confirmed PTE of 19.8 (13–42)% in a meta-analysis of 23 studies into suspected PTE.[10]

D-dimer concentration was measured in the week preceding the CTPA in 331 patients (62% of those undergoing CTPA). Of the 423 patients

Table 1. Breakdown of patients undergoing CTPA by number, age, sex and CTPA result.

Variable	Value
Number of patients	528
Mean (range) age, years	63.93 (20–94)
N (%)	
Patients aged >50 years	423 (80)
Patients aged >70 years	228 (43)
Patients aged >80 years	83 (16)
Males	221 (42)
Patients with risk factors obtainable from information included in clinical indication for CTPA request: history of recent surgery history of cancer history of previous PTE/DVT	 67 (13) 84 (16) 43 (8)
Patients with recent D-dimer concentration Patients aged >50 years with recent D-dimer concentration (as percentage of patients >50 years of age)	328 (62) 263 (62)
CTPA scans confirming PTE	95 (18)

aged >50 years undergoing CTPA, 264 (62%) had D-dimer concentration measured. The D-dimer concentration was less than the calculated age-adjusted threshold in 28 patients, none of whom had PTE evident on CTPA. This included six patients who had a D-dimer level below the traditional threshold of 500 μg/l. Thus 22 of the 423 patients aged >50 years had D-dimer concentrations that were elevated according to the traditional threshold but would have been interpreted as normal using the age-adjusted threshold. At Crosshouse Hospital in this 13-month period, this represented 5.2% of the patients aged >50 years and 4.2% of all patients undergoing CTPA for suspected PTE. Furthermore, this represented 8.3% of patients aged >50 years who underwent D-dimer testing.

Discussion

PTE constitutes part of the differential diagnosis for a variety of common clinical presentations including chest pain and dyspnoea. The annual incidence of diagnosed PTE is reported as 150-200 per 100,000, whilst post-mortem evidence indicates a large percentage of PTE remain undiagnosed at time of death.[11]

When we retrospectively applied the age-adjusted D-Dimer threshold to all patients undergoing CTPA for suspected PTE in a 13-month period in a District General Hospital, we showed that 8.3% of patients aged >50 years (who had a D-dimer concentration measured prior to CTPA) had a D-dimer level below the age-adjusted threshold but above the traditional threshold. This suggests that CTPA may have been avoidable in up to an additional 8.3% of older patients. Unfortunately, due to limited information availability on electronic requests for CTPA it was not possible to calculate modified Geneva scores for each patient. Therefore, it is uncertain how many of the patients would have required CTPA due to high clinical risk regardless of the D-dimer concentration.

D-dimer testing was not carried out in 38% of older patients. There are several potential explanations for this: patients may have had high clinical risk of PTE (in which case D-dimer is insufficient to exclude PTE), or have had known conditions that would have produced an elevated D-dimer level (e.g. recent surgery, metastatic malignancy). In addition, published comment has suggested that D-dimer testing is of limited use in older patients, due to the tests diminished specificity in the elderly population.[12] Therefore, the perceived inadequacy of the D-dimer test in older patients may account for some of these patients not having D-dimer levels measured. However, in the present study there was no significant difference in the proportion of patients in whom a D-dimer concentration was measured between patients aged <50 years and those aged >50 years, suggesting that age did not deter clinicians from requesting D-dimer measurement.

The data collected would not support raising the D-dimer threshold regardless of patient age for exclusion of PTE. There were four patients with D-dimer levels of 500–800 μg/l who had PTE evident on subsequent CTPA. Three of these patients were aged <50 years, and in the fourth patient the age-adjusted threshold was less than the D-dimer concentration (D-dimer 656 μg/l, age 54 years).

There are several limitations to this study. First, its retrospective nature and sampling of only the patients who proceeded to CTPA rather than all patients in whom the diagnosis of PTE was considered meant we were unable to calculate the sensitivity and specificity of the age-adjusted threshold, nor compare the proportion for whom D-dimer testing could exclude PTE between the traditional and age-adjusted thresholds. Second, the sample group is likely to be biased towards positive results of PTE, as an unknown proportion of patients will have had PTE excluded by the combination of clinical risk scoring and D-dimer measurement. However, even in this group skewed towards a positive diagnosis of PTE, the age-adjusted D-dimer score was able to safely exclude PTE. Third, as previously stated, we were unable to retrospectively apply a clinical risk stratification score to the patients undergoing CTPA, and therefore it is uncertain the proportion of patients that would have necessitated CTPA to exclude PTE regardless of D-dimer concentration.

Further prospective study is required to further test this age-adjusted threshold. We look forward in particular to the 'Age-adjusted D-dimer Cut-off Levels to Rule Out Pulmonary Embolism: a Prospective Outcome Study (ADJUST)' registered on the National Institutes of Health (NIH) website (NCT01134068).[13] In particular, the hope that application of this D-dimer threshold will in clinical practice reduce the rate of CTPA, reduce the necessity for anticoagulation whilst imaging is awaited and expedite discharge requires substantiation.

Additional areas of interest for future study include whether such an age-adjusted approach to D-dimer interpretation might also safely exclude deep venous thrombosis in elderly patients. The approach of tailoring D-dimer interpretation thresholds to the individual patient may be able to improve the specificity of the test, and whether consideration of further patient variables would allow further safe adjustment of the D-dimer threshold is unknown.

The D-dimer assay, when applied appropriately, can rapidly exclude PTE allowing patients to avoid the potential adverse events associated with CTPA and anticoagulation, and allowing clinicians to refine their differential diagnosis. The age-adjusted threshold for D-dimer interpretation proposed by Douma *et al.* is a simple measure to improve the specificity of this test in the elderly population. This study provides corroborative evidence that application of an age-adjusted D-dimer threshold may help to reduce the need for CTPA to exclude PTE in an elderly population, and further supports the case for ongoing research into its application.

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