American Journal of Emergency Medicine 37 (2019) 845–850

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Comparison of the age-adjusted and clinical probability-adjusted D-dimer to exclude pulmonary embolism in the ED

Sameer Sharif, MD [a,*], Michelle Eventov [b], Clive Kearon, MB PhD [c], Sameer Parpia, PhD [d], Meirui Li, MD [e], River Jiang [f], Paula Sneath [f], Carmen Otero Fuentes, MD [g], Christopher Marriott, PhD MD [h], Kerstin de Wit, MBChB MD [a]

[a] Department of Medicine, Division of Emergency Medicine McMaster University, Canada
[b] Wayne State University School of Medicine, USA
[c] Department of Medicine, Division of Hematology and Thromboembolism, McMaster University, Canada
[d] Department of Oncology, Department of Clinical Epidemiology & Biostatistics, McMaster University, Canada
[e] Department of Pathology and Laboratory Medicine, Schulich School of Medicine and Dentistry, Western University, Canada
[f] Michael G. DeGroote School of Medicine, McMaster University, Canada
[g] Department of Diagnostic Imaging, McMaster University, Canada
[h] Department of Nuclear Medicine, McMaster University, Canada

ARTICLE INFO

Article history:
Received 5 June 2018
Received in revised form 23 July 2018
Accepted 29 July 2018

Keywords:
Pulmonary embolism
D-dimer
Diagnostic imaging

ABSTRACT

Background: Diagnosing pulmonary embolism (PE) in the emergency department (ED) can be challenging because its signs and symptoms are non-specific.
Objective: We compared the efficacy and safety of using age-adjusted D-dimer interpretation, clinical probability-adjusted D-dimer interpretation and standard D-dimer approach to exclude PE in ED patients.
Design/methods: We performed a health records review at two emergency departments over a two-year period. We reviewed all cases where patients had a D-dimer ordered to test for PE or underwent CT or VQ scanning for PE. PE was considered to be present during the emergency department visit if PE was diagnosed on CT or VQ (subsegmental level or above), or if the patient was subsequently found to have PE or deep vein thrombosis during the next 30 days. We applied the three D-dimer approaches to the low and moderate probability patients. The primary outcome was exclusion of PE with each rule. Secondary objective was to estimate the negative predictive value (NPV) for each rule.
Results: 1163 emergency patients were tested for PE and 1075 patients were eligible for inclusion in our analysis. PE was excluded in 70.4% (95% CI 67.6–73.0%), 80.3% (95% CI 77.9–82.6%) and 68.9%; (95% CI 65.7–71.3%) with the age-adjusted, clinical probability-adjusted and standard D-dimer approach. The NPVs were 99.7% (95% CI 99.0–99.9%), 99.1% (95% CI 98.3–99.5%) and 100% (95% CI 99.4–100.0%) respectively.
Conclusion: The clinical probability-adjusted rule appears to exclude PE in a greater proportion of patients, with a very small reduction in the negative predictive value.

1. Introduction

Diagnosing pulmonary embolism (PE) in the emergency department (ED) can be challenging because the symptoms and signs of PE are often non-specific, such as fatigue, breathlessness and chest pain. Consequently, PE can be over-investigated by ED physicians because it may be suspected in patients who present with a broad range of symptoms. For instance, in North America only about 5% of patients who are investigated for PE have the diagnosis confirmed [1-3]. Furthermore, imaging for PE is increasing much more quickly than population growth and the rate of positive scans is decreasing [4, 5]. The ED is now often the most common place that CT angiograms are ordered within hospitals [6-9]. As a result, CT pulmonary angiography is one of the top five overused tests identified by the American College of Chest Physicians and the American Thoracic Society in their 'Choosing Wisely' campaign [10]. In North America, there is marked variation in PE diagnostic practices among ED physicians with some using gestalt and others using clinical decision rules [11, 12].

CT angiography has several disadvantages. Firstly, the average lifetime risk for cancer from a single CT pulmonary angiogram varies from 57/100,000 for females 17–19 years old to 8/100,000 for males and females 80–89 years old [13]. Second, CT angiograms delay patient

* Corresponding author at: c/o Melissa Hymers, 237 Barton Street, 2nd Floor McMaster Wing, Room 252, Mailbox – 354, Hamilton, ON L8L 2X2, Canada.
E-mail address: sameer.sharif@medportal.ca (S. Sharif).

https://doi.org/10.1016/j.ajem.2018.07.053

flow and prolong ED visits. Third, CT angiograms tie up hospital resources and are expensive.

Use of clinical probability assessment and D-dimer testing have been shown to reduce the use of CT angiography in patients who are suspected of having PE [7, 14]. PE is excluded with a low or moderate clinical probability and a negative D-dimer test [15]. Recent efforts have focused on increasing the proportion of patients with suspected PE who are categorized as having a negative D-dimer result so that more patients can have PE excluded without the need for imaging studies. Righini et al. validated a strategy for exclusion of PE which uses a progressively higher D-dimer cut-off to categorize results as abnormal as patient's age increases above 50 years (i.e., age × 10, termed “age-adjusted D-dimer interpretation”) [16]. Linkins et al. validated a strategy for exclusion of deep vein thrombosis (DVT) which uses a D-dimer cut-off that is twice as high in patients with a low clinical probability (i.e., 1000 μg/L FEU if low and 500 μg/L FEU if moderate clinical probability, termed “clinical probability-adjusted D-dimer interpretation”) [17].

We performed this analysis to compare the efficacy and safety of using age-adjusted D-dimer interpretation, clinical probability-adjusted D-dimer interpretation and a standard D-dimer approach to exclude PE in ED patients of all ages with either a low or a moderate clinical probability for PE.

2. Methods

2.1. Study design and setting

This was a health records review of all ED patients 18 years or older investigated for PE at two hospital sites of the same Canadian city over a two-year period (April 2013 to March 2015). The two hospitals serve an urban population of mixed socioeconomic status, include tertiary oncology, cardiac, neurosurgical and vascular services, and have around 95,000 ED visits each year. The Hamilton Integrated Research Ethics Board gave approval for the study.

During the 24 months of this study, ED physicians at the two hospital sites were encouraged (but not required) to do D-dimer testing in patients with a low clinical probability, and to consider PE excluded (without diagnostic imaging for PE), if the D-dimer level was below the standard cut-off of 500 μg/L FEU. All other patients were to have diagnostic imaging for PE. However, there was no specific protocol in place. CT angiography was the usual imaging test, but ventilation-perfusion (VQ) scanning (planar or SPECT) was used preferentially in younger patients and those with renal impairment.

2.2. Selection of participants

We used electronic hospital records to identify all ED patients who had a D-dimer ordered, a CT pulmonary angiogram, or VQ scan ordered by an ED physician to investigate for PE; these patients were considered to have had suspected PE. The current analysis was restricted to patients who had a low or moderate clinical probability (i.e., PE Wells Score 6.0 or less; Table 1) and who also had a D-dimer level measured. We did not include patients who had a high clinical suspicion because D-dimer is generally not used to evaluate PE in these patients.

2.3. Data collection

Previously published guidelines for completing medical record review studies were followed [18, 19]. Patient age, sex, date of attendance and D-dimer level was collected automatically from the electronic medical records. Using a standardized coding definition log and an electronic form, trained research students extracted each Wells score components (Table 1), CT angiogram result and VQ scan result. Every patient was followed through chart review at both hospitals for 30 days after the ED presentation, to determine whether PE or DVT was subsequently diagnosed in either of the two hospitals. The extractors examined the medical records as follows: ED physician record (which included the indication for testing), imaging reports, ED nursing records, vital signs, inpatient charts, consultations, clinic letters, and hospital discharge summaries. The first measurement of heart rate (taken at triage) was used. “Clinically suspected DVT” and “hemoptysis” were considered present if they were documented by the ED or other physician; otherwise, they were considered as absent. “Immobility” was considered present if there had been a hospital admission within the last 4 weeks or a physician had documented that the patient had been bed bound; there was no minimum length of immobilization that was required. “Alternative diagnosis is less likely than PE” was only considered present if a physician had documented that PE was the most likely diagnosis. If the ED physician documented that a Wells score item (e.g. hemoptysis) was absent but another physician documented that it was present, additional evidence was sought. If there was additional documentation that the Wells score item was present or absent, this was accepted. If there was no additional documentation, the ED physician's assessment was used. No formal measures were taken to ensure that clinical data, D-dimer results and imaging test results were abstracted independently of each other. However, abstractors were not aware that the data they recorded would be used to evaluate age-adjusted and clinical probability-adjusted D-dimer interpretation strategies. D-dimer was measured using the STA-Lia (Diagnostica Stago, Asnières, France) latex agglutination assay in the hospital laboratory.

Table 1
The clinical probability wells score.

Wells score variables	Points
Clinically suspected DVT	3.0
Alternative diagnosis is less likely than PE	3.0
Heart rate > 100	1.5
Immobilization or surgery in previous 4 weeks	1.5
History of VTE	1.5
Hemoptysis	1.0
Malignancy or treatment within 6 months	1.0
Total score	
Clinical probability	
Low	0–4.0
Moderate	4.5–6.0
High	≥6.5

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

2.4. Categorization of patients as having PE or no PE

Patients were categorized as having PE if, at initial presentation or within 30 days of their ED visit, they met any of the following criteria: PE was reported as being present on a CT angiogram or VQ scan; or DVT was diagnosed by an ultrasound examination. Non-diagnostic CT angiograms and VQ scans were considered to be negative. Patients were considered to have a missed PE at initial assessment if they subsequently had a positive CT angiogram, VQ scan, or leg ultrasound scan within 30 days of the index visit. Patients were categorized as not having PE at initial presentation if they met all of the following criteria: a CT angiogram and/or VQ scan at initial presentation did not report the presence of acute PE, or no CT angiography or VQ scanning was done; DVT was not diagnosed by ultrasound at initial presentation; and PE or DVT were not diagnosed at either hospital within 30 days of their ED visit. To assess the possibility that PE may have been diagnosed incorrectly in patients who were judged to have had PE excluded using any of the three D-dimer interpretation strategies that we were evaluating, the imaging studies (CT pulmonary angiograms or VQ scans) from these cases were reinterpreted by expert readers who were blinded to the initial interpretation, clinical probability assessment, and D-dimer results. The reinterpreted findings are described in this report, but the original reports were used in all analyses.

2.5. D-dimer interpretation strategy definitions

D-dimer levels were categorized as positive or negative for the three interpretation strategies as follows:

2.5.1. Age-adjusted strategy

D-dimer results were categorized as negative if: 1) in patients 50 years or younger, the D-dimer level was <500 μg/L FEU; or 2) in patients older than 50 years, the D-dimer level was less than the patient's age multiplied by 10 (e.g. <800 μg/L FEU if 80 years). This rule was used for all patients with a low or moderate clinical probability (Wells score of 6.0 or less).

2.5.2. Clinical probability-adjusted strategy

D-dimer results were categorized as negative if: 1) in patients with low clinical probability (Wells score of 4.0 or less), the D-dimer level was <1000 μg/L FEU; or 2) in patients with moderate clinical probability (Wells score of 4.5 to 6), the D-dimer level was <500 μg/L FEU.

Standard Strategy: D-dimer results were categorized as negative if, in patients with a low or a moderate clinical probability (Wells score of 6.0 or less), the D-dimer level was <500 μg/L FEU. This strategy was the reference standard.

2.6. Outcomes

The primary outcome was defined as the exclusion of PE with each D-dimer interpretation strategy. The secondary outcome was the negative predictive value (NPV) of each interpretation strategy.

2.7. Scan review

A chest radiologist and nuclear medicine physician re-read the CT and VQ scans for patients who were diagnosed with PE, but who would have had a false negative result for any of the three D-dimer rules. They were unaware of the clinical circumstances, D-dimer result and prior imaging reports.

2.8. Data analysis

The proportion of patients who had a negative D-dimer test and the associated NPV were calculated for each of the three interpretation strategies, along with 95% confidence intervals (CI) using the Wilson score method. Pairwise comparisons of the proportion of patients with negative D-dimer results were performed using the McNemar test, and 95% CIs for the absolute differences were calculated using the Agresti and Min approach [20]. Comparisons were considered significant if the two-sided *p*-values were <0.017. For the NPV, the method for paired data proposed by Leisenring, Alonzo and Pepe was used (generalized score statistic) [21]. Comparisons were considered significant if the two-sided p-values were <0.05. Analyses were performed using SAS (Cary, NC) version 9.4, and the *DTComPair* package in R version 3.2.3.

Additionally, to assess interobserver reliability of 1) whether PE was versus was not the most likely diagnosis in individual patients, and 2) categorization of patients as having PE versus no PE, data from a random sample of 10% of patients was independently extracted by two observers, and agreement was assessed using Cohen's kappa coefficient.

Sample size was based on precision around the estimate of proportion of patients who had PE excluded (negative D-dimer test) with each strategy. A sample size of 1000 patients would produce a 95% confidence interval with a width of approximately 5 units assuming the proportion is between 0.7 and 0.8 using the Wilson Score method. This sample size will give us 90% power to detect an absolute difference of at least 4% in the proportions of PE excluded between the clinical probability adjusted strategy and age-adjusted strategy using the McNemar test assuming a two-sided alpha of 0.017.

3. Results

Between April 2013 and March 2015, a total of 1163 patients were tested for PE (Fig. 1). Of these, 66 with a low or moderate clinical probability (Wells score ≤ 6.0) did not have D-dimer measured (13 were diagnosed with PE) and 22 had a high clinical probability (Wells score > 6.0; 10 were diagnosed with PE); therefore, 1075 patients were eligible for the current analysis. The average age of the 1075 included patients was 48, 69.6% were female, and 6.8% had an active malignancy (Table 2). A total of 38 patients in this analysis were diagnosed with PE; 35 at initial presentation (31 by CT and 4 by VQ scan); and 3 during 30-day follow-up (one diagnosed in a follow-up clinic by CT, one represented with suspected PE that was confirmed by CT, one diagnosed while admitted in hospital by CT). Of the 3 patients who were diagnosed during follow-up, 2 had a D-dimer >500 μg/L FEU at initial presentation but were not imaged, and 1 had a normal CT angiogram at presentation. The prevalence of PE was 3.7% (31/1017) in those with a low and 12.1% (7/58) in those with a moderate clinical probability.

The kappa coefficient for chart abstraction of whether PE was versus was not the most likely diagnosis was 0.54 (95% CI 0.37–0.71), and categorization of patients as having PE versus no PE was 1.0 (95% CI 0.86–1.00).

3.1. Findings with each of the three interpretation strategies

The proportion of patients who had a D-dimer test and, therefore, would not have imaging for PE was 71.8% (95% CI 69.1–74.4%) for the age-adjusted strategy, 82.0% (95% CI 80.0–84.1%) for the clinical probability adjusted strategy, and 68.6% (95% CI 65.7–71.3%) for the standard strategy (with D-dimer cutoff 500 μg/L FEU) (Table 3). The NPV was 99.7% (95% CI 99.0–99.9%) for the age-adjusted strategy, 99.1% (95% CI 98.3–99.5%) for the clinical probability adjusted strategy, and 100% (95% CI 99.4–100.0%) for the standard strategy (Table 3).

3.2. Comparison of the age-adjusted strategy and clinical probability-adjusted strategy

The proportion of patients who had a negative D-dimer test was higher with the clinical probability adjusted strategy than with the age-adjusted strategy (10.2% for difference; 95% CI 8.2–12.0; $p <$

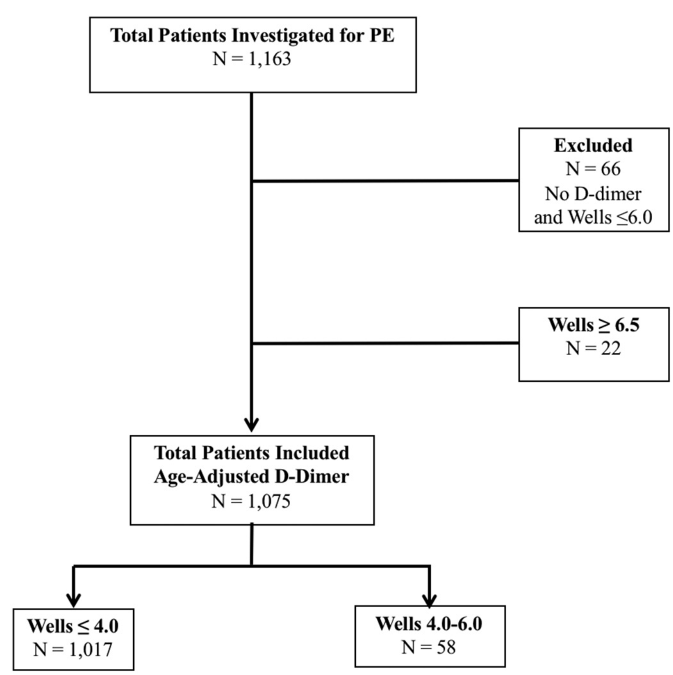

Fig. 1. Study flowchart.

Table 2
Patient characteristics.

Characteristics	Total ($N = 1075$), n (%)	PE patients ($N = 38$), n (%)	No PE ($N = 1037$), n (%)
Age (years), mean (SD)	47.5 (SD 17.9)	49.3 (SD 21.8)	47.5 (SD 17.8)
Women	748 (69.6)	24 (63.2)	724 (69.8)
Active malignancy	73 (6.8)	6 (15.8)	67 (6.5)
HR (beats/min), mean	90	92	89
Trauma in previous 4 weeks	5 (0.5)	0 (0.0)	5 (0.5)
Current Estrogen use	106 (9.9)	6 (15.8)	100 (9.6)
Past history of DVT or PE	81 (7.5)	7 (18.4)	74 (7.1)
Clinical signs and symptoms of DVT	23 (2.1)	1 (2.6)	24 (2.3)
Hemoptysis	25 (2.3)	1 (2.6)	24 (2.3)
Surgery in previous 4 weeks	41 (3.8)	4 (10.5)	37 (3.6)
Immobilization in previous 4 weeks	27 (2.5)	1 (2.6)	26 (2.5)
Wells ≤4.0	1021 (95.0)	28 (73.7)	993 (95.8)
Wells 4.5–6.0	54 (5.0)	10 (26.3)	44 (4.2)

Abbreviations: HR, heart rate; PE, pulmonary embolism; DVT, deep vein thrombosis.

0.001) (Tables 3 and 5). The NPV was lower with the clinical probability-adjusted than the age-adjusted strategy (0.6% for difference; 95% CI 0.1–1.2; $p = 0.02$) (Table 3).

3.3. Comparison of the age-adjusted strategy and standard strategy

The proportion of patients who had a negative D-dimer test was higher with the age-adjusted strategy than with the standard strategy (3.2% for difference; 95% CI 2.2–4.4; $p < 0.001$) (Table 3). The NPV was lower with the age-adjusted than the standard strategy (0.3% for difference; 95% CI −0.1–0.6; $p = 0.16$) (Table 3).

3.4. Comparison of the clinical probability-adjusted strategy and standard strategy

The proportion of patients who had a negative D-dimer test was higher with the clinical probability-adjusted strategy than with the standard strategy (13.4% for difference; 95% CI 11.3–15.4; p < 0.001) (Table 3). The NPV was lower with the clinical probability-adjusted than the standard strategy (0.9% for difference; 95% CI 0.3–1.5; $p = 0.004$) (Table 3).

Table 3
The proportion of patients with suspected PE who would have had PE excluded with each D-dimer interpretation strategy, the negative predictive value of each interpretation, and the percent difference between each strategy

D-dimer rules	Proportion of L-CPTP/M-CPTP Patients with PE excluded	Negative predictive value
Clinical probability-adjusted	82.0% (95% CI 80.0–84.1%) (881/1075)	99.1% (95% CI 98.3–99.5%)
Age-adjusted	71.8% (95% CI 69.1–74.4%) (772/1075)	99.7% (95% CI 99.0–99.9%)
Standard	68.9%; 95% CI 65.7–71.3% (737/1075)	100.0% (95% CI 99.4–100.0%)
Difference between standard D-dimer, clinical probability-adjusted, and age-adjusted D-dimer		
Clinical probability-adjusted vs standard	13.4% (95% CI 11.3–15.4; p < 0.001)	0.9% (95% CI 0.3–1.5; p = 0.004)
Age-adjusted vs standard	3.2% (95% CI 2.2–3.4; $p <$ 0.001)	0.3% (95% CI −0.1–0.6; p = 0.16)
Clinical probability-adjusted vs age-adjusted	10.2% (95% CI 8.2–12.0; p < 0.001)	0.6% (95% CI 0.1–1.2; p = 0.02)

Abbreviations: L-CPTP, low moderate clinical pre-test probability (Wells 0–4.0); M-CPTP, moderate clinical pre-test probability (Wells 4.5–6.0).

3.5. Findings according to patient age

3.5.1. 50 years or younger

606 (55.2%) patients were 50 years or younger. The age-adjusted strategy and the standard strategy, which used a cut-off of 500 μg/L FEU in all of these patients, categorized 78.9% (95% CI 75.4–81.9%) as negative, and had a NPV of 100% (95% CI 99.0–100.0%). The clinical probability-adjusted strategy categorized 89.4% (95% CI 86.7–91.6%) as negative, and had a NPV of 99.4% (95% CI 98.4–99.8%).

3.5.2. Older than 50 years

491 (44.8%) patients were older than 50 years. The age-adjusted D-dimer strategy categorized 59.9% (95% CI 55.4–64.1%) as negative, and had a NPV of 99.3% (95% CI 97.4–99.8%). The clinical probability-adjusted D-dimer strategy categorized 69.0% (95% CI 64.8–72.9%) as negative, and had a NPV of 98.5% (95% CI 96.8–99.3%). The standard strategy categorized 52.5% (95% CI 48.1–56.9%) as negative, and had a NPV of 100.0% (95% CI 98.2–100.0%).

3.6. Findings according to clinical probability

3.6.1. Low clinical probability

1017 (92.7%) patients had low clinical probability. The age-adjusted D-dimer strategy categorized 745 (73.3%) as negative, and had a NPV of 99.7% (95% CI 98.9–99.9%). The clinical probability-adjusted D-dimer strategy categorized 859 (84.5%) as negative and had a NPV of 99.1% (95% CI 98.3–99.5%). The standard strategy categorized 713 (70.1%) as negative, and had a NPV of 100.0% (95% CI 99.3–100.0%).

3.6.2. Moderate clinical probability

58 (5.3%) patients had moderate clinical probability. The age-adjusted D-dimer strategy categorized 27 (46.6%) as negative and had a NPV of 100% (95% CI 84.5–100.0%). The clinical probability-adjusted strategy categorized 22 (37.9%) patients as negative and had a NPV of 100% (95% CI 81.5–100.0%). The standard strategy categorized 24 (41.3%) patients as negative and had a NPV of 100.0% (95% CI 82.3–100.0%).

3.7. Re-interpretation of false negative patient scans

Blinded re-interpretation of CT and VQ scans disagreed with the original PE report in three cases (Table 4). All three were patients with a false negative clinical probability-adjusted strategy. One scan was reported as showing no PE and another two as probably no PE (<20% chance of PE).

4. Discussion

The purpose of this study was to compare the efficacy and safety of standard D-dimer cutoff, the age-adjusted D-dimer and clinical probability-adjusted D-dimer to exclude PE in the ED.

Both the clinical probability-adjusted (negative in 82.0%) and the age-adjusted (negative in 71.8%) strategies were able to categorize more low and moderate clinical probability patients as having a negative D-dimer than the standard interpretation strategy (negative in 68.9%) and, therefore, reduce the need for diagnostic imaging. The NPV was 99% or higher with all three strategies, although the 95% CI on the paired differences suggested that the NPV could be as much as 1.5% higher with the standard compared to the clinical probability strategy. Compared to both the age-adjusted (negative in 78.9%) and the standard (negative in 79.0%) strategy, the clinical probability-adjusted

Table 4
Characteristics of the patients whose D-dimer results were categorized as negative but PE was present on initial presentation

Age	Wells score	D-dimer	How PE was diagnosed	Imaging re-interpretation
Age-adjusted D-dimer and clinical probability-adjusted D-dimer falsely negative				
59	1.5	580	Segmental PE on CT	PE
68	0	640	Subsegmental PE on CT	PE
Clinical probability-adjusted D-dimer falsely negative only				
52	0	790	Lobar PE on CT	PE
75	0	930	Subsegmental PE on CT	No PE probable
32	0	530	High probability for PE on VQ	PE
39	3	940	High probability for PE on VQ	No PE probable
19	1.5	990	High Probability for PE on VQ	No PE
54	1.5	730	Segmental PE on CT	PE
Age-adjusted D-dimer falsely negative only				
No patients in this category				

Abbreviations: PE, pulmonary embolism; CT, computed tomography; VQ, SPECT ventilation-perfusion.

strategy (negative in 89.4%) was particularly helpful for avoiding PE imaging in younger patients (i.e., <50 years), who might be a greater risk of radiation-induced cancer.

Our results are in keeping with other studies evaluating the age-adjusted strategy for D-dimer interpretation. In a systematic review, Schouten et al. found that the use of age-adjusted compared to standard D-dimer interpretation would reduce imaging from 71.2% to 59.6% in patients over 50 with non-high clinical probability of PE [22]. Furthermore, the NPV of the age-adjusted D-dimer was above 99%. The ADJUST-PE study (Age-Adjusted D-dimer cutoff levels to rule out Pulmonary Embolism) found that use of the age-adjusted compared to standard D-dimer interpretation would reduce imaging from 71.8% to 60.2% [16]. Mullier et al. found the NPV for age-adjusted D-dimer interpretation to be >99% in patients with a non-high clinical probability of PE [23]. The Clinical Guidelines Committee of the American College of Physicians (ACP) recommends using age-adjusted D-dimer cutoffs [15].

Kline et al. showed that using a D-dimer of 1000 ng/mL compared to 500 ng/mL to exclude PE with 'PE unlikely' patients would reduce the use of CT angiography from 84% to 69%, but would be associated with a decrease in NPV from 96.4% to 94.7% [25]. However, in this analysis, 10 of the 11 PEs that were present in patients were subsegmental PE of uncertain clinical significance (8 of the 11 PEs were present in patients with a D-dimer level of 500 to 999 ng/mL). In our study, re-interpretation of the false negative CT and VQ scans suggested that 3 of the 6 false negative cases with the clinical probability-adjusted D-dimer may not actually have had PE, meaning we may have underestimated the NPV of the rule. In a randomized trial, Linkins et al. found that a D-dimer of <1000 μg/L could be used to exclude DVT in patients with low clinical probability without a decrease in NPV [17]. A retrospective analysis of data from two studies found that clinical probability-adjusted strategy for D-dimer interpretation was able to exclude DVT or PE in a higher proportion of patients that either a standard or an age-adjusted strategy, without a decrease in NPV [26]. However, a more recent retrospective analysis showed a greater NPV for the age-adjusted D-dimer in comparison to the clinical probability-adjusted strategy [27]. Van der Hulle et al. evaluated exclusion of PE with a D-dimer of <1000 ng/mL if patients had none of three pre-specified Wells score items (clinical signs of DVT, hemoptysis, and whether PE is the most likely diagnosis) and a D-dimer <500 ng/mL if patients had one or more of these items [28]. Compared to using a standard for D-dimer interpretation, this approach substantially reduced the need for CT angiography examinations and had a NPV of 99.4%. These findings were supported in a 2018 prospective observational study by Kabrhel et al. where fewer patients would have had imaging had the YEARS algorithm been used without a decrease in NPV [29].

The strength of our analysis is that we included a large number of consecutive patients who were tested for PE in two hospitals. We are confident that we did not miss patients since we used a very inclusive method for their identification. Our D-dimer results were directly abstracted electronically from the medical records as was age, meaning that our age-adjusted D-dimer calculations are valid.

There are a number of limitations with this study relating to its retrospective nature. First, although we standardized data abstraction for the Wells score components, retrospective data collection may not accurately reflect the clinical findings. In particular, we were stringent in allocating 3.0 points for 'another diagnosis is less likely than PE'. For example, it is possible that physicians considered that "another diagnosis is less likely than PE" without documenting this assessment; in this situation, our data abstraction would underestimate the Wells score and the physician's assessment of clinical probability. Likewise, we may have missed the presence of hemoptysis or a history of prior venous thrombosis, which would also lead us to underestimate the Wells score. Because of this, we may have overestimated the proportion of patients who would not require imaging and underestimated the NPV associated with each of the D-dimer interpretation strategies. Second, by relying on health records at two hospitals to identify VTE recurrence as opposed to direct patient contact, we may have missed some episodes of recurrent VTE during follow-up, which would lead to an over estimation of NPV. Third, we took no specific steps to ensure independence of clinical data abstraction, D-dimer levels and imaging study results; this could have led to a biased assessment of agreement between these findings. Fourth, we used the original reports of imaging studies to decide if patients had PE for our main analyses rather than having all imaging studies reinterpreted; this is likely to have resulted in some incorrect diagnoses.

5. Conclusion

Both the clinical probability-adjusted D-dimer and age-adjusted D-dimer strategies would have led to fewer imaging tests in comparison to the standard D-dimer strategy. This retrospective analysis suggests that the clinical probability-adjusted strategy may result in the fewest imaging tests for PE.

Meetings

Canadian Association of Emergency Physicians Conference – June 2017, Whistler BC, Canada

Table 5
Comparison of the age-adjusted strategy and the clinical probability strategy with prevalence of venous thromboembolism according to agreement

		Clinical probability-adjusted strategy		Total
		D-dimer negative	D-dimer positive	
Age-adjusted strategy	D-dimer negative	767 2 VTE (0.26%)	5 0 VTE (0%)	772 2 VTE (0.26%)
	D-dimer positive	114 6 VTE (5.3%)	189 30 VTE (15.3%)	303 36 VTE (11.6%)
	Total	881 8 VTE (0.91%)	194 30 VTE (14.9%)	1075 38 VTE (3.4%)

Abbreviations: VTE, venous thromboembolism.
Note: This table only includes patients with a Wells score ≤ 6.0.

International Society on Thrombosis and Haemostasis Congress – July 2017, Berlin, Germany

Grant

Hamilton Niagara Haldimand Brant Emergency Services Steering Committee Grant. Dr. de Wit is supported by Hamilton Health Sciences Early Career Award and the Physicians Services Incorporation Knowledge Translation Fellowship.

Conflict of interest

None.

Acknowledgements

K. de Wit conceived the study, and obtained research funding. C. Kearon, S. Sharif, and K. de Wit designed the study. S. Sharif and K. de Wit supervised the conduct of the study and data collection. S. Sharif, C. Otero Fuentes, C. Marriott, M. Li, M. Eventov, R. Jiang, P. Sneath, and R. Leung were involved in data collection. S. Parpia provided statistical advice and analyzed the data. S. Sharif, C. Kearon, and K. de Wit drafted the manuscript, and all authors reviewed the manuscript. S. Sharif takes responsibility for the paper as a whole.

References

[1] Wang RC, Brent S, Weber E, Neilson J, Smith-Bindman R, Fahimi J. The impact of clinical decision rules on computed tomography use and yield for pulmonary embolism: a systematic review and meta-analysis. Ann Emerg Med 2016;67:693–701.
[2] Dalen J, Waterbrook AL. Why are nearly all CT pulmonary angiograms for suspected pulmonary embolism negative. Am J Med 2017;130:247–8.
[3] Perelas A, Dimou A, Saenz A, et al. CT pulmonary angiography utilization in the emergency department: diagnostic yield and adherence to current guidelines. Am J Med Qual 2014;30:571–7.
[4] Zompatori M, Attinà D, Niro F, Palareti G. Subsegmental pulmonary embolism: is the emperor still naked? Radiol Med 2013;118:901–8.
[5] Schissler AJ, Rozenshtein A, Kulon ME, et al. CT pulmonary angiography: increasingly diagnosing less severe pulmonary emboli. PLoS ONE 2013;8:e65669.
[6] Ong CW, Malipatil V, Lavercombe M, et al. Implementation of a clinical prediction tool for pulmonary embolism diagnosis in a tertiary teaching hospital reduces the number of computed tomography pulmonary angiograms performed. Intern Med J 2013 Feb;43:169–74.
[7] Chandra S, Sarkar PK, Chandra D, Ginsberg NE, Cohen RI. Finding an alternative diagnosis does not justify increased use of CT-pulmonary angiography. BMC Pulm Med 2013;13:9.
[8] Mamlouk MD, van Sonnenberg E, Gosalia R, et al. Pulmonary embolism at CT angiography: implications for appropriateness, cost, and radiation exposure in 2003 patients. Radiology 2010 Aug;256:625–32.
[9] Mitchell AM, Jones AE, Tumlin JA, Kline JA. Prospective study of the incidence of contrast-induced nephropathy among patients evaluated for pulmonary embolism by contrast-enhanced computed tomography. Acad Emerg Med 2012 Jun;19:618–25.
[10] Wiener RS, Ouellette DR, Diamond E, et al. An official American thoracic society/American college of chest physicians policy statement: the choosing wisely top five list in adult pulmonary medicine. Chest 2014;145:1383–91.
[11] Chen Y, Gray BG, Bandiera G, MacKinnon D, Deva DP. Variation in the utilization and positivity rates of CT pulmonary angiography among emergency physicians at a tertiary academic emergency department. Emerg Radiol 2014:1–9.
[12] Costa A, Basseri H, Sheikh A, Steill I, Dennie C. The yield of CT pulmonary angiograms to exclude acute pulmonary embolism. Emerg Radiol 2014;21:133–41.
[13] Woo JKH, Chiu RYW, Thakur Y, Mayo JR. Risk-benefit analysis of pulmonary CT angiography in patients with suspected pulmonary embolus. Am J Roentgenol 2012;198:1332–9.
[14] Kline JA, Jones AE, Shapiro NI, et al. Multicenter, randomized trial of quantitative pretest probability to reduce unnecessary medical radiation exposure in emergency department patients with chest pain and dyspnea. Circ Cardiovasc Imaging 2014;7:66–73.
[15] Raja AS, Greenberg JO, Qaseem A, Denberg TD, Fitternamn N, Schuur JD. Clinical guidelines committee of the American College of Physicians evaluation of patients with suspected acute pulmonary embolism: best practice advice from the clinical guidelines committee of the American College of Physicians. Ann Intern Med 2014;163:701–11.
[16] Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA 2014;311:1117–24.
[17] Linkins LA, Bates SM, Lang E, et al. Selective D-dimer testing for diagnosis of a first suspected episode of deep venous thrombosis: a randomized trial. Ann Intern Med 2013;158:93–100.
[18] Worster A, Haines T. Advanced statistics: understanding medical record review (MRR) studies. Acad Emerg Med 2004;11:192–7.
[19] Worster A, Bledsoe RD, Cleve P, Fernandes CM, Upadhye S, Eva K. Reassessing the methods of medical record review studies in emergency medicine research. Ann Emerg Med 2005;45:448–51.
[20] Agresti A, Min Y. Simple improved confidence intervals for comparing matched proportions. Stat Med 2005;24:729–40.
[21] Leisenring W, Alonzo T, Pepe MS. Comparison of predictive values of binary medical diagnostic tests for paired designs. Biometrics 2000;56:345–51.
[22] Schouten HJ, Geersing GJ, Koek HL, et al. Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. BMJ 2013;346:f2492.
[23] Mullier F, Vanpee D, Jamart J, et al. Comparison of five D-dimer reagents and application of an age-adjusted cut-off for the diagnosis of venous thromboembolism in emergency department. Blood Coagul Fibrinolysis 2014;25:309–15.
[25] Kline JA, Hogg MM, Courtney DM, Miller CD, Jones AE, Smithline HA. D-dimer threshold increase with pretest probability unlikely for pulmonary embolism to decrease unnecessary computerized tomographic pulmonary angiography. J Thromb Haemost 2012;10:572–81.
[26] Lapner ST, Julian JA, Linkins LA, Bates S, Kearon C. Comparison of clinical probability-adjusted D-dimer and age-adjusted D-dimer interpretation to exclude venous thromboembolism. Thromb Haemost 2017;117:1937–43.
[27] Lapner ST, Stevens SM, Woller SC, Snow G, Kearon C. Age-adjusted versus clinical probability-adjusted D-dimer to exclude pulmonary embolism. Thromb Res 2018;167:15–9.
[28] van der Hulle T, Cheung WY, Kooij S, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet 2017;390:289–97.
[29] Kabrehl C, Vlieg AVH, Muzikanski A, et al. Multicenter evaluation of the YEARS criteria in emergency department patients evaluated for pulmonary embolism. Acad Emerg Med 2018. https://doi.org/10.1111/acem.13417.