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## D-dimer can help differentiate suspected pulmonary embolism patients that require anti-coagulation

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### ABSTRACT

**Objectives:** Determine whether D-dimer concentration in the absence of imaging can differentiate patients that require anti-coagulation from patients who do not require anti-coagulation.

**Methods:** Data was obtained retrospectively from 366 hemodynamically stable adult ED patients with suspected pulmonary embolism (PE).

Patients were categorized by largest occluded artery and aggregated into: 'Require anti-coagulation' (main, lobar, and segmental PE), 'Does not require anti-coagulation' (sub-segmental and No PE), 'High risk of deterioration' (main and lobar PE), and 'Not high risk of deterioration' (segmental, sub-segmental, and No PE) groups.

Wilcoxon rank-sum test was used for 2 sample comparisons of median D-dimer concentrations. Receiver operating characteristic (ROC) curve analysis was utilized to determine a D-dimer cut-off that could differentiate 'Require anti-coagulation' from 'Does not require anti-coagulation' and 'High risk of deterioration' from 'Low risk of deterioration' groups.

**Results:** The 'Require anti-coagulation' group had a maximum area under the curve (AUC) of 0.92 at an age-adjusted D-dimer cut-off of 1540 with a specificity of 86% (95% CI, 81–91%), and sensitivity of 84% (79–90%). The 'High risk of deterioration' group had a maximum AUC of 0.93 at an age-adjusted D-dimer cut-off of 2500 with a specificity of 90% (85–93%) and sensitivity of 83% (77–90%).

**Conclusions:** An age-adjusted D-dimer cut-off of 1540 ng/mL differentiates suspected PE patients requiring anti-coagulation from those not requiring anti-coagulation. A cut-off of 2500 differentiates those with high risk of clinical deterioration from those not at high risk of deterioration. When correlated with clinical outcomes, these cut-offs can provide an objective method for clinical decision making when imaging is unavailable.

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## 1. Introduction

### 1.1. Pulmonary emboli in the emergency department

Pulmonary embolism (PE), a manifestation of venous thromboembolism (VTE) disease, is a potentially fatal condition often seen in the emergency department (ED) [1,2]. Emboli most commonly arise from a thrombus in the deep veins of the legs or pelvis and travel to the pulmonary arteries, leading to occlusion of blood flow [1].

It is estimated that 1 in every 400–1500 adults in the ED will be diagnosed with a PE [2]. All-cause 30-day mortality after diagnosis of PE

is 8%, making it the second leading cause of unexpected death in outpatients [2].

### 1.2. Management and treatment of PE in the ED

In patients with acute PE, current treatment guidelines recommend anti-coagulation as first line therapy and inferior vena cava (IVC) filter or direct thrombolysis in a small set of unstable or very high risk patients [3,4].

Presentation of PE varies from asymptomatic to hemodynamic collapse and shock, making it a diagnostic challenge. To aid in diagnosis, a D-dimer assay can be performed to rule out PE in patients with low pre-test probability [3]. D-dimer is a non-invasive, low-cost clinical assay that measures cross-linked fibrin degradation products. If a patient has a positive D-dimer test (usually >500 ng/mL) or has an intermediate or high pre-test probability based on clinical presentation, the patient should receive advanced imaging, such as computed tomography pulmonary angiogram (CTPA) or ventilation/perfusion scan (V/Q)

**Abbreviations:** PE, Pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism; CTPA, computed pulmonary tomography angiography; V/Q scan, perfusion ventilation scan; DOAC, direct oral anti-coagulant; LMWH, low molecular weight heparin; ACCP, American College of Chest Physicians.

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[5]. The 500 ng/mL D-dimer cut-off has shown to have a better predictive value when replaced with the age-adjusted cut-off using the formula: age (in years)  $\times$  10 for patients 50 years or older [6].

Mortality and disease recurrence rate is lower in patients with isolated sub-segmental PE and higher in patients with more proximally located PE (main and lobar pulmonary arteries). This has led to discussion on which patients would benefit from anti-coagulation [7-9]. Recent guidelines by the American College of Emergency Physicians (ACEP) and American College of Chest Physicians (ACCP) suggest to consider not anti-coagulating patients with isolated sub-segmental PE and no proximal deep vein thrombosis (DVT) [3,4].

### 1.3. Management of PE when imaging is not available

Advanced imaging may not always be readily available, and CTPA is contraindicated in certain situations. This includes patients with contrast allergies, severe renal disease, recent contrast load, and those in whom there is a concern of radiation, such as children and pregnant women. V/Q scans are utilized if patients cannot undergo a CTPA but are cumbersome, require skilled technicians, and use technetium radioisotopes.

In the absence of confirmatory imaging, ED providers must balance the risks and benefits of starting empiric treatment. Unnecessary anti-coagulation presents a danger of bleeding [10-12]. On the other hand, not treating a PE could lead to further embolization with resultant hemodynamic collapse and death, especially in patients with larger, more proximal emboli [9,13-16].

The ability to predict which patients suspected of PE require anti-coagulation when imaging is not available could aid in clinical decision making, decrease time to treatment, and prevent unnecessary bleeding risk. A D-dimer cut-off value would provide an objective tool to be used along with clinical gestalt while waiting for confirmatory imaging or in instances where imaging is not possible.

The goal of this study was to establish a relationship between D-dimer concentration and PE location, and then to utilize this relationship to assess sensitivity and specificity of different D-dimer cut-points that stratify patients as needing or not needing empiric anti-coagulation.

## 2. Methods

### 2.1. Study population

We performed a retrospective analysis on adult ED patients from our hospital system spanning 5 years (2014–2018). Patients were identified by querying central patient databases for all patient visits to the ED where both a D-dimer and CTPA were administered. Building a PE patient database using this querying method was validated in a prior study by our investigators on adolescent PE in the ED by Sharaf et al [17]. Our research protocol was reviewed and approved by the hospital's institutional review board.

Our study was performed in a hospital system with 12 EDs across 2 states with a total average annual census of 500,000 adult and pediatric patients. Inclusion and exclusion criteria are outlined in Fig. 1. Key exclusion criteria included not having a D-dimer and CTPA within 24 h of presentation to the ED and presence of factors that affect baseline D-dimer levels (active cancer, active use of anti-coagulation, chronic PE).

The 5-year time span of our study was selected due to enterprise changeover of D-dimer assay to Siemens INNOVANCE® in 2014. This assay is a quantitative, latex enhanced immunoturbidimetric assay that reports values in fibrinogen equivalent units (FEU) [18]. For patients older than 50, age-adjusted D-dimer concentrations were utilized for our study using the following formula: Adjusted D-dimer concentration = Actual D-dimer concentration - (10  $\times$  ([Age-50])).

There were 183 PE cases that met our study inclusion criteria. These patients were matched to negative controls from the same study period based on age ( $\pm$  2 years), sex, exogenous estrogen use, and recent prolonged immobilization (defined as either hospitalization or surgery requiring overnight stay <30 days from ED visit or extended travel noted in chart by ED provider). Negative controls consisted of patients with suspected PE that met our study inclusion criteria, including receiving a CTPA and D-dimer within 24-h of entering the ED, but did not have a PE based on imaging results.

### 2.2. Study variables and outcomes

Clinical variables, D-dimer concentration, and PE location were obtained from patient charts by trained abstractors.

Patients were categorized by largest artery occluded as noted by radiology attending and further grouped based on a) requirement of anti-coagulation according to ACEP/ACCP guidelines and b) risk of clinical deterioration into the following: 'Requires anti-coagulation' (main, lobar and segmental PE), 'Does not require anti-coagulation' (sub-segmental and No PE), 'High risk of deterioration' (main and lobar PE), and 'Not high risk of deterioration' (segmental, sub-segmental, and No PE) groups. All 'Sub-segmental PE' patients had no evidence of proximal DVT as confirmed by venous duplex imaging.

### 2.3. Statistical analysis

Age is presented as mean (standard deviation), D-dimer as median (interquartile range), and all categorical variables as count (percentage). Student's *t*-test were used to assess group differences with respect to mean age. Chi-square tests were used to assess group differences with respect to categorical variables including sex, race, exogenous estrogen use, and recent immobilization.

Wilcoxon rank-sum tests were used to assess for differences amongst the patient groups with respect to median adjusted D-dimer concentration. Additionally, the mean age adjusted D-dimer concentration was calculated for each of the four patient groups and a Welch's test was used to determine if difference in means were statistically significant while accommodating the unequal group variances.

Separate receiver operating characteristic curve (ROC) analyses were performed to differentiate between the 'Requires anti-coagulation' versus 'Does not require anti-coagulation' groups and the 'High risk of deterioration' versus 'Not high risk of deterioration' groups. Risk factors for PE were not included in the prediction model as the aim of our study was to utilize D-dimer concentration alone to determine whether a patient requires anti-coagulation. The sensitivity and specificity with 95% confidence interval (CI) were reported for the optimal D-dimer cut-off value simultaneously maximizing sensitivity and specificity, plus 3 other potentially clinically relevant cut-off values of 750, 2000, and 3000 ng/mL.

All tests were two-sided and a significance level of 0.05 was utilized. Statistical analysis was performed using SAS JMP Pro Version 13 (SAS Institute, Cary, NC).

## 3. Results

### 3.1. Patient characteristics and D-dimer concentrations

There were 366 patients included in our study (Fig. 1). Patient characteristics and age-adjusted D-dimer concentrations are presented in Table 1 for 'Requires Anti-Coagulation' and 'Does not require anti-coagulation' groups and in Table 2 for 'High risk of deterioration' and 'Not high risk of deterioration' groups. All D-dimer concentrations are reported in ng/mL.

Age-adjusted D-dimer concentrations increase with more proximal PE location (Fig. 2). There was a significant difference in median adjusted D-dimer concentration amongst the 'Requires Anti-Coagulation'

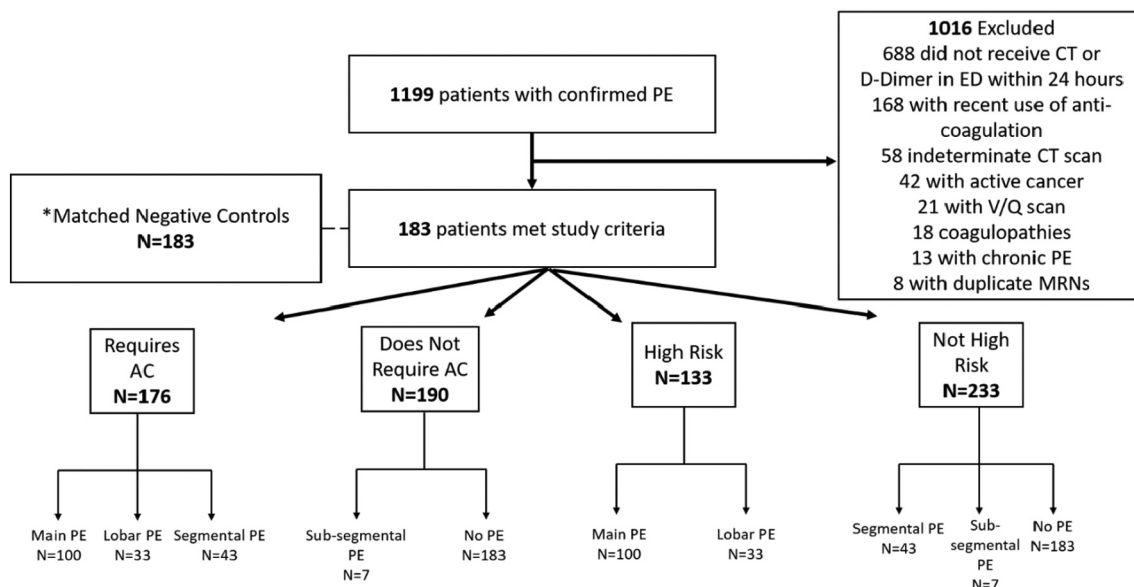


Fig. 1. Study consort Diagram. AC = anti-coagulation, PE = pulmonary embolism.

Table 1

Patient characteristics and D-dimer concentrations for suspected PE patients for whom anti-coagulation would and would not be appropriate.

	Requires anti-coagulation	Does not require anti-coagulation	p-Value
# of patients	176	190	
Mean age (SD)	56.5 (14.9)	55.7 (15.0)	0.63
Females	87 (49.4%)	98 (51.6%)	0.68
Race			0.70
White	118 (67.0%)	135 (71.0%)	
Black	47 (26.7%)	44 (23.2%)	
Other	11 (6.3%)	11 (5.8%)	
Exogenous estrogen use (% of females)	15 (17.2%)	19 (19.4%)	0.88
Recent IMMOBILIZATION	28 (15.9%)	29 (15.3%)	0.86
Age-adjusted median D-dimer (IQR) (ng/mL)	4925 (2020,9768)	655 (510,1062)	<0.0001

All categorical values are reported as N (%). SD = standard deviation, IQR = interquartile range.

Table 2

Patient characteristics and D-dimer concentrations for suspected PE patients with a high risk of deterioration and those not at high risk of deterioration.

	High risk of deterioration	Not high risk of deterioration	p-Value
# of patients	133	233	
Mean age (SD)	57.3 (14.5)	55.4(15.1)	0.23
Females	65 (48.9%)	120 (51.6%)	0.68
Race			0.32
White	86 (64.7%)	167 (71.7%)	
Black	39 (29.3%)	52 (22.3%)	
Other	8 (6.0%)	14 (6.0%)	
Exogenous estrogen use (% Females)	9 (13.8%)	25 (20.8%)	0.41
Recent Immobilization	23 (17.3%)	34 (14.6%)	0.49
Age-adjusted median D-dimer (IQR) (ng/mL)	6400 (3350–11,455)	830 (535–1470)	<0.0001

All categorical values are reported as N (%). SD = standard deviation, IQR = interquartile range.

4925 (IQR = 2020–9768) and 'Does not require anti-coagulation' 655 (IQR = 510–1062) groups (Fig. 3a,  $p < 0.0001$ ). There was also a significant difference in median adjusted D-dimer concentration amongst the 'High risk of deterioration' 6400 (IQR = 3350–11,455) versus 'Not high

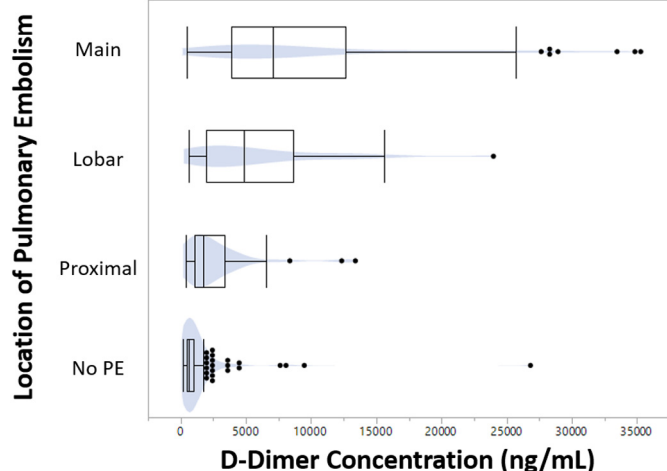


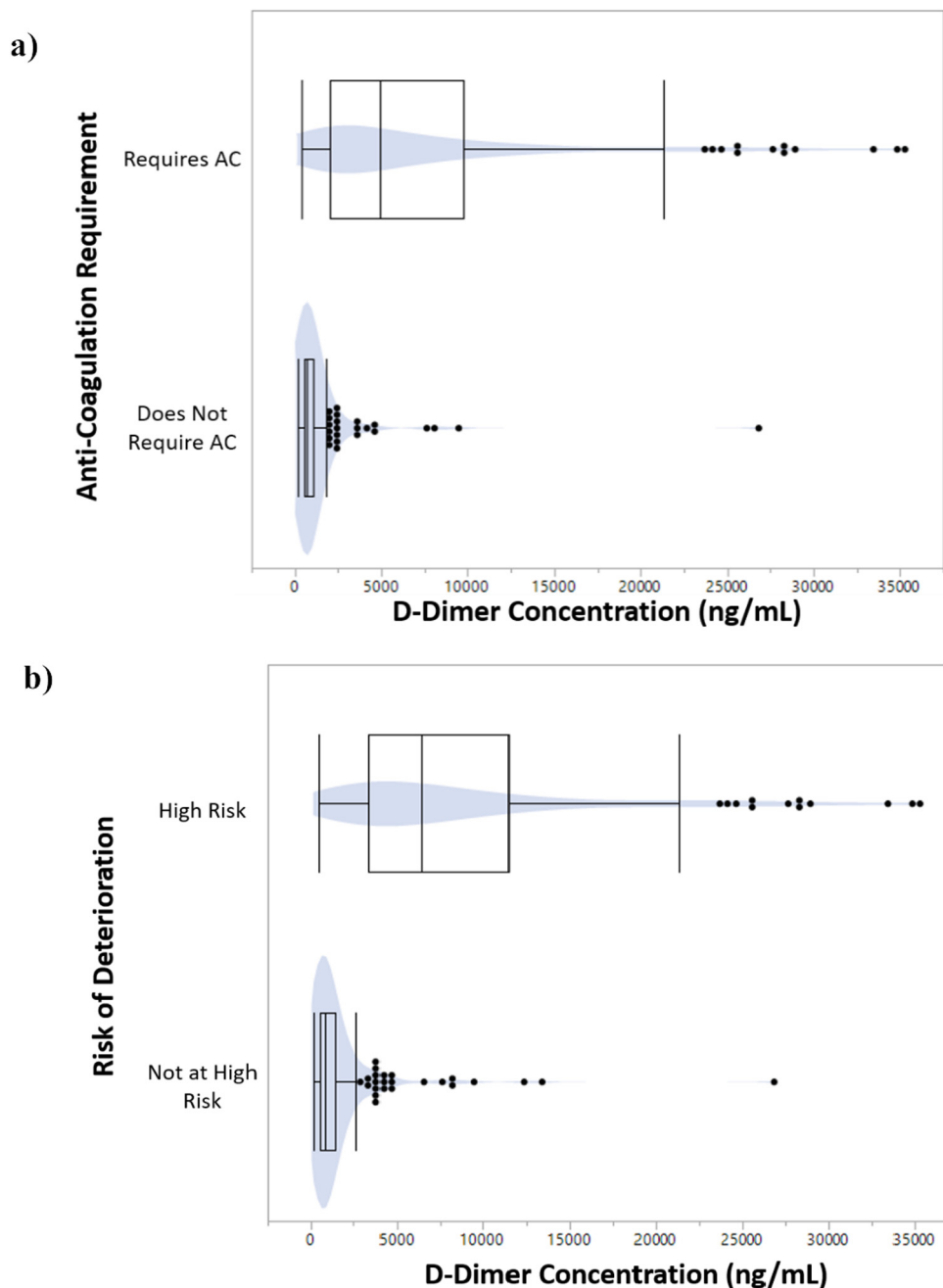
Fig. 2. Relationship of age-adjusted D-dimer concentrations and PE location. Median (IQR) D-dimer concentration in ng/mL are: 'No PE' 630 (490–1010), 'proximal' 1750 (1033–3343) (combination of sub-segmental and segmental PE), 'lobar' 4850 (1925–8625), and 'main' 7095 (3888–12,653).

risk of deterioration' 830 (IQR = 535–1470) patient groups (Fig. 3b,  $p < 0.0001$ ).

Mean (SD) age-adjusted D-dimer concentration for 'Requires Anti-Coagulation' was 7437 (7552) and 'Does not require anti-coagulation' was 1185 (2223) giving a mean difference between the two groups of 6252 ( $p < 0.0001$ ). Mean (SD) D-dimer concentration for 'High risk of deterioration' was 8957 (7976) and 'Not high risk of deterioration' was 1471 (2409) giving a mean difference between the two groups of 7486 ( $p < 0.0001$ ).

### 3.2. ROC analysis

ROC analysis was performed to differentiate 'Requires anti-coagulation' from 'Does not require anti-coagulation' patient groups based on age-adjusted D-dimer. (Fig. 4a). The association had an AUC of 0.92 and the cut-off of 1540 resulted in a specificity of 86% (95% CI, 81–91%), and sensitivity of 84% (79–90%). Similar analysis



**Fig. 3.** a) Age-adjusted D-dimer concentrations of suspected PE patients that require AC (anti-coagulation) and those that do not require AC. Median D-dimer (IQR) for 'Requires AC' 5010 (2190–9982) and 'Does Not Require AC' 780 (600–1372)  $p < 0.0001$ . b) Age-adjusted D-dimer for suspected PE patients at high risk of deterioration and those not at high risk of deterioration. Median D-dimer (IQR) for 'High Risk' 6400 (3350–11,455) and 'Not High Risk' 830 (535–1470)  $p < 0.0001$ .

differentiating 'High risk of deterioration' and 'Not high risk of deterioration' via age-adjusted D-dimer showed a maximum AUC of 0.93 and the cut-off of 2500 resulted in a specificity of 90% (85–93%) and sensitivity of 83% (77–90%). Potential clinically relevant D-dimer cut-off values with their respective sensitivity and specificity were calculated and included for comparison (Table 3).

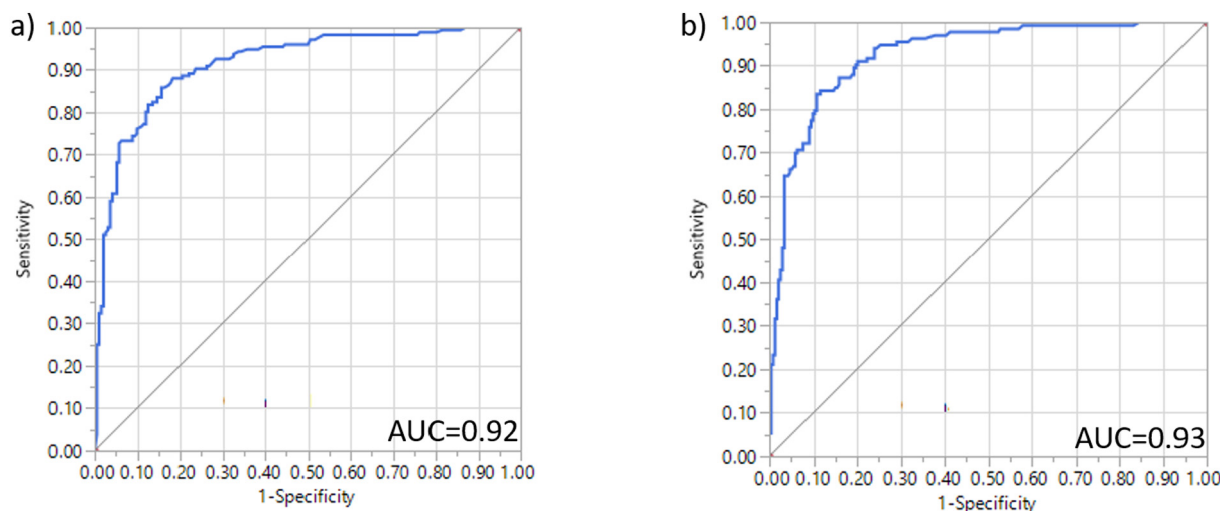
## 4. Discussion

### 4.1. Risks of initiating or withholding empiric anti-coagulation

ED physicians are faced with a difficult task when evaluating a patient with suspected PE, especially when confirmatory imaging is

delayed or unavailable. The risks and benefits of beginning empiric anti-coagulation need to be weighed carefully [19].

Empiric anti-coagulation without imaging confirmation has inherent risks including bleeding, medication allergy, and heparin induced thrombocytopenia (HIT). Hogg et al. reviewed the probability of adverse events for one, two, and 7 days of heparin therapy in suspected PE patients in the ED [13]. This study found that regardless of the presence of PE, patients receiving empiric systemic coagulation were significantly more likely to be admitted to the ICU (12.6% vs. 2.8%) and had a higher in-house mortality rate (3.2% vs 1.0%). They further estimated that 0.3%–0.4% of patients receiving empiric systemic anti-coagulation will experience a serious adverse event (designated as HIT, intracranial or retroperitoneal bleeding, or any bleeding leading to death or



**Fig. 4.** a) ROC analysis differentiating suspected PE patients that require anti-coagulation versus those who do not require anti-coagulation. b) Differentiating suspected PE patients at high risk of deterioration versus those not at high risk of deterioration. *AUC = area under the curve.*

**Table 3**

a) ROC table of age-adjusted D-Dimer concentrations differentiating suspected PE patients that require AC versus those who do not require AC. b) Differentiating suspected patients at high risk of deterioration versus those not at high risk of deterioration.

D-Dimer Cut-off	Specificity	CI (95%)	Sensitivity	CI (95%)
a)				
700	96%	93–99%	54%	47–61%
1540 <sup>a</sup>	86%	81–91%	84%	79–90%
2000	76%	69–82%	90%	86–94%
3100	65%	58–72%	95%	92–98%
b)				
1000	61%	55–68%	97%	94–100%
2500 <sup>a</sup>	90%	85–93%	83%	77–90%
3100	90%	86–94%	77%	70–85%
4000	94%	91–97%	68%	61–76%

<sup>a</sup> Indicates cut-off value for maximum AUC.

transfusion). These values were then used to predict which pre-test probabilities of PE should be used as a guide to begin empiric anti-coagulation, concluding that for 1 day of heparin treatment pre-test probability should be at least 30% to offset the risks of anti-coagulation. However, this study estimate was based on limited data and highlighted a need for a numerical cut-off for clinical decision making [13]. Bleeding risks of short-term empiric anti-coagulation exposure in the ED for VTE have not been studied in randomized trials of cohort studies, but have been characterized via statistical modeling and clinical case reports [10–12]. In addition, patients with isolated sub-segmental PE without proximal DVT have been shown to have similar clinical outcomes independent of anti-coagulation treatment, though bleeding risk was higher in the anti-coagulated group [7]. A recent meta-analysis by Beriteau et al. investigated outcomes of patients with sub-segmental PE that received or did not receive anti-coagulation. VTE reoccurred in 5.3% (95%CI 1.6%–10.9%) of anti-coagulated patients versus 3.9% (4.8%–13.4%) in non-anticoagulated patients [7].

Withholding anti-coagulation, especially in patients with proximal clots, can increase risk of clinical deterioration due to further embolization, vasospasm, cardiac arrhythmias, or respiratory failure [1,9]. Smith et al. showed that delayed diagnosis of PE is associated with increased mortality and adverse hospital events. 30-day mortality rates of patients diagnosed in the ED was 4.4% compared to 15.3% in patients diagnosed after admission [14]. These results were replicated by Jelinek et al., who showed an adjusted odds ratio for 30-day mortality of 0.30 (95% confidence interval 0.20–0.44) in patients diagnosed with PE in the ED versus

after admission [15]. Studies of shorter delays (several hours) on the diagnosis of PE have not been published, so we must extrapolate based on these existing longer term studies.

#### 4.2. Utility of an objective D-dimer cut-off for suspected PE patients

We have shown that there is a relationship between D-dimer concentration and PE location. This relationship can be used to develop objective cut-off values that can be combined with clinical gestalt to reduce the risks of initiating or withholding anti-coagulation in suspected PE patients.

While controlling for key confounding variables including age, gender, exogenous estrogen use, and recent immobilization, an age-adjusted D-dimer cut-off of 1540 had a specificity of 86% (95% CI, 81–91%) and sensitivity of 84% (79–90%) to differentiate suspected PE patients that do not require anti-coagulation (patients with No PE or sub-segmental PE without evidence of proximal DVT) based on ACEP/ACCP guidelines. We envision using this cut-off to avoid initiating empiric anti-coagulation in patients with D-dimer concentrations below this cut-off to avoid bleeding and adverse medication reaction risks. Conversely, to reduce the risk of clinical deterioration due to withholding anti-coagulation, an age-adjusted D-dimer cut-off of 2500 had a specificity of 90% (85–93%) and sensitivity of 83% (77–90%) in differentiating suspected PE patients with proximal clots (main or lobar pulmonary arteries) that are at highest risk for clinical deterioration. When combined with clinical gestalt, we envision this cut-off to be used to initiate empiric anti-coagulation on patients with an adjusted D-dimer concentration above this value to reduce the risks of withholding anti-coagulation. In our study sample, 185 (50.5%) patients had an age-adjusted D-dimer concentration below the 1540 cut-off, 45 (12.3%) patients had a D-dimer in the indeterminate zone of 1541–2499, and 136 (37.2%) patients had a D-dimer concentration above 2500.

We do not endorse using these cut-offs of 1540 and 2500 to diagnose a PE. Numerous studies and current ACEP guidelines indicate that D-dimer alone should not be used for diagnostic purposes. Instead, these cut-offs should serve as a clinical decision making tool to initiate or withhold empiric anti-coagulation in patients with a D-dimer above or below our threshold respectively to avoid clinical deterioration or unnecessary bleeding risk when imaging is delayed or unavailable.

Our findings suggest that clinicians can identify patients needing anti-coagulation based on D-dimer concentration if imaging results are not available, potentially decreasing time to treatment when indicated and decreasing the risk from anti-coagulation when necessary.

Although CT has become a widespread diagnostic modality in most EDs, locations such as resource limited EDs, critical access EDs, and other clinical settings (e.g. urgent care, offices, clinics) may not have timely access to advanced imaging. In addition, CT scanners may be off-line for a variety of reasons, including decontamination (especially important in the era of COVID-19), mechanical breakdown, and routine maintenance [20]. Moreover, in any busy, high volume crowded ED with only one CT scanner, ED patients are frequently “backed up” waiting in a queue to be scanned. In these cases, trauma patients, brain attack patients, patients going to the operating room, and other groups often take precedence over patients waiting for a CTPE scan. This latter group may wait hours not only for their scan, but also for the radiology read. With increased crowding in EDs across the nation, the mean time to undergo a CT scan and obtain a final read in a high resource center is estimated to be 6 h [21]. This time could be significantly greater for V/Q scans. Furthermore, CT scans may not be possible in certain populations, including pregnant women, morbidly obese patients, and those with advanced renal disease that cannot handle contrast loads.

A relationship between D-dimer concentration and VTE location has been described in previous studies. De Monye et al. performed a prospective study on 314 adult inpatients and outpatients and showed a relationship of increasing D-dimer concentration with more proximally located clots [22]. A study from our investigators in a pediatric ED population by Sharaf et al. showed that in pediatric patients distal PEs had a median D-Dimer in ng/mL (IQR) of 2327 (1273,3381), 3758 (1841,5676) in lobar PEs, and of 4795 (3465,6125) in central PEs [17]. However, using this relationship to determine which patients suspected of PE should receive anti-coagulation has not been studied.

Singer et al. recently performed a prospective study of 1752 low to moderate risk VTE ED patients [23]. They defined proximal PE as segmental, lobar, or main artery and proximal DVT as proximal to calf trifurcation. Our study differs from Singer et al. in that we only included data about PE and not DVT. Patients with DVT are inherently more stable than PE patients, so the urgency to diagnose and treat is not as great. They concluded that there is a relationship between VTE location and D-dimer concentration, but a D-dimer value alone cannot predict whether a patient has a distal VTE due to low sensitivity (40.7%) and NPV (52.1%). We believe that our sensitivity and NPV for D-Dimer and distal PE were higher because our patient sample only included patients with suspected PE, unlike Singer et al. which included patients with both suspected DVT and PE.

#### 4.3. Study limitations and strengths

Limitations of our study include the retrospective nature of the work, which depends on physician charting that may possibly be incomplete. We were restricted to our enterprise's electronic health record (EHR), so if a patient was recently admitted to another hospital we would not be able to identify that in our study. We did not evaluate clinically unstable patients. Further study is required to validate whether our D-dimer cut-off can be applied to this population and to patients where CT scans are not feasible including pregnant women, obese patients who cannot fit in scanners, and those with renal disease. Our D-dimer concentration cut-offs are comparable to CTPA (86% and 98% respectively) [24]. In addition, these cut-offs from our study population are superior to the current alternative of having no objective information or relying on gestalt alone for clinical decision making.

We did not correlate clinical outcomes with our proposed D-dimer cut-offs, which could be evaluated in additional studies to prove that these cut-offs should be included in clinical decision rules when evaluating PE in adult ED patients.

Strengths of this study include a large sample size and mix of adult patients from several locations ranging from a quaternary academic site to community EDs, enhancing external validity. In contrast to other PE studies, we focused solely on ED patients. Including an inpatient population could alter results as these patients are at an increased

risk of VTE due primarily to stasis. We also controlled for several key confounding variables by matching (including gender, age, use of exogenous estrogen, and recent prolonged immobilization) and age-adjusting D-dimer concentrations.

#### 4.4. Conclusion

This study establishes a relationship between age-adjusted D-dimer concentration and PE location in adult hemodynamically stable ED patients. Higher D-dimer concentrations are associated with more proximal clots. This relationship was utilized to create objective cut-offs of 1540 and 2500 with high sensitivity and specificity to minimize the risks of withholding and initiating anti-coagulation treatment respectively. In the absence of confirmatory imaging results and when combined with clinical gestalt, patients with an age-adjusted D-dimer concentration below 1540 should potentially have anti-coagulation withheld, while patients with an age-adjusted D-dimer concentration above 2500 should potentially have anti-coagulation initiated. Further well-controlled, prospective follow-up studies correlating clinical outcomes are needed to establish whether our cut-offs could be included in clinical decision rules when evaluating adult patients with PE in the ED.

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#### Declaration of competing interest

All authors report no conflict of interest.

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#### Author credit statement

JN contributed to research conception and design, collection of data, data analysis, interpretation of results, and writing of manuscript. ASN contributed to data analysis, interpretation of results, and writing of manuscript. SSS and PRW contributed to collection of data and writing of manuscript. SEM contributed to research conception and design, and writing of manuscript.

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