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Age adjusted D-dimer excludes pulmonary embolism and reduces unnecessary radiation exposure in older adults: retrospective study

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ABSTRACT

Background: Patients in whom a diagnosis of pulmonary embolism (PE) is suspected and whose D-dimers are elevated frequently require CT pulmonary angiogram (CTPA) for diagnosis. Because D-dimer rises with age, an age-adjusted D-dimer threshold may prevent unnecessary radiation exposure from CTPA in older patients.

Objective: To determine the efficacy and safety of implementing an age-adjusted D-dimer threshold to exclude PE.

Design, settings and patients: Retrospective comparison of conventional and age adjusted D-dimer thresholds in 1000 consecutive patients who had both D-dimer and CTPA.

Main outcome measures: Conventional and age adjusted D-dimer thresholds for excluding PE were less than 250ng/ml and 5x age for patients older than 50 years respectively. We defined patients as unlikely to have PE using the revised Geneva score (RGS) and two different categories of clinical risk: $RGS \leq 5$ and $RGS \leq 10$.

Results: We diagnosed PE by CTPA in 244 (24.4%) patients. 3/86 patients (3.5%) whose D-dimer was below the conventional threshold of 250ng/ml had PE (RGS 3, 9 and 14), all of which were judged to be light clot load (Group 1). 3/108 patients (2.8%) whose D-dimer lay between 250ng/ml and the age-adjusted threshold had PE (RGS 6, 8 and 9), all of which were again judged to be light clot load (Group 2). 62/108 Group 2 patients with $RGS \leq 5$ were considered unlikely to have PE as were 102/108 using the RGS clinical risk category ≤ 10 . None of the 62 patients with $RGS \leq 5$ had PE while 3/102 patients with $RGS \leq 10$ had PE. 236/806 patients (29.3%) whose D-dimer was above the age-adjusted threshold had PE (Group 3).

Conclusions: In a consecutive series of 1000 patients an $RGS \leq 5$ and an age-adjusted D-dimer would have led to 62 fewer CTPA at a cost of no missed PEs.

Word count: 2127 excluding abstract

Key Words: Pulmonary embolism; D-dimer; age-adjusted D-Dimer; CTP

MAIN MESSAGES

- Age adjusted D-dimer can limit unnecessary radiation exposure from CTPA in older subjects suspected of having PE when their clinical probability is low.
- There is a trade off between the radiation exposure saved and PEs missed that is dependent on the level of clinical risk chosen to determine whether a patient should undergo CTPA.
- In our study a revised Geneva score ≤ 5 would have led to 62 fewer CTPA among 108 low risk patients whose D-dimer lay between the conventional and age-adjusted thresholds at a cost of no missed PEs.

RESEARCH QUESTIONS

- Our study included a relatively small number of patients whose D-dimer lay between conventional and age adjusted thresholds.. Therefore, our results should be validated prospectively in a larger study.
- Further research might include an outcome study using different CDR thresholds in combination with D-dimer testing.
- Because we did not include patients with suspected recurrent PE the performance of the CDRs in this group will need additional research.

INTRODUCTION

Pulmonary embolism (PE) is both over and under-diagnosed and D-dimer is essentially a rule-out test. These two statements underpin the diagnostic algorithm for suspected PE which is to assess clinical probability using a clinical decision rule and follow this with a D-dimer if the patient's risk of PE is low or CTPA if PE risk is high. Patients considered unlikely to have PE by clinical decision rules whose D-dimer is elevated are usually advised to undergo CTPA(1).

A difficulty with this approach is that D-dimer increases with age(2,3) and for many other reasons including malignancy, inflammation and sepsis(2). As a direct result a significant number of patients, particularly older patients, are exposed to unnecessary radiation when they have their CTPA, which is only positive for PE in around 20% cases in most studies(4,5). A further reason for wishing to avoid unnecessary CTPA is the risk of contrast nephropathy, which may be at least as common as a diagnosis of PE after CTPA and is associated with a significant risk of severe renal failure and death(6).

It has therefore been suggested that an increase in the D-dimer threshold for CTPA in older patients would reduce unnecessary CTPAs by increasing the number in whom imaging could safely be avoided. An age adjusted D-dimer threshold of 10x age in patients aged 50 years or older (when using an assay with an upper limit of 500ng/ml) has since been derived from a cohort of hospital patients with low or intermediate risk of PE(7) and subsequently validated for PE in patients presenting to their Emergency Departments(7-9). This approach has recently been endorsed by the Clinical Guidelines Committee of the American College of Physicians to determine whether imaging is warranted when PE is suspected(10).

Against this background we have undertaken an analysis of D-dimer and CTPA in a consecutive series of patients who had both tests. We were not primarily interested in whether all patients had a clinical risk assessment before considering a D-dimer because in the real world patients frequently have both. Instead the main purpose of our study was to determine the trade off between imaging saved and missed cases among older patients whose D-dimer levels lay between the conventional and age adjusted thresholds.. We used the revised Geneva score (RGS) as our clinical decision rule.

METHODS

This was a retrospective study conducted in Dumfries and Galloway Royal Infirmary, a district general hospital covering a population of 147,000 in South west Scotland. We did not seek ethical approval as no patient identifiable data was included in the analysis, in keeping with our health board's policy. We selected patients for analysis if they had undergone CTPA for suspected PE. We then established which of these patients had had a D-dimer measurement as part of their assessment. Starting in March 2016 we worked backwards to September 2012 until we had a total of 1422 patients with CTPA, 1000 of whom also had a D-dimer. Twelve more CTPAs were performed during this period but were excluded due to technical failure (failure to achieve diagnostic contrast injection as a result of equipment malfunction or poor venous access).

We measured D-dimer using the HemosIL assay, the normal range for which is $<250\text{ng/ml}$. This value is expressed in D dimer units (DDU) rather than in fibrinogen-equivalent units (FEU), as described in other papers. The mass of one FEU is twice the mass of one DDU, and we therefore calculated an age adjusted threshold by multiplying age by 5 (instead of 10) for patients aged 50 years or older. We subsequently divided our 1000 patients into three groups based on their D-dimer levels and examined these in more detail as follows: Group 1 consisted of all patients with D-dimer levels $< 250\text{ng/ml}$, Group 2 were patients with D-dimer levels $\geq 250\text{ng/ml}$ but $< 5 \times \text{age}$ while Group 3 were patients with D-dimer levels $\geq 5 \times \text{age}$.

We derived RGS from the casenotes of patients whose D-dimer levels lay between the conventional and age-adjusted threshold in all patients whose casenotes could be retrieved. Using the revised Geneva score we considered a patient as being unlikely to have PE by two different categories of clinical risk: first as RGS ≤ 5 as recommended by BMJ Best Practice(11) and others(9); and second as RGS ≤ 10 which was the cutpoint used in two of the three published studies to have assessed the pros and cons of an age adjusted D-dimer(7,8). We derived confidence intervals for binomial proportions using the Clopper-Pearson method(12) and R version 3.2.4(13)

RESULTS

Our 1000 patients consisted of 444 (44.4%) men and 556 (55.6%) women. Average age for men was 68.0 years (range 15-102 years). Corresponding values for women were 66.6 (17-100) years. 853 patients were 50 years or older. We diagnosed PE by CTPA in 244/1000 (24.4%), and in 212/853 (24.9%) of those who were 50 years or older. Sensitivity of D-dimer for PE was high. There were only 3 false negatives using the conventional threshold, which had a sensitivity of 98.8% (95% CI 96.4 to 99.7%) and negative predictive value (NPV) 96.5% (89.4 to 99.1%); and only 3 more false negatives using the age adjusted threshold, giving sensitivity 97.5% (94.7 to 99.1%) and NPV 96.9% (93.1 to 98.7%). Specificity of D-dimer for PE was low: 11.0% (95%CI 8.8 to 13.4%) by the conventional threshold increasing to 24.9% (95%CI 21.8 to 28.1%) by the age adjusted threshold. We also diagnosed PE in 73/422 (17.3%) patients who had CTPA without a preceding D-dimer but do not consider this group further.

Group 1

86 patients had a D-dimer below the conventional threshold of 250ng/ml. Three of these 86 patients (3.5%) had PE. The three were a 51 year old male presenting for the first time with distal type chronic thromboembolic pulmonary hypertension; a 66 year old male with PE 5 years previously who was no longer taking anticoagulant; and a 23 year old female with Protein S deficiency and recurrent VTE who had just been switched from warfarin to rivaroxaban because of time spent outside therapeutic range. Their RGS were 3, 9 and 14 respectively. All three were judged to have light clot load (Table 1). We did not attempt to document the Geneva scores of the other 83 patients in this group and cannot therefore say whether the decision to request CTPA followed current guidelines in every case.

Table 1 about here

Group 2

One hundred and eight of the 853 patients aged 50 years or older had D-dimer that lay between 250ng/ml and the age adjusted threshold (5x their age) and three of these

(2.8%) had PE (Figure 1 and Table 1). These were a 92 year old male who had undergone surgery 9 weeks previously; an 84 year old female with no obvious risk factors for VTE; and a 57 year old male who had recently flown to the UK from Egypt. RGS were 6, 8 and 9 respectively. All three were judged to have light clot load (Table 1). We were able to calculate RGS from the notes of 102 of the 108 patients in this group: 62 patients were judged to be PE unlikely using RGS ≤ 5 while all 102 were PE unlikely using the higher cutpoint of ≤ 10 . None of the 62 PE unlikely patients had PE using the lower RGS cutpoint while 3/102 PE unlikely patients had PE using the higher RGS cutpoint (Table 2).

Table 2 and Figure 1 about here

Group 3

Two hundred and thirty eight of 806 patients (29.5%) whose D-dimer was above the age-adjusted threshold had PE. We divided these 806 patients into tertiles with D-dimer cutpoints of 589 and 1246 ng/ml. 31/269 (11.5%) of patients in the lowest tertile had PE. Corresponding numbers and percentages for the middle and upper tertiles were 69/269 (25.7%) and 138/268 (51.5%) respectively.

DISCUSSION

In this retrospective cohort study of 1000 patients with suspected PE who had undergone both D-dimer testing and CTPA, application of a clinical decision rule and an age adjusted D-dimer threshold would have increased the number of patients in whom PE could have been ruled out without further imaging. Using the revised Geneva score and a rule out cutpoint of ≤ 5 , 62 patients would have been spared CTPA at a cost of no PEs missed. Had we used a higher rule out cutpoint of ≤ 10 then 99 patients would have been spared CTPA at a cost of 3 PEs missed.

Central to the question whether an age adjusted D-dimer threshold can increase the number of patients spared further imaging without missing PEs is the choice of clinical decision rule and the risk category at which CTPA is justified in order to rule out or rule in a diagnosis of venous thromboembolism(14). Three studies incorporating 7 cohorts of patients with suspected PE have addressed an age adjusted D-dimer threshold. Two of

these cohorts used a Wells score ≤ 4 (7), four a revised Geneva score ≤ 10 (7,8) while one used a simplified revised Geneva score ≤ 4 or a Wells score ≤ 4 (9) (Table 3). The prevalence of PE in these studies ranged from 10.1 to 20.7%. False negative rates using a conventional D-dimer threshold ranged from 0.0-0.6% and were only slightly higher in the range 0.2-0.8% using an age adjusted threshold. An age-adjusted threshold would have led to 836 fewer CTPAs among 7288 (11.5%) patients at a cost of 16 missed PEs in these studies (Table 3). Righini(15) and Vossen(16) examined the clinical usefulness of adjusted D-dimer cut off values to exclude PE but did not adjust these for age. Sharp(17) did adjust for age but didn't risk stratify. For these reasons we did not include these studies in Table 3.

Table 3 about here

In our study we chose to use the revised Geneva score rather than the Wells score. This was because the latter contains a subjective question, the answer to which is not always available by retrospective case sheet review: do you think that a diagnosis other than PE is likely to account for the patient's symptoms? The revised Geneva score which was previously only available as a three category scale (low, intermediate and high risk) has recently been converted to a two category scale (PE likely or unlikely) to bring it into line with the other scores. The optimal cutpoint for the two category scale was found to be ≤ 5 and >5 from the area under the receiver operating curve. Douma et al have validated the two category revised Geneva score in a cohort of 807 consecutive patients with suspected PE and found only 1 PE among 185 patients who were PE unlikely and had a normal D-dimer(18). For this reason we chose to compare the efficacy and safety of two clinical risk categories: ≤ 5 as recommended by Douma et al(18) and recently endorsed by BMJ Best Practice(11); and ≤ 10 in keeping with the published work on age adjusted D-dimer(7,8).

Our study has several strengths. It was a single centre study of all patients who had undergone CTPA at one hospital in south west Scotland over a period of 3 years. We excluded only 12 CTPAs due to technical failure. The scans were reviewed by one of us (PH) who was unaware of the D-dimer results and we were able to review the notes of patients whose D-dimer lay between the conventional and age adjusted D-dimer thresholds in order to obtain revised Geneva scores in 102/108 cases.

We recognise limitations. We do not know how many patients had a D-dimer measurement without CTPA during the study period. We also have no way of telling whether clinicians who requested D-dimer and CTPA based their decision on the clinical likelihood of PE. Reassuringly we do know that the incidence of PE among those who had D-dimer and CTPA (24.2%) is similar to the incidence of PE in studies in which clinical probability rules were followed (Douma 2010). We also know that none of the patients in Group 2 had RGS >10 which is at least consistent with advice to proceed directly to CTPA without measuring D-dimer in such patients..

In summary, we have shown that an age adjusted D-dimer has the potential to limit unnecessary radiation exposure from CTPA in older subjects suspected of having PE when their clinical probability is low. There is however a trade off between the radiation exposure saved and PEs missed that is dependent on the level of clinical risk chosen to determine whether a patient should undergo CTPA. In our study a revised Geneva score ≤ 5 would have led to 62 fewer CTPA among 108 low risk patients whose D-dimer lay between the conventional and age-adjusted thresholds at a cost of no missed PEs. A larger prospective study is required to confirm these results before implementation of an age-adjusted D-dimer cut-off in daily practice.

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Legend to Figure 1

Relation between D-dimer and age for patients aged 50 years and over with D-dimer below conventional (Group 1) and age adjusted (Group 2) thresholds showing those with and without PE

Table 1. Clinical details of PE patients with D-dimer below conventional (Group 1) and age adjusted (Group 2) thresholds

Age/ gender	D-dimer ng/ml	Revised Geneva score	Clinical details	Clot load	CTPA
Group 1					
51M	208	3	Distal type chronic pulmonary hypertension	Light	Probably chronic PE - segmental occlusion of RLL pulmonary artery branch
66M	<150	9	Previous PE	Light	Probably chronic PE - thin linear filling defect in right lower lobar pulmonary artery, similar to previous CTPA
23F	150	14	Protein S deficiency and recurrent VTE on rivaroxaban	Light	Possible PE - lingular consolidation with poor opacification of feeding artery.
Group 2					
92M	258	6	9 weeks post surgery	Light	Acute PE - segmental clot in left lower, right lower and middle lobes.
84F	306	8	Unprovoked PE	Light	Acute PE - small clot in segmental branch of RLL pulmonary artery
57M	254	9	Recent flight to UK from Egypt	Light	Acute PE - small segmental clot in LUL and RLL branch

Group 1 = D-dimer <250ng/ml; Group 2 = D-dimer between 250ng/ml and age adjusted threshold; Group 3 = D-dimer above age adjusted threshold. PE unlikely = revised Geneva score ≤5; PE likely = revised Geneva score >5.

Table 2. Number and percentage of patients in each group and 95% confidence interval for proportion in each group

	D-dimer	Number of patients	Number with PE	Percent with PE (95%CI)
Group 1	<250	86	3	3.5 (0.7-9.9)
Group 2	≥ 250 and $< 5 \times$ age	108	3	2.8 (0.6-7.9)
PE unlikely (RGS ≤ 5)	≥ 250 and $< 5 \times$ age	62	0	0 (0-5.8)
PE likely (RGS > 5)	≥ 250 and $< 5 \times$ age	40	3	7.5 (1.6-20.4)
PE unlikely (RGS ≤ 10)	≥ 250 and $< 5 \times$ age	102	3	2.9 (0.6-8.4)
PE likely (RGS > 10)	≥ 250 and $< 5 \times$ age	0	0	0
No Geneva score	≥ 250 and $< 5 \times$ age	6	0	0
Group 3	$\geq 5 \times$ age	806	238	29.5 (26.4-32.8)
All patients		1000	244	24.4 (21.8-27.2)
No D-dimer		422	73	17.3 (13.8-21.3)

Legend: PE= Pulmonary Embolism; RGS= Revised Geneva Score

Table 3. Imaging avoided and diagnoses missed in low clinical probability PE according to conventional and age adjusted D-dimer cut offs

	Type of study	% with diagnosis	Definition Low Clinical Probability	Low Clin Prob	Neg D-dimer (Conventional cut off)	False neg (%)	Neg D-dimer (Age adjusted cut off)	False neg (%)	Imaging avoided (%)	Diagnoses missed
Douma 2010 Derivation	Retrospective multicenter	NG	Wells ≤ 4	1331	477	0 (0.0)	560	1 (0.2)	83 (9.7)	1
Douma 2010 Validation 1	Retrospective multicenter	20.4	Wells ≤ 4	2158	983	2 (0.2)	1093	7 (0.6)	110 (9.4)	5
Douma 2010 Validation 2	Retrospective multicenter	20.7	Revised Geneva ≤ 10	1643	561	0 (0.0)	663	2 (0.3)	102 (9.4)	2
Penaloza 2012	Retrospective 3 cohorts	10.1	Revised Geneva ≤ 10	4383	2287	13 (0.6)	2491	20 (0.8)	204 (9.7)	7
Righini 2014	Prospective multicenter	19.0	Simplified RGS ≤ 4 or Wells ≤ 4	2898	817	1 (0.12)	1158	2 (0.17)	337 (16.1)	1
All studies				12413	5125	16 (0.3)	5965	32 (0.54)	836 (11.5)	16

Legend: RGS = Revised Geneva Score. Percentage imaging avoided = difference between conventional and age adjusted D-dimers that were negative/number of patients with low clinical probability who would have required further imaging because D-dimer > conventional cut off.