

## ORIGINAL ARTICLE

# D-dimer threshold increase with pretest probability unlikely for pulmonary embolism to decrease unnecessary computerized tomographic pulmonary angiography

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**Summary.** *Background:* Increasing the threshold to define a positive D-dimer could reduce unnecessary computed tomographic pulmonary angiography (CTPA) for a suspected pulmonary embolism (PE) but might increase rates of a missed PE and missed pneumonia, the most common non-thromboembolic diagnosis seen on CTPA. *Objective:* Measure the effect of doubling the standard D-dimer threshold for 'PE unlikely' Revised Geneva (RGS) or Wells' scores on the exclusion rate, frequency and size of a missed PE and missed pneumonia. *Methods:* Patients evaluated for a suspected PE with 64-channel CTPA were prospectively enrolled from emergency departments (EDs) and inpatient units of four hospitals. Pretest probability data were collected in real time and the D-dimer was measured in a central laboratory. Criterion standard was CPTA interpretation by two independent radiologists combined with clinical outcome at 30 days. *Results:* Of 678 patients enrolled, 126 (19%) were PE+ and 93 (14%) had pneumonia. Use of either Wells'  $\leq 4$  or RGS  $\leq 6$  produced similar results. For example, with RGS  $\leq 6$  and standard threshold ( $< 500 \text{ ng mL}^{-1}$ ), D-dimer was negative in 110/678 (16%), and 4/110 were PE+ (posterior probability 3.8%) and 9/110 (8.2%) had pneumonia. With RGS  $\leq 6$  and a threshold  $< 1000 \text{ ng mL}^{-1}$ , D-dimer was negative in 208/678 (31%) and 11/208 (5.3%) were PE+, but 10/11 missed PEs were subsegmental and none had concomitant DVT. Pneumonia was found in 12/208 (5.4%) with RGS  $\leq 6$  and D-dimer  $< 1000 \text{ ng mL}^{-1}$ . *Conclusions:* Doubling the threshold for a positive D-dimer with a PE unlikely pretest probability

could reduce CTPA scanning with a slightly increased risk of missed isolated subsegmental PE, and no increase in rate of missed pneumonia.

**Keywords:** fibrin fragment D, medical decision making, spiral computed, tomography, venous thromboembolism.

## Introduction

In the past decade, the D-dimer has become integral to the evaluation of patients with a suspected acute pulmonary embolism (PE). Published clinical guidelines recommend that a PE can be safely excluded with the combination of a normal quantitative D-dimer value and a low pretest probability assessment [1,2]. The first quantitative D-dimer assay to receive marketing clearance by the Food and Drug Administration (FDA) for this indication used a threshold of  $500 \text{ ng mL}^{-1}$  (VIDAS; Biomérieux, Durham, NC, USA). In conjunction with a low pretest probability this  $500 \text{ ng mL}^{-1}$  threshold produces nearly 100% diagnostic sensitivity for detection of an acute PE, and thus has provided the benchmark for subsequent commercial D-dimer assays [3]. Simultaneously, in the past decade, multidetector-row computerized tomographic pulmonary angiography (CTPA) has become the imaging mainstay in the diagnosis and exclusion of an acute PE. CTPA can also disclose clinically important alternative diagnoses, most often pulmonary infiltrates suggestive of pneumonia [4,5]. However, CTPA can cause direct and indirect adverse effects. Two direct adverse effects of CTPA are an increased lifetime risk of cancer from radiation exposure and the risk of contrast nephropathy [6–9]. An indirect effect of CPTA stems from the increasing resolution afforded by 64-channel CT equipment, which has increased the frequency of PE diagnosis based upon an isolated subsegmental filling defect – a finding that definitely causes clinical uncertainty and in the absence of concomitant DVT, may lead to overtreatment [8–13]. Additionally, at one US

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hospital, almost 40% of patients who had one CTPA underwent a second CTPA that was negative for PE within the next few years [14]. These concerns prompted the National Quality Forum to issue an imaging efficiency measure (NQF #IEP-005-10) intended to reduce CTPA usage in low-risk and D-dimer negative patients.

Judicious use of D-dimer-based screening can decrease unnecessary CTPA usage, but some clinicians may be reticent to use D-dimer in patients with risk factors for a false-positive D-dimer, including age > 70 years, active malignancy or pregnancy [15–17]. Several authors have proposed increasing the D-dimer threshold based upon the pretest probability, or the patient's age or comorbidity [18–21]. The central hypothesis of this work stems from the concept that one D-dimer threshold does not fit all patients equally, and that the threshold for abnormal can be safely increased under two circumstances: (i) in patients who have a condition that predict an elevated D-dimer concentration even in the absence of PE, or (ii) those with a low enough pretest probability. Increasing the D-dimer threshold would probably increase the exclusion rate, but potentially at the cost of increasing the false-negative rate. No previous study has enrolled a large, prospective, multicenter sample of inpatients and outpatients who have all undergone CTPA testing, standardized quantitative D-dimer testing and with the methodology to determine how many of these false-negative cases are isolated subsegmental filling defects. Moreover, a sensible study of D-dimer should also acknowledge the potential clinical significance of alternative diagnoses revealed by CTPA, most often infiltrate suggesting pneumonia [4,5,22–25]. The primary goal of the present study was to measure the change in the frequency of PE exclusion, the coincident change in the frequency and size of missed PE, and the posterior probability of pneumonia produced when the D-dimer threshold is doubled for the subset of patients aged  $\geq 70$  years or for patients with a PE unlikely pretest probability.

## Methods

### Study design

This was a four center, prospective, non-interventional study of diagnostic accuracy, conducted in accordance with the guidelines set out by the STARD criteria [26].

### Study setting and population

Prospective enrollment occurred in the emergency department (ED), inpatient wards, intensive care units and radiology suites of four academic medical centers in the US (Carolinas Medical Center, Charlotte, NC; Northwestern Memorial Hospital, Chicago, IL; Wake Forest University, Baptist Hospital, Winston-Salem, NC; and Baystate Hospital, Springfield, MA). The study protocol was registered on clinicaltrials.gov prior to enrollment (NCT00368836).

Experienced research coordinators initiated the screening process based upon discovery of an order entry for a CTPA from anywhere within the hospital, 6 days per week, 12 h per day. Based upon preliminary work that showed CTPA scans were ordered in equal proportions for inpatients and ED patients, the screening process was designed to produce equal proportions of enrolled inpatients and outpatients. Inclusion criteria required that CTPA was ordered, and to further restrict the population to those patients with one of 15 signs or symptoms of PE and one of 21 known risk factors for PE (Table 1) [10]. All patients provided written informed consent and the study was approved by the institutional review board. Patients were excluded if they were unlikely to provide follow-up data (imprisonment, homelessness, no telephone and a history of non-compliance) or if they were hemodynamically unstable, intubated, had fibrinolytic treatment within 48 h, had a PE diagnosed within the last 6 months and were currently receiving systemic anticoagulation or had known active tuberculosis.

### Study protocol

CTPA images were obtained at each site as part of standard care with a 64-channel, multi-detector equipment capable of  $\leq 2.5$  mm collimation [10].

### Clinical data, blood collection and D-dimer assay

Blood was drawn by a qualified phlebotomist into two (blue-top) tubes containing sodium citrate dihydrate (0.11 mM). These tubes were drawn and transported on ice and immediately centrifuged at  $2500\times g$  for 15 min and the plasma fraction separated from the red cell mass. Plasma was stored at  $-80^{\circ}\text{C}$  25. The plasma D-dimer concentration was measured in batches of single-freeze-thawed aliquots of plasma at a central site clinical laboratory using a well-validated commercial assay (VIDAS ELISA; Biomérieux) [3]. Study D-dimer results were not provided to any member of the clinical care team or to radiologists, but all sites had the ability to order a stat D-dimer at all times during the present study at the discretion of the attending physician. Key elements of clinical data were obtained in real time, as opposed to chart review, including all data in Table 1. Each data field had an explicit definition and coordinators were trained by the principal investigator according to an explicit set of standard operating procedures (SOPs) on how to collect these in a standardized method. Vital signs recorded were those closest in time to when the patient was enrolled, and all pulse oximetry readings were obtained with the patient breathing room air. Moreover, the factor termed by Wells *et al.* [27] as 'An alternative diagnosis is less likely than PE' that confers three points was determined by interview with the physician who ordered the CTPA prior to the time when CTPA results were known and was considered present if the physician answered yes to the question of whether he or she believed that a PE was the most likely diagnosis at the time the CTPA

**Table 1** Inclusion criteria for signs, symptoms and risk factors for a pulmonary embolism (PE)

Signs or symptoms for PE (at least one required for inclusion) (%)	
New onset dyspnea (58*)	Pulse $\geq 90$ beats $\text{min}^{-1}$ (34)
Dyspnea worse than baseline (16)	Dizziness (19)
Pleuritic chest pain (39)	Confusion/altered mental status (4)
Upper abdominal pain (9)	Respiratory rate $> 20$ breaths $\text{min}^{-1}$
Upper back pain (12)	Cough (38)
Syncope (3)	Patient or clinician observation of unilateral limb swelling (9)
Near Syncope (4)	Any pulse oximetry reading $< 95$ (13)
Hemoptysis (3)	
Risk factors for PE (at least one required for inclusion) (%)	
Age $> 49$ years (67)	Chronic neuromuscular disease with immobility ( $< 1$ )
Surgery (within previous 4 weeks requiring general endotracheal anesthesia) (16)	Body mass index $> 36$ $\text{kg m}^2$ (24)
Bed rest of hospitalization $> 72$ h (18)	Stroke, MI or arterial embolism within previous 30 days (2)
Current hospitalization for $> 11$ h trauma (2)	Congestive heart failure (8)
Trauma requiring hospitalization within the previous 2 weeks (2)	Active intravenous recreational drug use ( $< 1$ )
Personal history of thrombophilia (2)	Current DVT within past 3 months without known PE (5)
Active malignancy (currently under the care of an oncologist for treatment) (14)	Active connective tissue disease (lupus, MCTD or scleroderma) (5)
Any exogenous estrogen use (9)	Focal infection requiring hospitalization or observation (8)
Postpartum status (within past 2 weeks) (2)	Indwelling deep vein catheter or port (excludes pacemaker wire) (9)
Immobilization of an ankle, knee, hip or shoulder for $> 48$ h within the past 7 days (4)	Hemodialysis-dependent renal failure (within past 2 weeks) (2)
Paralysis of one or more limbs from prior stroke or spinal cord injury ( $< 1$ )	Any previous venous thromboembolism (16)

\*Percentage of  $n = 678$  with the feature present.

MI, myocardial infarction; DVT, deep vein thrombosis; MCTD, mixed connective tissue disease.

was ordered or if the clinical team initiated empiric heparin before knowing the results of the CTPA.

#### CTPA interpretation

An independent reference reading (IRR) laboratory (Medical Metrics, Inc., Houston, TX, USA) interpretation and the site interpretation were both integrated in this analysis. At the site hospitals, images were interpreted by board-certified hospital radiologists who had completed a fellowship in emergency radiology or body imaging. Later, at the IRR laboratory, images that were stripped of protected health information and any added comments or markings were interpreted by one of two board-certified radiologists who had completed fellowship training in body imaging. The IRR radiologists interpreted images as 'No PE', 'Positive for acute PE', 'Positive for chronic PE' and 'Positive for other finding,' which was further graded including a specific code for pulmonary infiltrate suggestive of pneumonia. Interpretations of CTPAs at each site were performed as part of the standard care, and the final, written interpretation entered into the medical record was abstracted using a standardized approach to determine the site reading. All scans read as positive for PE were further evaluated by the IRR radiologist for the location of the filling defect and the percentage obstruction of the vessel(s) using a modified version of the method described by Mastora *et al* [28]. If the IRR read no PE for a scan read as PE+ at the site, the percentage obstruction was set at 2.5%.

#### Clinical follow-up

All patients had a telephone follow-up at 30 and 90 days using scripted query and a specific data collection template designed to discover an interval diagnosis of PE and treatment status.

#### Criterion standard for acute PE and pneumonia and contrast induced nephropathy

The criterion standard defined PE+ if the initial CTPA was interpreted as positive for any filling defect consistent with PE by either the IRR or the site radiologist, or a repeat CTPA performed within 30 days was found to be positive for PE and the patient treated for 90 days with systemic anticoagulation. All other patients were considered PE (-). The PE was considered subsegmental if the total filling defect were  $< 5\%$  [28]. Pneumonia was considered present if the radiologist indicated the presence of an infiltrate and all three of the following were true: the patient received a new prescription or order for antibiotics within 24 h of enrollment and both the written discharge summary and the ICD-9 billing codes indicated a diagnosis of pneumonia. We assessed the frequency of contrast-induced nephropathy (CIN) in patients who had a serum creatinine (sCr) measured as part of standard care on the same day as CTPA was then repeated at 2–7 days postenrollment. We defined CIN as present as follows:  $[(\text{sCr}_{\text{baseline}} - \text{sCr}_{\text{repeat}}) / \text{sCr}_{\text{baseline}}] > 0.5$  (50% relative increase).

### Data archiving

Clinical data, centralized D-dimer results, radiological interpretations and follow-up data were abstracted from source documentation or obtained directly from the patient using study specific data templates by qualified clinical research associates in accordance with Good Clinical Practice guidelines. Data were then transferred in duplicate by independent coordinators to paper case report forms and then manually uploaded to a central server in an SQL database (Microsoft, Inc., Redmond, WA, USA). Each data element on each case report form (CRF) was inspected regularly during the conduct of the study against source documents for completeness, validity and between-CRF reproducibility by an experienced independent clinical study monitor (Southshore Clinical, Cornelius, NC, USA). The study monitor issued a written report that contained any queries about data fields. Data were exported from SQL to a spreadsheet to facilitate analysis for the present study.

### Data analysis

Previous literature has suggested that for age > 70 years or for a PE unlikely pretest probability, the D-dimer threshold could be doubled without compromising the posterior probability. We confirmed these cutoffs in our data by comparing the posterior probability of PE observed at increasing intervals of age and intervals of pretest probability at eight increasing D-dimer thresholds, starting with the standard threshold of 500 ng mL<sup>-1</sup>. A PE unlikely pretest probability was determined by dichotomizing the Wells' score and the revised Geneva score (RGS) [29,30]. In all, 95% confidence intervals (CI) were calculated from the exact (Clopper Pearson) method (StatsDirect v. 2.7.8, Cheshire, England). Quadratic regression was used to produce curves to show the relationship between the D-dimer concentration and patient age (SigmaPlot, v11.0, Systat Software, Chicago, IL, USA).

### Results

Patients were enrolled from 30 January 2007 to 27 April 2008. Figure 1 shows the flow diagram of patients starting with those subjects screened for inclusion to the point of final outcome with respect to PE diagnosis. Seven hundred and twenty-five patients signed a consent form and 678 had complete data. Table 1 presents the percentages of the 678 patients who were enrolled with complete data who had each inclusion criterion and Table 2 presents the demographic data and additional clinical characteristics of these 678 patients. One hundred and eleven (18%) patients were aged > 70 years.

The criterion standard for any filling defect consistent with PE was found in 126/678 patients (19%, 95% CI: 16–22%), including 108 with an acute PE only, nine with an acute and chronic PE and four with a chronic PE only. On follow-up, 60 (9%) patients had a repeat CTPA of which five (8%) showed interval development of a new, acute PE. None of these five

had been treated with systemic anticoagulation before the second CTPA. By 30 days follow-up, clinicians treated 124 patients who had any PE observed on CTPA with systemic anticoagulation, withholding anticoagulation in two patients with subsegmental PE, neither of whom developed any thrombotic event within 90 days. Fifty-four of the 126 PE cases (42%) were isolated subsegmental (total pulmonary vascular occlusion < 5%). The criterion standard for pneumonia was found in 93/678 patients (14%, 95% CI: 11–17%). The posterior probabilities of PE and pneumonia in the presence of a normal D-dimer using the conventional cutoff of 500 ng mL<sup>-1</sup> was 8/152 (5%) and 16/152 (10.5%), respectively.

To illustrate the relationship between D-dimer and age, Fig. 2 plots the D-dimer concentration vs. age and shows the best fit quadratic equation for D-dimer values for patients with and without PE. The splay in the curves shows widening at 70 years of age, providing support to the decision to increase the D-dimer threshold at this age.

To assess the relationship between the size of the PE and D-dimer, Fig. 3A plots the D-dimer concentration as a function of the fraction of pulmonary vascular obstruction for the entire range of D-dimer concentrations. The plot shows no evidence of overall correlation [Pearson's correlation coefficient (*r*) value < 0.1], even with multiple attempts at data transformation. However, Fig. 3B, which displays the area shown in the lower left corner of Fig. 2A, does convey important information about the size of PEs in the range of D-dimer values that might be used for exclusion. Dots to the left of the vertical dotted line represent subsegmental PEs. The major point of this plot is that the majority of patients with PE and a D-dimer concentration below 1000 ng mL<sup>-1</sup> have subsegmental PEs.

Table 3 presents a matrix designed to systematically examine the posterior probability of PE in the presence of eight increasing D-dimer thresholds according to the age of each patient, stratified into four ranges intervals (< 30, 30–49, 50–69 and ≥ 70 years) and according to the Wells' and RGS scores, stratified into three intervals (< 2, 2–6, > 6 for the Well's score and < 4, 4–10 or > 10 for RGS) and then at the single most useful cutoff for each (≤ 4 for Well's and ≤ 6 for RGS). The purpose of Table 3 was to inspect each cell for the posterior probability to estimate the optimal cutoff in D-dimer and age or pretest probability score, respectively.

Taken together, data in Figs 1 and 2 and Table 3 indicate that posterior probability could be maintained and rule out the rate for PE could be increased if the D-dimer cutoff were increased up to 1000 ng mL<sup>-1</sup> for age > 70 years or Wells' score ≤ 4 or RGS ≤ 6. These cutoffs in D-dimer, age and pretest probability agree with previous studies [18,21,31].

Table 4 presents the main findings of the present study, including the exclusion rate and posterior probability for eight different D-dimer-based screening strategies. Table 4 first shows the performance of the quantitative site D-dimer that was ordered as part of standard care in 286 patients. Curiously, the site D-dimer was negative in 40 patients (6% of the cohort) who underwent CTPA, only one of whom had a PE, suggesting

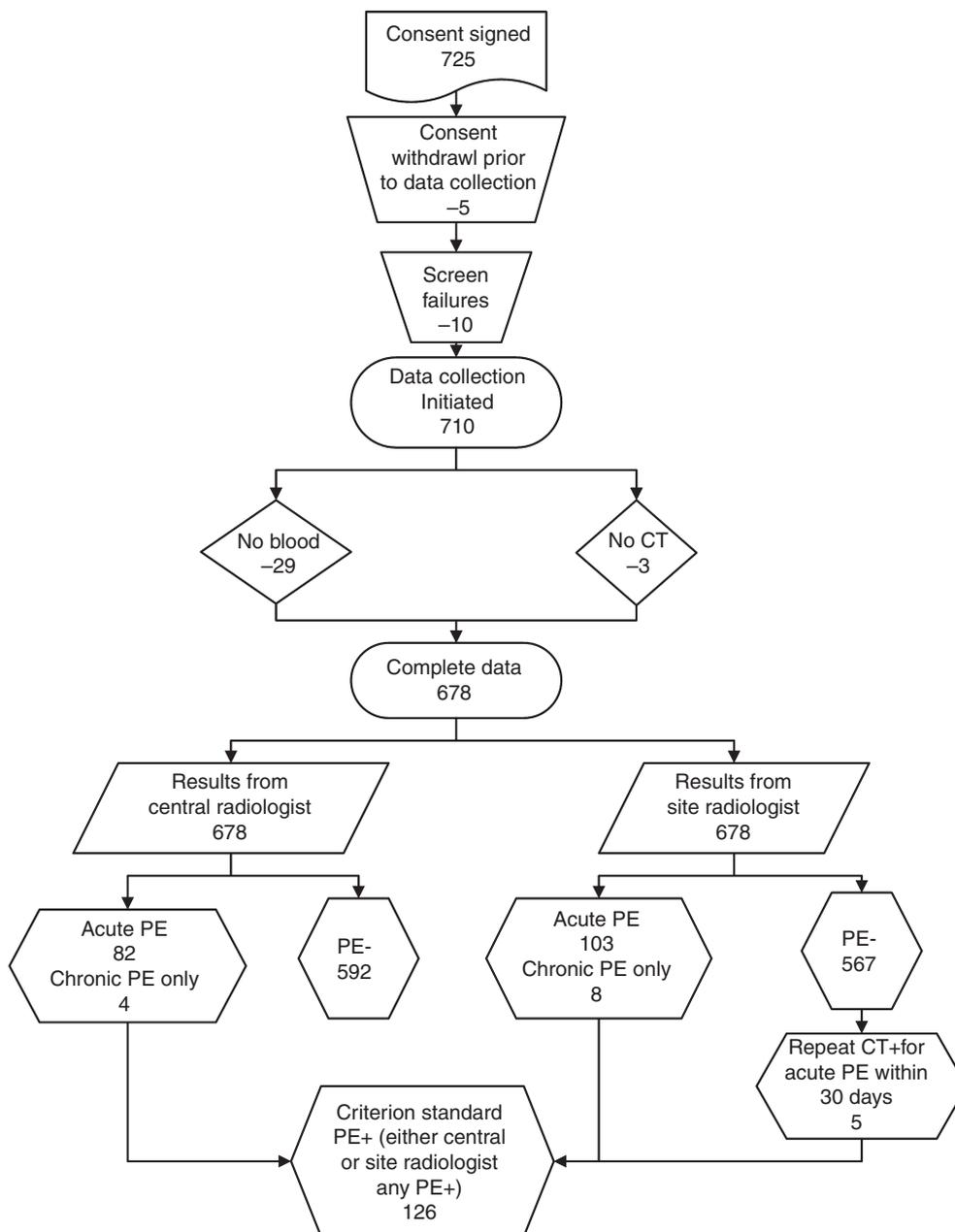


Fig. 1. Flow diagram showing the number of patients screened, enrolled and reasons for exclusions.

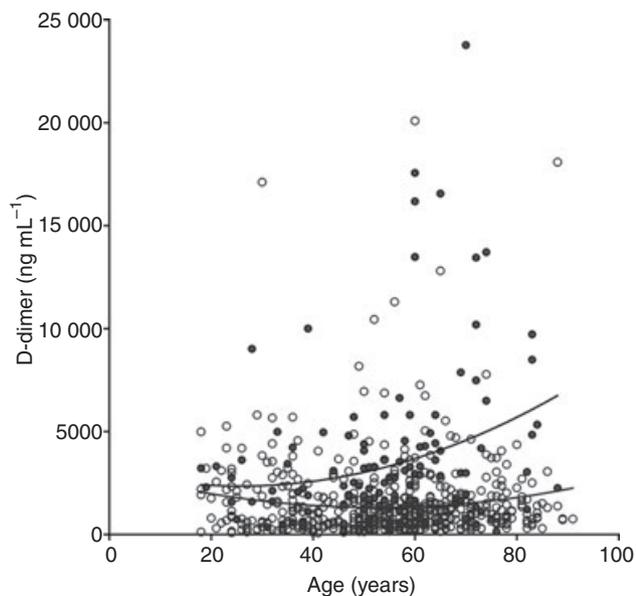
either an uncoupling of test ordering from subsequent behavior or that clinicians may order the CTPA to diagnose other conditions besides PE. Table 4 then shows the diagnostic performance of the study D-dimer at a standard threshold ( $< 500 \text{ ng mL}^{-1}$ ) and at  $< 1000 \text{ ng mL}^{-1}$  alone and under three assumptions: age  $> 70$  years, a Wells' score  $\leq 4$  or an RGS  $\leq 6$ . With any of these three strategies, the net rule out rate could have been substantially increased by doubling the D-dimer threshold, and with minimal cost in terms of increased posterior probability of segmental or larger PE. For example, for patients with a Wells' score  $\leq 4$  and the standard D-dimer threshold, the exclusion rate was 16% (95% CI: 13–19%) and the posterior probability was 4/106 or 3.8% (95% CI: 1–9.3%)

whereas with a Wells' score  $\leq 4$  and a D-dimer  $< 1000 \text{ ng mL}^{-1}$  the exclusion rate increased to 33% (95% CI: 29–36%), and the posterior probability of PE was 12/221 or 5.4% (95% CI: 2.8–9.3%). Likewise, for patients with an RGS  $\leq 6$  at standard D-dimer threshold, the exclusion rate was 110/678 (16%, 95% CI: 14–19%) with a 4/110 or 3.6% (95% CI 1–10%) posterior probability whereas for an RGS  $\leq 6$  and D-dimer  $< 1000 \text{ ng mL}^{-1}$ , the exclusion rate increased to 208/678 (31%, 95% CI 27–44%) with a posterior probability of 11/208 (5.3%, 95% CI 3.0–9.2%). The same four patients with PE were missed by the Wells' score  $\leq 4$ , and the RGS  $\leq 6$  and D-dimer  $< 500 \text{ ng mL}^{-1}$ , and three of these four had subsegmental PE and one had a PE with 19% obstruction.

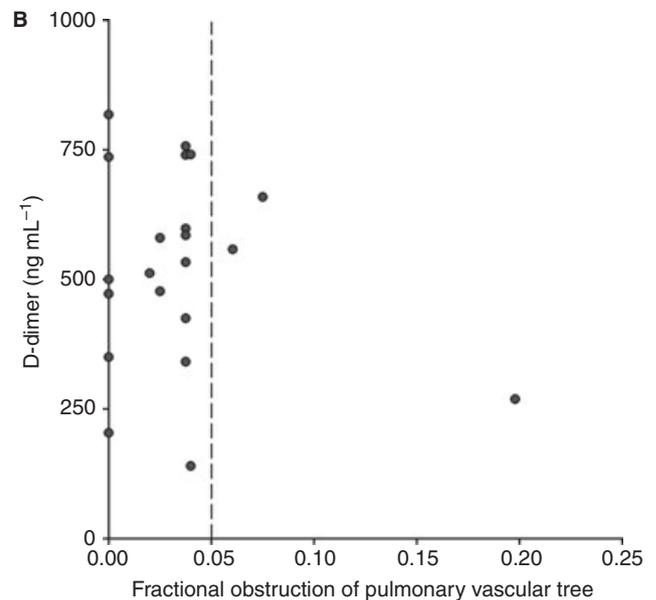
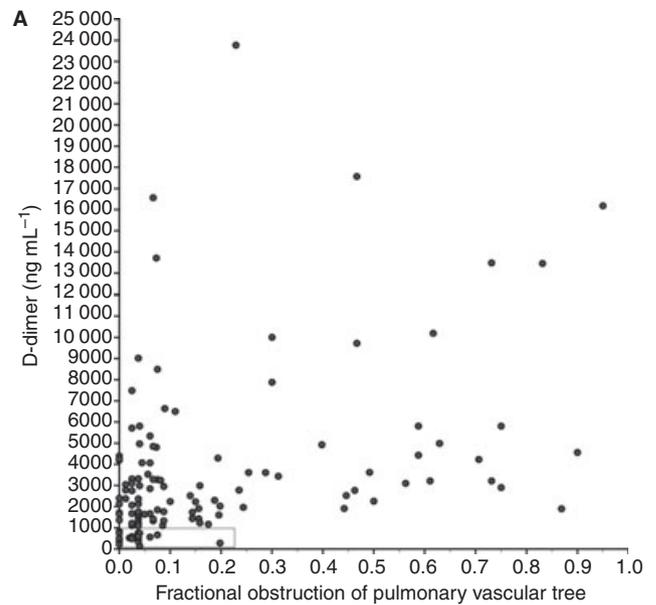
**Table 2** Clinical characteristics of the study population

Variable	Mean or <i>n</i>	SD or %
<b>Vital sign data</b>		
Pulse rate (beats min <sup>-1</sup> )	84	18
Respiratory rate (breaths min <sup>-1</sup> )	19	4
Pulse oximetry	97	2
Systolic blood pressure (mmHg)	128	21
<b>Patient location</b>		
Inpatient	335	49%
Emergency department	334	49%
Rehabilitation unit	9	1%
<b>Demographic data</b>		
Age (years)	55	16
Body weight (lbs)	194	56
Black race	218	32%
Native American race	2	0%
Caucasian race	446	66%
Asian race	2	0%
Other race	10	1%
Male sex	258	38%
<b>Risk factors for PE</b>		
Wells' score	3.0	1.9
Revised Geneva Score	6.7	3.4
Chronic obstructive pulmonary disease	74	11%
Warfarin within past 7 days	89	13%
Current smoker	258	38%
Sickle cell disease	2	0%
<b>Other diagnostic tests done</b>		
Ultrasound of leg	144	21%
Ultrasound of arm	13	2%
D-dimer at site	286	42%
Echocardiography	286	42%

PE, pulmonary embolism.



**Fig. 2.** Scatter plot of the plasma D-dimer concentration vs. patient's age. Red circles represent pulmonary embolism (PE)+ patients and open blue circles represent PE- patients. The curved lines are best fit quadratic equations (PE+:  $D\text{-dimer} = 3096 - 58 \cdot \text{age} + 1.13 \cdot \text{age}^2$ ; PE-:  $D\text{-dimer} = 3052 - 66 \cdot \text{age} + 0.63 \cdot \text{age}^2$ ).



**Fig. 3.** (A) Scatter plot of the D-dimer vs. the percentage of pulmonary vasculature obstructed on computerized tomographic pulmonary angiography (CTPA) for all patients with a pulmonary embolism (PE) and (B) shows data for the rectangle at the lower left corner; all red circles to the left of the vertical dotted line represent a subsegmental PE.

We then examined the size of the filling defects of patients present when the patient had a PE unlikely pretest probability and a D-dimer  $< 1000 \text{ ng mL}^{-1}$ . Among the 12 false-negative cases produced by the Wells' score  $\leq 4$  and a D-dimer threshold of  $1000 \text{ ng mL}^{-1}$ , 10 of these 12 false-negative PEs were isolated, subsegmental filling defects and no patient with a D-dimer  $< 1000 \text{ ng mL}^{-1}$  was diagnosed with concomitant DVT and one had active malignancy. Among the 11 patients with an RGS  $\leq 6$  and a D-dimer  $< 1000 \text{ ng mL}^{-1}$ , 10 of these 11 had isolated, subsegmental filling defects, and none had DVT and one had active malignancy. Seven of the patients

**Table 3** Posterior probabilities for pulmonary embolism stratified for age, pretest probability at increasing thresholds for a normal D-dimer

Adjustment criteria		Cutoff for an abnormal D-dimer concentration in ng mL <sup>-1</sup>							
		500 (%)	750 (%)	1000 (%)	1250 (%)	1500 (%)	5000 (%)	10 000 (%)	25 000 (%)
Age	0–29	0/12 (0)	1/18 (6)	1/22 (5)	1/23 (4)	1/23 (4)	8/48 (17)	9/51 (18)	9/51 (18)
	30–49	5/56 (9)	8/81 (10)	8/88 (9)	9/101 (9)	10/110 (9)	26/169 (15)	28/174 (16)	28/175 (16)
	50–69	2/69 (3)	6/125 (5)	8/148 (5)	12/187 (6)	18/213 (8)	58/312 (19)	63/323 (20)	67/331 (20)
	70–100	1/15 (7)	4/34 (12)	4/52 (8)	6/63 (10)	7/77 (9)	13/110 (12)	18/116 (16)	22/121 (18)
	All ages	8/152 (5)	19/258 (7)	21/310 (7)	28/374 (7)	36/423 (9)	105/639 (16)	118/664 (18)	126/678 (19)
Wells' score	< 2	3/80 (4)	8/139 (6)	9/165 (5)	10/185 (5)	14/212 (7)	36/292 (12)	38/301 (13)	39/304 (13)
	2–6	3/68 (4)	9/113 (8)	9/134 (7)	15/174 (9)	19/196 (10)	59/316 (19)	68/328 (21)	72/336 (21)
	> 6	2/4 (50)	2/6 (33)	3/11 (27)	3/15 (20)	3/15 (20)	10/31 (32)	12/35 (34)	15/38 (39)
	≤ 4	4/106 (4)	11/186 (6)	12/221 (5)	16/260 (6)	21/299 (7)	54/434 (12)	57/445 (13)	60/452 (13)
Revised Geneva score	< 4	2/65 (3)	3/98 (3)	3/104 (3)	4/116 (3)	7/126 (6)	18/159 (11)	18/160 (11)	18/160 (11)
	4–10	4/75 (5)	13/139 (9)	14/178 (8)	19/220 (9)	24/256 (9)	64/398 (16)	72/413 (17)	77/424 (18)
	> 10	2/12 (17)	3/21 (14)	4/28 (14)	5/38 (13)	5/41 (12)	23/82 (28)	28/91 (31)	31/94 (33)
	≤ 6	4/110 (4)	10/179 (6)	11/208 (5)	15/241 (6)	19/273 (7)	45/366 (12)	48/373 (13)	51/377 (14)

**Table 4** Diagnostic indexes produced by screening strategies for a pulmonary embolism (PE) that include an increased D-dimer threshold

Screening strategy	TP	TN	FN	FP	n	Exclusion rate (%)	Sens (%)	Spec (%)	LR (-)	Posterior	FN with Subseg*	CIN <sup>†</sup>
										probability (%)		
Site D-dimer, standard threshold*	35	39	1	211	286	6	97.2	15.6	0.18	2.5	0	0
D-dimer < 500 ng mL <sup>-1</sup>	118	144	8	408	678	22	93.7	26.1	0.24	5.3	7	3
D-dimer < 1000 ng mL <sup>-1</sup>	105	289	21	263	678	46	83.3	52.4	0.32	6.8	17	11
D-dimer < 500 or < 1000 if Age > 70	116	175	10	377	678	27	92.1	31.7	0.25	5.4	9	6
Wells ≤ 4 and D-dimer < 500 ng mL <sup>-1</sup>	122	102	4	450	678	16	96.8	18.5	0.17	3.8	4	2
Wells ≤ 4 and D-dimer < 1000 ng mL <sup>-1</sup>	114	209	12	343	678	33	90.5	37.9	0.25	5.4	10	10
RGS ≤ 6 and D-dimer < 500 ng mL <sup>-1</sup>	122	106	4	446	678	16	96.8	19.2	0.17	3.6	4	2
RGS ≤ 6 and D-dimer < 1000 ng mL <sup>-1</sup>	115	197	11	355	678	31	91.3	35.7	0.24	5.3	10	9

TP, true positive; TN, true negative; FN, false negative; FP, false positive; sens, sensitivity; spec, specificity; LR(-), likelihood ratio negative; DVT, deep venous thrombosis; CIN, number of patients with contrast-induced nephropathy (defined as a 50% increase in serum creatinine within 2–7 days); RGS, revised Geneva score.

\*Number of patients with false-negative PEs that were subsegmental; †number of cases of contrast-induced nephropathy in the true-negative group.

with false-negative PEs (12 with Wells' ≤ 4 and 11 with RGS ≤ 6) had a lower extremity ultrasound and three others underwent lower extremity CT venogram which was negative for DVT. The only PE that was larger than subsegmental that was missed by both strategies was the same PE with 19% obstruction missed by the D-dimer < 500 ng mL<sup>-1</sup>.

To assess the rate of contrast-induced nephropathy, we examined data from 224 patients who had a serum creatinine measured before CTPA and again at 2–7 days post enrollment as part of standard care. Of the 224 patients with paired serum creatinine measurements, 37 (17%, 95% CI: 12–22%) developed contrast-induced nephropathy, using the definition of a 50% relative increase in creatinine value. In the last column on the right, Table 4 presents the number of cases of CIN that could have been prevented with each screening strategy. Ten patients with CIN had a Wells' score ≤ 4 and a D-dimer < 1000 ng mL<sup>-1</sup> and nine with CIN had RGS ≤ 6 and D-dimer < 1000.

When the data were restricted to inpatients only, we found a trend towards reduced protocol efficiency. For example, among inpatients, the combination of a Wells' score ≤ 4 and a D-dimer < 500 ng mL<sup>-1</sup> would have allowed a rule out rate

of 12% producing a posterior probability of PE of 6.8% whereas a Wells' score ≤ 4 and a D-dimer < 1000 ng mL<sup>-1</sup> would have ruled out 26% producing a posterior probability of PE of 7.7%.

Because active cancer is known to elevate the D-dimer and sharply reduce the test specificity, we examined the impact of D-dimer at a threshold at 1000 ng mL<sup>-1</sup> for patients aged > 70 years or with active cancer and 500 ng mL<sup>-1</sup> for all others [32]. This strategy would have led to 195 (28.7%) patients with a negative screen, with 12 (6.1%) false negatives, and thus provided a minimal incremental increase in rule out rate.

Regarding potential alternative diagnoses on CTPA, radiologists found at least one pathologic finding on 425/552 CTPA scans that did not have PE. Both radiologists agreed that infiltrate was present in 93 patients who received antibiotics within 24 h and had a discharge diagnosis that included pneumonia. Thus, pneumonia was present in 14% (95% CI: 11–17%) of patients who underwent CTPA for a suspected PE, and pneumonia accounted for most clinically important acutely life-threatening, alternative diagnoses seen on CTPA. Other diagnoses seen on CTPA included aortic dissection (9),

**Table 5** Diagnostic indexes for pneumonia using the proposed D-dimer-based screening strategies

Screening strategy	TP	TN	FN	FP	<i>n</i>	Sensitivity (%)	Specificity (%)	LR(-)	Posterior probability (%)
D-dimer < 500 ng mL <sup>-1</sup>	77	136	16	449	678	82.8	23.2	0.74	10.5
D-dimer < 1000 ng mL <sup>-1</sup>	66	283	27	302	678	71.0	48.4	0.60	8.7
D-dimer < 500 or < 1000 if Age > 70	75	167	18	418	678	80.6	28.5	0.68	9.7
Wells ≤ 4 and D-dimer < 500 ng mL <sup>-1</sup>	83	96	10	489	678	89.2	16.4	0.66	9.4
Wells ≤ 4 and D-dimer < 1000 ng mL <sup>-1</sup>	76	204	17	381	678	81.7	34.9	0.52	7.7
RGS ≤ 6 and D-dimer < 500 ng mL <sup>-1</sup>	84	101	9	484	678	90.3	17.3	0.56	8.2
RGS ≤ 6 and D-dimer < 1000 ng mL <sup>-1</sup>	81	196	12	389	678	87.1	33.5	0.39	5.8

TP, true positive; TN, true negative; FN, false negative; FP, false positive; sens, sensitivity; spec, specificity; LR(-), likelihood ratio negative; DVT, deep venous thrombosis; CIN, contrast-induced nephropathy (defined as a 50% increase in serum creatinine within 2–7 days); RGS, revised Geneva score.

thoracic aneurysm (10) and pneumothorax (3). Table 5 shows the diagnostic indexes for each putative strategy for pneumonia. The primary findings in Table 5 was that the strategy of doubling the D-dimer for age < 70, was not an efficient screening tool for pneumonia because, whereas the combination of an RGS ≤ 6 and a D-dimer < 1000 led to the lowest posterior probability of pneumonia. Plain film chest radiographs were ordered on 565 patients (83%) and among these, 200 (35%) were interpreted as normal and 58 (10%) were interpreted as positive for infiltrate. Surprisingly, only 21 of these 58 were interpreted as positive for infiltrate on CTPA. These data suggest substantial discordance between plain film chest radiographs and the CTPA.

## Discussion

The present study examines the hypothesis that selected use of an elevated threshold for a normal D-dimer concentration can decrease the need for CTPA scanning for PE. As has been reviewed recently, extensive previous literature has been published to suggest that D-dimer can be elevated in the elderly, in patients with certain comorbidities and in patients with a low pretest probability [31]. The present study was designed specifically to address this question, after years of planning, and using methods designed to enhance the generalizability of results. We enrolled a sample of patients who represent the whole population of patients undergoing 64 channel CTPA at four large hospitals, including a balance of ED and hospitalized patients [33]. We used a rigorous criterion standard inasmuch all CTPA scans were read by two independent radiologists and the central radiologist graded the size of PE; we also included clinical follow-up. D-dimer concentrations were measured in a central laboratory using a well-studied D-dimer assay that was the first cleared by the FDA as an aid to exclusion of PE. Recognizing the possibility that in clinical practice, some physicians eschew the D-dimer and order a CTPA to help them evaluate non-thromboembolic pathology, we also examined the ability of D-dimer to exclude pneumonia, the most common important alternative diagnosis seen on CTPA scans [4,5].

These resultant data allow several clinically important observations. First, the data in Table 4 show that physicians

sometimes order a D-dimer at the site and then disregard the result. In fact, the site D-dimer was negative in 40 patients who underwent CTPA, and only one of whom had a PE. Second, most patients with a PE in the presence of D-dimer concentrations below 1000 ng mL<sup>-1</sup> had very small PEs. Had a high sensitivity D-dimer been ordered in all patients regardless of pretest probability and using the standard threshold of 500 ng mL<sup>-1</sup>, 152 (22%) of CTPA scans could have been obviated. Importantly, these 152 patients included 8 (5.3%) possible false-negative D-dimer patients who had filling defects on CTPA suggestive of PE, and only 1 of these 8 patients had a filling defect in an artery that was larger than subsegmental. Had a more liberal definition of 1000 ng mL<sup>-1</sup> been used, the exclusion rate would have increased to 310 (46%), but at a cost of a false-negative rate of 21/310 (6.8%) including four patients with a filling defect larger than subsegmental. This rate would appear unacceptably high, and underscores the need for additional criteria. The third main observation was that increasing the normal D-dimer threshold to < 1000 ng mL<sup>-1</sup> for patients with a 'PE unlikely' pretest probability, based upon either the Wells' score ≤ 4 or an RGS ≤ 6, would potentially obviate one-third of CTPA scans with isolated subsegmental filling defects accounting for most of the false negatives. In addition to preventing radiation exposure, this strategy would have potentially prevented at least 10 cases of contrast induced nephropathy, using a very strict definition [34]. The potentially simpler strategy of elevating the D-dimer threshold to 1000 ng mL<sup>-1</sup> only for patients over 70 years had similar results, but adding active malignancy had a marginal value. Our data also show some support for the D-dimer as a screening tool for pneumonia, particularly for an RGS ≤ 6, and a D-dimer < 1000 ng mL<sup>-1</sup> the combination of which significantly lowered the posterior probability of pneumonia from a baseline of 14% (95% CI: 11–17%) to 5.8% (95% CI 3–10%). The final salient observation was the remarkably high rate of subsegmental PE (42% of PEs), which raises a question as to whether the sample may have spectrum or severity bias, or if this reflects the effect of 64 channel multi-row detector CTPA and a criterion standard of PE seen by either the site radiologist or the IRR radiologist.

The present study must be interpreted with caution because of the absence of clear data on the significance of an

isolated subsegmental PE, which comprised almost all of the false-negative cases, and most of these patients were treated with anticoagulation. Observational studies suggest the outcomes of patients with isolated subsegmental PE who are not treated have similar outcomes to those who are treated with anticoagulation, although the literature lacks a randomized trial to address this question [8,12,13,35]. Indeed, the present study only tests the hypothetical contribution of elevating the threshold to define an abnormal D-dimer concentration, as opposed to examining outcomes of patients in a management study. Thus, the next step should be an outcomes trial that randomizes low pretest probability patients to one of two groups, both of which would have anticoagulation withheld: D-dimer at a standard threshold or D-dimer 'at twice the local threshold'. The rationale for stating the D-dimer 'at the local threshold' as opposed to  $500 \text{ ng mL}^{-1}$  is that thresholds for abnormal vary with many quantitative D-dimer assays. Indeed, in the present study, each of the four hospitals used a different local D-dimer assay, each with a different threshold for abnormal. Another limitation involves the interpretation of the significance of the D-dimer as a screen for pneumonia, because we assume that some clinicians are motivated to order CTPA to evaluate for alternative diagnoses such as pneumonia, a point that is based upon experience of the authors. Lastly, in the interest of brevity, we did not use all potentially valid pretest probability methods [29].

In conclusion, a screening strategy that doubles the threshold for an abnormal D-dimer concentration for patients over 70 years old or patients with a Wells' score  $\leq 4$  or an RGS  $\leq 6$  could significantly reduce the rate of CTPA with no net increase in the rate of missing a larger than subsegmental PE and no increase in the rate of missed pneumonia.

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### Disclosure of Conflict of Interest

The authors state that they have no conflict of interest.

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