



## Original Contribution

## D-dimer levels in VTE patients with distal and proximal clots☆



Adam J. Singer, MD<sup>a,\*</sup>, Hui Zheng, PhD<sup>b</sup>, Samuel Francis, MD<sup>c</sup>, Gregory J. Fermann, MD<sup>d</sup>, Anne Marie Chang<sup>e</sup>, Blair A. Parry, BA<sup>f</sup>, Nick Giordano, MD<sup>f</sup>, Christopher Kabrhel, MD, MPH<sup>f</sup>

<sup>a</sup> Department of Emergency Medicine, Stony Brook University, Stony Brook, NY, United States

<sup>b</sup> Department of Biostatistics, Massachusetts General Hospital, Boston, MA, United States

<sup>c</sup> Department of Emergency Medicine, Duke University, Durham, NC, United States

<sup>d</sup> Department of Emergency Medicine, University of Cincinnati, United States

<sup>e</sup> Department of Emergency Medicine, Jefferson University, Philadelphia, PA, United States

<sup>f</sup> Center for Vascular Emergencies, Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA, United States

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## ABSTRACT

**Objectives:** There is growing evidence that venous thromboembolism (VTE) patients with distal clots (distal calf deep vein thrombosis [DVT] and sub-segmental pulmonary embolism [PE]) may not routinely benefit from anticoagulation. We compared the D-dimer levels in VTE patients with distal and proximal clots.

**Methods:** We conducted a multinational, prospective observational study of low-to-intermediate risk adult patients presenting to the emergency department (ED) with suspected VTE. Patients were classified as distal (calf DVT or sub-segmental PE) or proximal (proximal DVT or non-sub-segmental PE) clot groups and compared with univariate and multivariate analyses.

**Results:** Of 1752 patients with suspected DVT, 1561 (89.1%) had no DVT, 78 (4.4%) had a distal calf DVT, and 113 (6.4%) had a proximal DVT. DVT patients with proximal clots had higher D-dimer levels (3760 vs. 1670 mg/dL) than with distal clots. Sensitivity and negative predictive value (NPV) for proximal DVT at an optimal D-dimer cutoff of 5770 mg/dL were 40.7% and 52.1% respectively. Of 1834 patients with suspected PE, 1726 (94.1%) had no PE, 7 (0.4%) had isolated sub-segmental PE, and 101 (5.5%) had non-sub-segmental PE. PE patients with proximal clots had higher D-dimer levels (4170 vs. 2520 mg/dL) than those with distal clots. Sensitivity and NPV for proximal PE at an optimal D-dimer cutoff of 3499 mg/dL were 57.4% and 10.4% respectively.

**Conclusions:** VTE patients with proximal clots had higher D-dimer levels than patients with distal clots. However, D-dimer levels cannot be used alone to discriminate between VTE patients with distal or proximal clots.

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## 1. Introduction

Venous thromboembolism (VTE) has a disease spectrum from asymptomatic distal deep vein thrombosis (DVT) to fatal pulmonary embolism (PE) [1]. Because VTE is potentially fatal and can easily be missed, efforts to improve identification of VTE have included the introduction of biomarkers (such as D-dimer) as well as advanced imaging technologies such as multi-detector computed tomographic pulmonary angiography (CTPA) and venous duplex ultrasound (US). This has led to an increasing number of patients being diagnosed with VTE [2,3] and the identification of more distal clots (such as isolated subsegmental PE or calf-vein DVT) [4] that may have been missed with earlier, less-advanced imaging.

There is considerable controversy whether to anticoagulate patients with isolated, distal calf DVT or subsegmental PE. Studies suggest that many subsegmental PE and distal DVT are, in fact, false positives [4,5]. Even if true positives, diagnosing subsegmental PE in many cases may be irrelevant [6,7], exposing patients to radiation, potentially harmful intravenous contrast agents and the risks of bleeding when anticoagulation is not truly indicated [7]. A retrospective study including 60 patients with subsegmental PE and no proximal DVT who were not anticoagulated reported no episode of recurrent VTE [7]. In contrast, another study found that the risk of recurrent VTE in patients with subsegmental PE who were anticoagulated was similar to that of patients with more proximal PE and higher than those with no PE at all [8]. Recent guidelines issued by the American College of Chest Physicians address these issues. They suggest that patients with isolated calf DVT and subsegmental PE without cancer do not require anticoagulation [9]. Regardless, efforts to identify patients with distal clots using clinical information or the results of D-dimer assays have the potential to reduce the associated unnecessary risks and costs of imaging and anticoagulation in these low-risk patients.

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\* Corresponding author at: Department of Emergency Medicine, HSC-L4-080, 8350 SUNY, Stony Brook, NY 11794, United States.

E-mail address: [adam.singer@stonybrook.edu](mailto:adam.singer@stonybrook.edu). (A.J. Singer).

The first goal of the current study was to determine the incidence of distal calf DVT and subsegmental PE in a large contemporary cohort of emergency department (ED) and outpatient clinic patients with suspected VTE. The second goal was to determine whether patient characteristics and D-dimer levels could discriminate between patients with distal and more proximal VTE. We hypothesized that D-dimer levels would be significantly lower in patients with isolated calf DVT or subsegmental PE than in patients with more proximal DVT and PE.

## 2. Methods

### 2.1. Study design and setting

We conducted a multi-center, international, prospective, observational study of adult ED patients with suspected PE or DVT. The centers included academic and non-academic emergency departments from the United States ( $n = 18$ ) and Europe ( $n = 6$ ). The study was part of another study evaluating a novel D-dimer assay that was not used for clinical purposes. The study was sponsored by Siemens Healthcare Diagnostics (Newark, DE), which had no role in data analysis or interpretation. The study was approved by all institutional review boards and all patients gave written, informed consent.

### 2.2. Patients

We included a convenience sample of patients ages 18 years and older who presented to an ED or outpatient clinic with suspected PE or DVT who were referred for objective testing and were able to give written informed consent. We only included patients with low-to-intermediate risk of VTE based on Wells criteria ( $\leq 6$  for PE and  $< 2$  for DVT). For suspected PE, objective testing was based on a CTPA. For suspected DVT, objective testing was based on venous US. Patients receiving anticoagulants for  $>24$  h prior to enrollment were excluded as well as pregnant women and patients at high-risk of VTE (i.e., Wells PE score  $> 6$ , Wells DVT score  $\geq 2$ ).

### 2.3. Measures

We used a structured electronic data collection form to record baseline patient demographics and clinical characteristics including age, sex, race, clinical D-dimer assays, imaging results, three-month outcome and final diagnosis.

### 2.4. Outcomes

All patients underwent a diagnostic criterion standard evaluation for VTE. A PE was diagnosed during the index visit if the patient had a filling defect in a pulmonary artery on CTPA. DVT was diagnosed if the patient had a venous ultrasound demonstrating a non-compressible clot in their leg. Clots were considered to be proximal if the PE was in a segmental or larger pulmonary artery or if the DVT was proximal to the calf trifurcation (i.e., in or above the popliteal vessels). All diagnoses were confirmed by a three-member adjudication committee.

### 2.5. Data analysis

Dichotomous data are presented as numbers and percentages frequency of occurrence and compared using the Chi-square or Fisher's exact tests. Continuous data are presented as means with standard deviations (SD) or medians with inter-quartile ranges (IQR) and compared with the Mann Whitney  $U$  test or analysis of variance. Multivariable adjustment was performed using linear regression for continuous data and logistic regression for dichotomous data. Receiver operating characteristic (ROC) analyses and area under the curve (AUC) calculations were performed to determine optimal D-dimer thresholds using the Youden index for discriminating between distal and proximal clots

for PE and DVT separately. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

## 3. Results

### 3.1. General study population

We enrolled a total of 3586 patients across the study sites. Of these, there were 1752 patients (48.9%) with suspected DVT. Their mean (SD) age was 53.1 ( $\pm 16.2$ ) years; 1042 (59.5%) were female and 1172 (66.9%) were white. There were also 1834 patients (51.1%) with suspected PE. Their mean (SD) age was 47.7 ( $\pm 15.8$ ) years, 1158 (63.1%) were female and 1081 (58.9%) were white. VTE was confirmed in 191 patients (11.1%) with suspected DVT and in 108 patients (5.9%) with suspected PE.

### 3.2. Patients with suspected DVT

Of 1752 patients with suspected DVT, 1561 (89.1%) had no DVT, 78 (4.4%) had a distal calf DVT, and 113 (6.4%) had a proximal DVT. A comparison of patients by presence or absence of clot, and location of clot is presented in Table 1. The results of multivariable analysis are presented in Table 2.

DVT patients with a proximal clot were more commonly male (62.0% vs. 48.7%; OR 1.85 [95% CI, 1.33–2.59]), more likely to have a high clinical suspicion of DVT (81.4% vs. 66.7%; OR 1.82 [95% CI, 1.02–3.24]) and had higher D-dimer levels (3760 vs. 1670 mg/dL,  $P < 0.001$ ) than DVT patients with distal clots. Patients with no DVT were younger (52.8 vs. 55.0 years,  $P = 0.02$ ), more likely female (61.4% vs. 43.5%,  $P < 0.001$ ), less likely to have calf swelling (14.0% vs. 24.1%,  $P < 0.001$ ), less likely to have a history of cancer (3.8% vs. 7.3%,  $P = 0.02$ ), and had lower D-dimer levels than those with any clot (520 mg/dL vs. 2570 mg/dL,  $P < 0.001$ ).

The optimal D-dimer cut-off value for discriminating between proximal and distal DVT was 5770 mg/dL with an area under the curve of 0.68 (95% CI, 0.61 to 0.76, Fig. 1). The test characteristics using this threshold are presented in Table 3.

### 3.3. Patients with suspected PE

Of 1834 patients with suspected PE, 1726 (94.1%) had no PE, 7 (0.4%) had isolated sub-segmental PE, and 101 (5.5%) had non-sub-segmental PE. Thus, 6.4% of all PE were isolated subsegmental. A comparison of patient characteristics by presence or absence of clot, and location of clot is presented in Table 4. The results of multivariable analysis are presented in Table 5.

PE patients with proximal clots were younger (56.5 vs. 67.3 years,  $P < 0.001$ ), more likely to have a Well's score  $\geq 4$  (47.0% vs. 14.3%, OR 4.82 [95% CI, 3.03–7.67]), and had higher D-dimer levels (4170 vs.

**Table 1**  
Univariate associations between predictor variables and deep vein thrombosis.

	No DVT <sup>a</sup>	Distal DVT	Proximal DVT	P value
Mean (SD) age	52.78 (16.31)	55.29 (14.95)	56.17 (15.5)	0.048
Females, no. (%)	959 (61.43)	40 (51.28)	43 (38.05)	<0.001
Race, no. (%)				
White	1040 (66.62)	49 (62.82)	83 (73.45)	0.171
Black	427 (27.35)	24 (30.77)	24 (21.24)	
Hispanic	73 (4.68)	2 (2.56)	4 (3.54)	
Asian	8 (0.51)	2 (2.56)	2 (1.77)	
Other	13 (0.83)	1 (1.28)	0 (0)	
Prior cancer, no. (%)	59 (3.78)	5 (6.41)	9 (7.96)	0.059
Bedridden, no. (%)	145 (9.29)	10 (12.82)	11 (9.73)	0.580
Calf swelling, No. (%)	218 (13.97)	12 (15.38)	34 (30.09)	<0.001
Calf tenderness, no. (%)	607 (38.89)	41 (52.56)	41 (36.28)	0.043
Median (IQR) D-dimer	520 mg/dL	1670 mg/dL	3760 mg/dL	<0.001

<sup>a</sup> DVT = deep vein thrombosis.

**Table 2**  
Multivariate association between predictor variables and proximal DVT<sup>a</sup>.

Variable	Odds ratio	95% CI	P-value
Age (per one year increase)	1.00	0.99–1.01	0.9457
Male sex	1.85	1.33–2.59	0.0003
White race	0.85	0.57–1.28	0.4439
High clinical suspicion for DVT	1.82	1.02–3.24	0.0003

<sup>a</sup> DVT = deep vein thrombosis.

2520 mg/dL), than PE patients with distal clots. While there was a significant difference among patients with no PE, distal PE, and proximal PE, the difference in D-dimer levels between those with a distal and proximal clot was not statistically significant ( $P = 0.21$ ). The difference in D-dimer levels between patients with no PE or a distal PE was significant ( $P = 0.004$ ). The presence of tachycardia, signs of DVT, and hemoptysis did not differ among the groups.

Patients with no PE were younger (47.1 vs. 60.0 years,  $P < 0.001$ ), more likely female (63.9% vs. 50.9%,  $P = 0.007$ ), less likely to have a recent history of immobilization (9.4% vs. 20.4%,  $P < 0.001$ ), less likely to have a previous VTE (8.5% vs. 23.1%,  $P < 0.001$ ), and had lower D-dimer levels (440 mg/dL vs. 4110 mg/dL,  $P < 0.001$ ) than patients with any clots (both proximal and distal).

The optimal D-dimer cut-off value for discriminating between proximal and distal PE was 3499 mg/dL with an area under the curve of 0.64 (95% CI, 0.43 to 0.86, Fig. 2). The test characteristics using this threshold are presented in Table 6.

**4. Discussion**

The results of our prospective, observational international study indicate that distal calf DVT and especially sub-segmental PE are relatively rare in low-to-intermediate risk adult patients presenting to the ED or outpatient setting with suspected VTE. The incidence of subsegmental PE in our investigation is consistent with a prior VTE study [6]. Our results also show that D-dimer levels in patients with distal clots are significantly lower than those in patients with proximal clots while being significantly higher than in those patients without any clots. Our result also shows that, in general, traditional predictors of having any

**Table 3**  
Diagnostic test characteristics using the optimal D-dimer cutoff point (5770 mg/dL) for discriminating between distal and proximal deep vein thrombosis.

	Estimate and 95% CI
Sensitivity	40.7% (32.1–49.9%)
Specificity	93.6% (85.8–97.2%)
PPV	90.2% (79.0–95.6%)
NPV	52.1% (43.9–60.3%)

clot are more common in those with proximal clots than distal clots. However, the low sensitivities and negative predictive values of the D-dimer when using the thresholds suggested by the Youden indices are not accurate enough to identify patients with distal clots. This question is especially important if one considers that some patients with distal clots may not require anticoagulation at all based on the evidence and recent guidelines [9]. Despite being incorporated into the ACCP Guidelines there remains equipoise among the thrombosis community due to the absence of a large randomized clinical trial investigating the topic [10].

The overall rate of subsegmental PE in our study was low (about 6% of all PE). Other studies suggest that improvements in CTPA have led to a doubling in the rate of diagnosing subsegmental PE from 5 to 10% [6,11,12]. Some studies have reported rates of subsegmental PE on CTPA as high as 15–25% [13,14]. As a result, some experts have voiced concern that the increased incidence of PE in recent years (together with no increase in mortality) is the result of identification of small distal clots by more sensitive CT scanners. However, the fact that the overwhelming majority of PEs in our study are proximal reduces this concern. It is possible that in our study, the radiologists were more attuned to the interrater unreliability of CTPA for small subsegmental PE [14] and were aware of the new Chest guidelines of not treating isolated subsegmental PE [9]. As a result, there were less likely to call an isolated, possible small filling defect, as positive.

Prior studies have also evaluated the association of D-dimer levels and clot burden or location. Ghanima et al. studied 100 consecutive outpatients diagnosed with PE [15]. There was a significant association between log D-dimer and between log RV/LV ratio ( $r = 0.45$ ), pulmonary artery obstruction index ( $r = 0.50$ ), and PaO<sub>2</sub> ( $r = 0.40$ ). There was also a significant association between the D-dimer level and the most proximal level of PE ( $P < 0.005$ ). Galle et al. studied 104 hemodynamically stable patients with PE [16]. Median plasma D-dimer levels were higher in patients with >50% perfusion defects compared to those with <30% defects (7950 mg/dL vs. 2731 mg/dL,  $P = 0.001$ ).

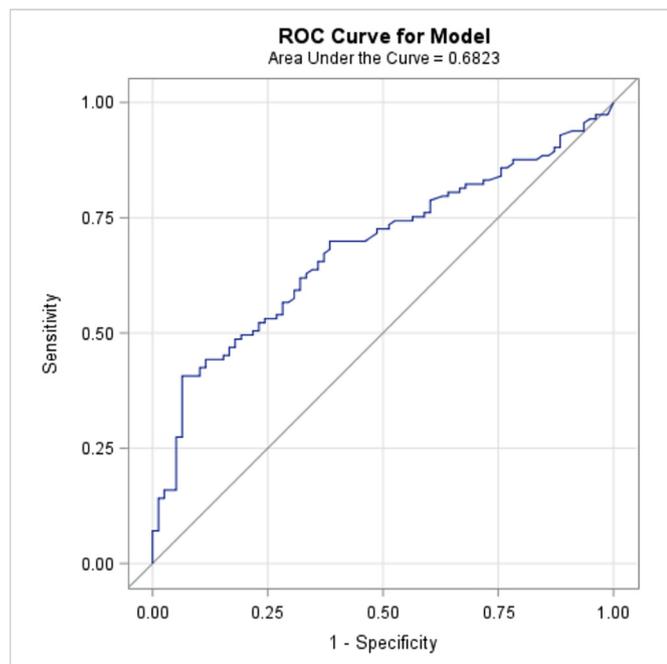


Fig. 1. Area under the curve for deep vein thrombosis.

**Table 4**  
Univariate associations between predictor variables and pulmonary embolism.

	No PE <sup>a</sup>	Distal PE	Proximal PE	P value <sup>b</sup>
Mean (SD) age	47.1 (15.57)	67.3 (10.31)	56.5 (16.6)	<0.001
Females, no. (%)	1103 (63.9%)	3 (42.86%)	52 (51.49%)	0.023
Race, no. (%)				
White, no. (%)	1007 (58.34)	3 (42.86)	71 (70.3)	0.093
Black	525 (30.42)	3 (42.86)	25 (24.75)	
Hispanic	141 (8.17)	0 (0)	4 (3.96)	
Asian	18 (1.04)	0 (0)	0 (0)	
Other	35 (2.03)	1 (14.29)	1 (0.99)	
Wells score > 4, no. (%)	244 (14.14)	1 (14.29)	47 (47)	<0.001
Signs of DVT, no. (%)	132 (7.65)	0 (0)	13 (12.87)	0.124
Tachycardia, no. (%)	486 (28.17)	3 (42.86)	32 (31.68)	0.523
Immobilization, no. (%)	162 (9.39)	1 (14.29)	21 (20.79)	<0.001
Previous DVT/PE, no. (%)	147 (8.52)	0 (0)	25 (24.75)	<0.001
Hemoptysis, no. (%)	47 (2.72)	0 (0)	2 (1.98)	0.820
Cancer, no. (%)	115 (6.67)	4 (57.14)	12 (11.88)	<0.001
Median (IQR) D-dimer	440 mg/dL	2520 mg/dL	4170 mg/dL	<0.001

<sup>a</sup> PE = pulmonary embolism.

<sup>b</sup> The P value indicates whether there is a difference among the 3 groups: no clot, distal clot or proximal clot.

**Table 5**  
Multivariate association between predictors variables and proximal pulmonary embolism.

Variable	Odds ratio	95% CI	P-value
Age (per 1 year increase)	0.97	0.96–0.99	0.0001
Female sex	1.38	0.87–2.20	0.1686
White race	0.81	0.49–1.33	0.3993
Wells score > 4	4.82	3.03–7.67	<0.0001

In another cohort of 674 consecutive patients with confirmed PE, high D-dimers (>3000 mg/dL) were associated with mortality (OR 7.29). They were also associated with central location of emboli, active malignancy and age [17]. Aujesky et al. studied 366 patients with PE diagnosed at four emergency departments [18]. Patients who died had higher median D-dimer levels than those who survived (4578 mg/dL vs. 2946 mg/dL,  $P = 0.005$ ). Patients with D-dimers below 1500 mg/dL had very low mortality and the area under the ROC curve of D-dimer for predicting overall mortality was 0.69 (95% CI, 0.58–0.80). Hochuli et al. assessed D-dimers in 254 patients with suspected PE [19]. The prevalence of PE increased with D-dimer levels and was 7% at D-dimer levels of 500–1000 mg/dL, reaching >90% at D-dimer levels exceeding 9000 mg/dL ( $P < 0.001$ ). High D-dimer levels (above 4000 mg/dL) were also associated with significantly higher clot burden in pulmonary arteries and thrombus in the main pulmonary artery. Similar results were found for distal versus proximal DVT.

## 5. Strengths and limitations

Our study has several strengths and some limitations. We employed a prospective, real-world design, with pre-test probability assessment and blood sampling performed prior to the clinical diagnosis or exclusion of VTE. Our study was performed in a large number of emergency departments in various regions throughout the United States and Europe, and should therefore be generalizable to a broad population of emergency patients. Last, the large number of subjects enrolled resulted in tight confidence intervals for our primary analysis and permitted several sub-analyses.

A major limitation of our study is that not all patients underwent diagnostic imaging for VTE. Some patients had VTE excluded with a

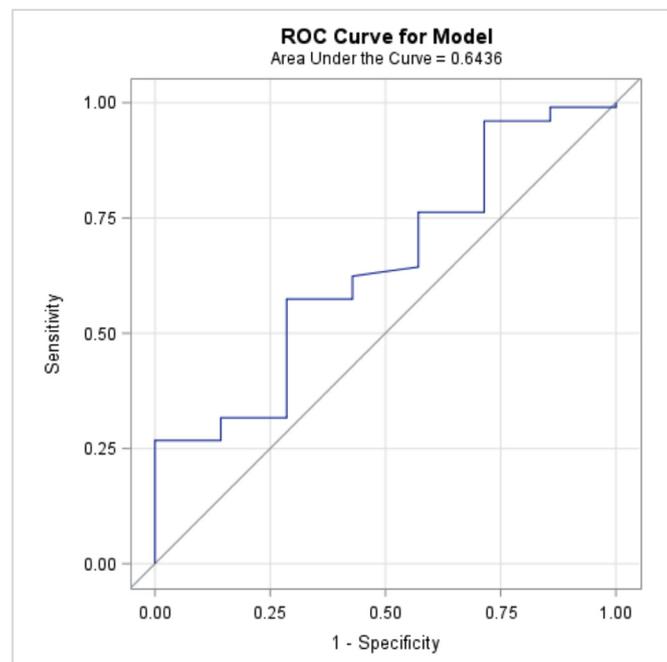
**Table 6**  
Diagnostic test characteristics using the optimal D-dimer cutoff point (3499 mg/dL) for discriminating between distal and proximal pulmonary embolism.

	Estimate and 95% CI
Sensitivity	57.4% (47.7–66.6%)
Specificity	71.4% (34.9–91.5%)
PPV	96.7% (88.7–99.0%)
NPV	10.4% (4.6–22.2%)

combination of low pre-test probability, a negative clinical D-dimer and follow-up. This is consistent with previous studies and the standard of care [20]. Therefore, it would not be ethical to expose patients with negative D-dimer results to unnecessary imaging. Some patients were lost to follow-up. These patients were considered not to have clinically significant VTE based on the results of their workup during the index visit, but we cannot exclude the possibility that some had VTE during the follow-up period. However, standard clinical care permits the exclusion of VTE in low and intermediate probability patients based on negative testing in the emergency department, and our results are consistent with this approach. A final limitation is that most patients did not have both imaging of their legs and their lungs. As a result, there were very few patients in whom a concomitant DVT and PE were confirmed. Thus, we could not perform a separate analysis to determine whether D-dimer levels can be used to identify patients with clots (distal or proximal) in one location (leg or lung) who were more likely to have another clot (distal or proximal) in the other location (lung or leg).

## 6. Conclusions

The overall incidence of distal calf DVT and isolated sub-segmental PE is relatively low in adult patients presenting to the ED or outpatient clinic with suspected VTE of low-to-intermediate probability. VTE patients with proximal clots were more likely to have a high clinical suspicion for VTE and had higher D-dimer levels than patients with more distal clots. However, due to poor sensitivity and NPV, D-dimer levels cannot be used alone to discriminate between VTE patients with distal or proximal clots.



**Fig. 2.** Area under the curve for pulmonary embolism.

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