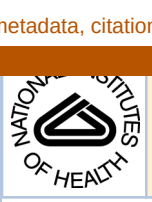

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Factors Associated With Positive D-dimer Results in Patients Evaluated for Pulmonary Embolism

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Abstract

Objectives—Available D-dimer assays have low specificity and may increase radiographic testing for pulmonary embolism (PE). To help clinicians better target testing, this study sought to quantify the effect of risk factors for a positive quantitative D-dimer in patients evaluated for PE.

Methods—This was a prospective, multicenter, observational study. Emergency department (ED) patients evaluated for PE with a quantitative D-dimer were eligible for inclusion. The main outcome of interest was a positive D-dimer. Odds ratio (ORs) and 95% confidence intervals (CIs) were determined by multivariable logistic regression. Adjusted estimates of relative risk were also calculated.

Results—A total of 4,346 patients had D-dimer testing, of whom 2,930 (67%) were women. A total of 2,500 (57%) were white, 1,474 (34%) were black or African American, 238 (6%) were

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Hispanic, and 144 (3%) were of other race or ethnicity. The mean (±SD) age was 48 (±17) years. Overall, 1,903 (44%) D-dimers were positive. Model fit was adequate (c-statistic = 0.739, Hosmer and Lemeshow p-value = 0.13). Significant positive predictors of D-dimer positive included female sex; increasing age; black (vs. white) race; cocaine use; general, limb, or neurologic immobility; hemoptysis; hemodialysis; active malignancy; rheumatoid arthritis; lupus; sickle cell disease; prior venous thromboembolism (VTE; not under treatment); pregnancy and postpartum state; and abdominal, chest, orthopedic, or other surgery. Warfarin use was protective. In contrast, several variables known to be associated with PE were not associated with positive D-dimer results: body mass index (BMI), estrogen use, family history of PE, (inactive) malignancy, thrombophilia, trauma within 4 weeks, travel, and prior VTE (under treatment).

Conclusions—Many factors are associated with a positive D-dimer test. The effect of these factors on the usefulness of the test should be considered prior to ordering a D-dimer.

Keywords

D-dimer; pulmonary embolism; venous thromboembolism; testing

Plasma D-dimer measurement is commonly used as the first test in patients suspected of having acute pulmonary embolism (PE). D-dimer testing is noninvasive and rapid, so it is not surprising that the availability of these tests can increase the number of patients evaluated for possible PE.[1] However, low specificity limits the usefulness of D-dimer testing. Specificity is typically between 40% and 60%, leading to a high rate of false-positive results.[2]

Several factors, other than PE or deep vein thrombosis (DVT), are associated with positive D-dimer results. Some, such as advanced age, malignancy, and pregnancy, have been described in the medical literature.[3–9] However, most prior studies have evaluated D-dimer testing in a select population of patients with a particular risk factor, rather than in an undifferentiated population of patients evaluated for PE.[10–12] As a result, the ability to adjust results for the large variety of conditions that may elevate the D-dimer has been limited. In addition, risk factors have generally been studied as broad categories (e.g., recent surgery, history of cancer), but whether the described effects are consistent across more detailed subcategories (e.g., type of surgery, active vs. inactive malignancy) is not well known. We used data obtained from a large multicenter study of emergency department (ED) patients evaluated for PE to identify factors associated with a positive D-dimer result and quantify the effect of each factor in a multivariable analysis.

Methods

Study Design

This was a prospective, multicenter, observational study of ED patients undergoing testing for possible PE. The institutional review board of each participating institution approved the protocol.

Study Setting and Population

Data were collected from May 1, 2003, to March 31, 2007. This study analyzed data from 10 academic medical centers and two community hospitals in the United States.

Patients were eligible for enrollment if the treating clinician ordered a D-dimer to rule out PE. All D-dimer tests were ordered as part of an evaluation for acute PE, and studies ordered to evaluate DVT without PE, or other diagnoses, did not trigger enrollment.

Study Protocol

Details of study enrollment are described elsewhere.[10] After a diagnostic test for PE was ordered, but before results were known, we prospectively collected data describing patient demographics, presenting signs and symptoms, and comorbid illnesses. A study investigator uploaded data into a Web-based, secure, electronic data collection form.[13] The Web-based data collection instrument was programmed with logic that did not permit missing or nonsense data.

Potential predictors were collected prospectively at the time of the PE evaluation. Predictor variables described a variety of conditions, including demographics, past medical history and comorbidities, and medications (Table 1). Surgery and trauma were considered positive if they occurred in the past 4 weeks and if the trauma was significant enough to require hospitalization. Travel was defined as any travel lasting greater than 6 hours, occurring within the past 4 weeks.

The outcome of interest was a positive D-dimer result. The decision to order a D-dimer was at the discretion of the evaluating physician. D-dimer assays were those used for routine clinical care at participating institutions. We analyzed patients from participating institutions where a quantitative D-dimer assay was available, including Advanced (Dade Behring, Marburg, Germany), Biopool Minutex (diaPharma, West Chester, OH), Hemosil (Dade Behring), Liatest (Diagnostica Stago, Asnières sur Seine, France), MDA (bioMérieux SA, Marcy-l'Etoile, France, formerly Organon Teknika Corporation, Durham, NC), or VIDAS (bioMérieux SA). Tests were performed as a part of routine clinical care by personnel working in each hospital's laboratory, blinded to the goals of the study. The positive and negative cutoff for each assay was defined by the institution where the test was used and was generally consistent with manufacturers' recommendations. Liatest, VIDAS, and MDA D-dimers were considered positive at concentrations of ≥500 ng/mL, Biopool Minutex at ≥250 ng/mL, Hemosil at ≥244 ng/mL, and the Advanced D-dimer at ≥1.6 μg/mL.

Data Analysis

The purpose of our study was to provide guidance to physicians prior to ordering a D-dimer, so we included both true positive (positive D-dimer results in patients diagnosed with PE) and false positive (positive D-dimer results in patients not diagnosed with PE) in our analysis. We also performed a sensitivity analysis excluding patients diagnosed with PE (i.e., only including false-positive D-dimers).

We used SAS v 9.l (SAS Institute, Cary, NC) for all of our statistical calculations. Baseline characteristics are reported as simple proportions, means, and medians. In our primary analysis we calculated odds ratios (ORs) and 95% confidence intervals (95% CIs) using a multi-variable logistic regression model, which in addition to potential predictors of positive D-dimers, also included the D-dimer assay used. To adjust for the high frequency of our outcome, and better estimate the risk ratio (RR), we then transformed the OR using the method described by Zhang and Yu.[14] Predictor variables were included in the model first as general predictor categories (e.g., recent surgery). In the event that a predictor was found to be significantly associated with positive D-dimer results, data describing subcategories of the predictor (e.g., different types of surgery) were available, and if there were greater than 20 subjects in each subcategory, those subcategories of the predictor were included in the model. If a general category was found not to be associated with positive D-dimer results, subcategories of the predictor were not analyzed, but the predictor was kept in the model as a potential confounder. Age and body mass index (BMI) were considered categorical variables. However, a separate analysis was performed with these variables considered ordinal in the model. White race, age <30 years, and BMI <25 were reference groups. For

subcategories of diseases (e.g., active and inactive malignancy), lack of the disease (e.g., no cancer) was the reference group. Significant predictors were defined as those where the 95% CI did not cross unity. Table 1 lists the predictors included in the final multivariable model.

Results

In the original study, 7,940 patients were prospectively enrolled and 6,175 patients were enrolled in an institution where a quantitative D-dimer was available. Of these patients, 4,356 (71%) had a quantitative D-dimer performed and were therefore included in the current analysis (Figure 1). The Liatest was the most commonly performed assay (1,466, 34%), followed by the VIDAS (1,262, 29%). A total of 1,003 patients (44%) had a positive D-dimer. The overall mean age was 47.7(±16.7) years. Among patients with a negative D-dimer the mean age was 44.2 (±14.1) years, but among those with a positive D-dimer the mean age was 52.3 (±18.6) years. The majority of patients (2930, 67%) were female. Table 2 describes the baseline characteristics of enrolled patients, stratified by whether D-dimer was positive or negative.

Results of the multivariable model are presented in Table 3. Model fit was adequate (c-statistic = 0.739, Hosmer and Lemeshow test $p = 0.13$). Women were more likely to have a positive D-dimer than were men. Older age was highly associated with positive D-dimer (OR = 1.40 [95% CI = 1.32 to 1.47], adjusted RR = 1.19 [95% CI = 1.16 to 1.22] per 10 years after age 30, $p < 0.0001$). The association with age became statistically significant in the fourth to fifth decades of life. Patients of African American or black race were more likely to have a positive D-dimer compared to whites, but there was no observed association for other races. All categories of surgery were associated with positive D-dimer results. Active cancer was associated with positive D-dimer results (OR = 2.58 [95% CI = 1.84 to 3.63], adjusted RR = 1.55 [95% CI = 1.36 to 1.72], $p < 0.0001$), whereas inactive cancer was not. Immobility was associated with positive D-dimer results, with a 50% to 60% increase across all categories of immobility, although there was no association with travel. There was an increasingly positive association between trimester of pregnancy and positive D-dimers. The association in the first trimester of pregnancy was borderline, but nearly all (96%) women in the third trimester had a positive D-dimer. In terms of past medical history, connective tissue disease was associated with a roughly one-third higher risk of a positive D-dimer and end-stage renal disease with a 45% higher risk, but the strongest disease association was seen with sickle cell disease/trait (OR = 24.17 [95% CI = 3.08 to 189.53], adjusted RR = 2.18 [95% CI = 1.62 to 2.28], $p = 0.002$). Prior venous thromboembolism (VTE) was associated with a small increase in the odds of D-dimer positivity (OR = 1.41 [95% CI = 1.07 to 1.87], adjusted RR = 1.20 [95% CI = 1.04 to 1.36], $p = 0.016$), only if the patient was not actively being treated. The only factor with a significant " protective effect" was warfarin use; anti-platelet drugs had no such effect. Overall, variables not associated with positive D-dimer included antiplatelet drugs, anxiety, asthma, BMI, coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), diabetes, estrogen use, family history of PE, hypertension, (inactive) malignancy, stroke, thrombophilia, trauma within 4 weeks, travel, or VTE (under treatment).

Sensitivity Analysis

When we restricted our multivariable analysis to the 4,122 patients not diagnosed with PE (i.e., false-positive D-dimers), results were similar (Table 4). The only variables to change statistical significance were CAD, VTE not under treatment, and smoking, although point estimates were similar and the lower confidence bounds for these variables were close to unity in both analyses. Estimated ORs were also similar when we reran our model only including significant predictors.

Discussion

To our knowledge, this is the largest and most detailed study yet performed quantifying the association between clinical factors and positive D-dimer results. We found several factors to be highly associated with positive D-dimer results. This study has several advantages over previous studies; with our large sample size, we were able to adjust for a large number of covariates. This provides a more accurate estimate of the risk of a positive D-dimer, even for factors previously known to be associated with positive results. In addition, we were able to identify several factors not previously known to be associated with positive D-dimer results and describe the association of subcategories of malignancy, surgery, connective tissue disease, lung disease, and pregnancy—describing the relationship between these factors and D-dimer results in more detail than was previously available.

We found several findings of particular interest. We confirmed strong associations with age, surgery, and malignancy, previously described. We also found associations with immobility and sickle cell disease that were not well known. The adjusted relative risks for these associations are generally between 1.5 and 2. While this may seem low, it is important to consider that the baseline risk of a positive D-dimer was 44% in our study, so increasing the risk by 50% to 100% represents a significant change. We believe that identifying factors associated with positive D-dimer results, and understanding the strength of the associations, will help clinicians target their use of D-dimer testing to those patients where the result is likely to be the most useful. These results may also aid the development of decision instruments that guide the use of D-dimer testing and the evaluation of patients suspected of having PE.

Our data support the association between older age and positive D-dimer results that has been described previously.[8,9] There does not seem to be a great effect below the age of 50 years, with patients younger than 50 years having a negative D-dimer approximately 60% of the time. In contrast, there is a drop to 42% in patients 60–69 years old, to 31% in patients 70–79 years old, and only 17% in patients older than 80 years. Clinicians should consider the low likelihood of a negative D-dimer before ordering the test in patients more than 60 years old.

We also found that recent surgery increases the odds of a positive D-dimer by approximately 60%. More than two-thirds of our patients who had undergone recent surgery had a positive D-dimer. While elevated D-dimer values after surgery are understandable, most previous reports have studied enrolled patients at the time of surgery, showing that postoperative patients have a high rate of D-dimer positivity.[10–12] Our study is the most detailed exploration to date of the association between recent surgery and D-dimer results in patients being evaluated for PE. By studying an undifferentiated population of patients, and comparing those who had recent surgery to those who had not, we were also able to determine the relative effect of surgery on the odds of a positive D-dimer result.

We also studied the relationship between malignancy and D-dimer results. Previous authors have shown that patients with cancer were much more likely to have a positive D-dimer, with a number needed to rule out equal to 8.6.[6] However, our study has the advantage of being able to distinguish between active and inactive malignancy. Our results show a strong association for patients with malignancy that is actively being treated or palliated. However, we found no association in patients whose cancer is inactive or has been completely treated. Clinicians should distinguish between active and inactive cancer when assessing the likelihood of a positive D-dimer.

The association we found for immobility seems to vary little depending on the type of immobility. This is in contrast to a recent study from our database demonstrating that the

risk of PE is different depending on the type of immobility.[15] In our study, regardless of whether a patient's immobility was described as generalized, limb, or neurologic, the risk of a positive D-dimer increased by 50% to 60%. While immobility is known to be related to PE risk,[15] to the authors' knowledge, this is the first study to demonstrate an independent association between immobility and D-dimer positivity. Two prior studies investigated the issue of hypercoagulability during a simulated airplane flight in 10 healthy subjects and one subject who was heterozygous for factor V Leiden and found no association.[16,17] These results are consistent with our finding of no association between recent travel and D-dimer results. However, our definition of immobility included patients with prolonged or permanent immobility and complete or near complete inability to mobilize one or more limbs. This likely explains the significant association we found. We believe that the pathophysiology of hypercoagulability associated with immobility should be investigated further.

Our data support a strong association between sickle cell disease/trait and D-dimer positivity, such that D-dimer testing is likely to be of limited utility in ruling out PE in these patients. Prior studies have demonstrated elevated D-dimer levels in sickle cell patients, particularly during vaso-occlusive crises.[18,19] While we did not distinguish between patients having a painful crisis, it is reasonable to conclude that the high frequency of D-dimer positivity may be related to concomitant vaso-occlusive crises in patients with sickle cell disease. Clinicians should be aware of this possibility and treat their patients accordingly.

Finally, it is worth noting that many of the above conditions (e.g., age, immobility, malignancy, pregnancy) both increase the risk of PE and elevate the D-dimer. This is demonstrated in our data as well. We found that factors known to increase the risk of PE, such as immobility (except neurologic), active malignancy, thrombophilia, a history of VTE, and recent surgery (except chest surgery) all had ratios of false to true D-dimer results that were lower than that of the study population as a whole. For ordinal factors, such as increasing age and BMI, the ratio decreased linearly. Increasing physician estimate of pretest probability of PE was also inversely proportional to the ratio of false to true D-dimer results. These findings are consistent with known associations between these factors and the risk of PE and with our prior research.[20] Conversely, certain inflammatory conditions without well-established associations with the risk of PE (rheumatoid arthritis, sickle cell disease, asthma) had high ratios of false to true D-dimer results. D-dimer use in patients with these conditions is likely to yield a large number of false positives for each subject ruled out for PE. Interestingly, we found that some of the above conditions known to increase the risk of PE were not associated with increased D-dimer values. We found no association between BMI or smoking and D-dimer positivity, although large epidemiologic studies have demonstrated their association with PE.[20–24] Similarly, we found no association between known thrombophilia or family history of VTE and positive D-dimers. Thus, even in the presence of strong family history or known thrombophilia, D-dimer testing may be useful. We found no association with recent trauma, although trauma is a heterogeneous disease, and we did not attempt to quantify the amount of bleeding or clotting that might have occurred in each patient. Last, we found a relatively weak association between prior VTE and positive D-dimers, but only in patients who were not being actively treated.

Limitations

This was a large multicenter study with an observational design. The selection of patients appropriate for D-dimer testing was left to the discretion of the treating physician, which may have biased the results. It is possible that, because patients with conditions (e.g., malignancy) known to elevate the D-dimer may not have been selected for testing, we have underestimated the association of these factors. However, many of the factors we describe,

including subcategories of known associations, were not previously so well known that they would likely have altered physician test ordering. Nonetheless, our results probably should not be compared to studies that purported to follow a rigid study protocol. We enrolled patients in academic and community centers, resulting in a heterogeneous population with a variety of D-dimer assays used. We adjusted our analysis for the D-dimer assay used, to account for differences in test characteristics across assays, but we did not specifically explore differences between assays. We included patients diagnosed with PE in our primary analysis. We did so to provide guidance to clinicians trying to determine whether a D-dimer is likely to be positive and therefore less useful in ruling out PE. It is likely that a homogenous population of patients with true-positive D-dimers would be different than one with false-positive D-dimers. However, we found no major differences in our associations when we performed a sensitivity analysis excluding PE-positive patients. Finally, our analysis was meant to be exploratory and was designed to identify as many predictors of positive D-dimers as possible. We did not seek to create the most efficient model, but rather to include a broad array of potential confounders. However, when we excluded nonsignificant predictors from our model, results were similar.

Conclusions

Many factors are associated with a positive D-dimer test. Age, surgery, immobility, and pregnancy are all strongly associated with D-dimer positivity. Active malignancy is associated, but inactive malignancy is not. Several factors that are known to be associated with pulmonary embolism are not associated with a positive D-dimer. Clinicians should consider these associations when they weigh the usefulness of D-dimer testing for patients with suspected pulmonary embolism.

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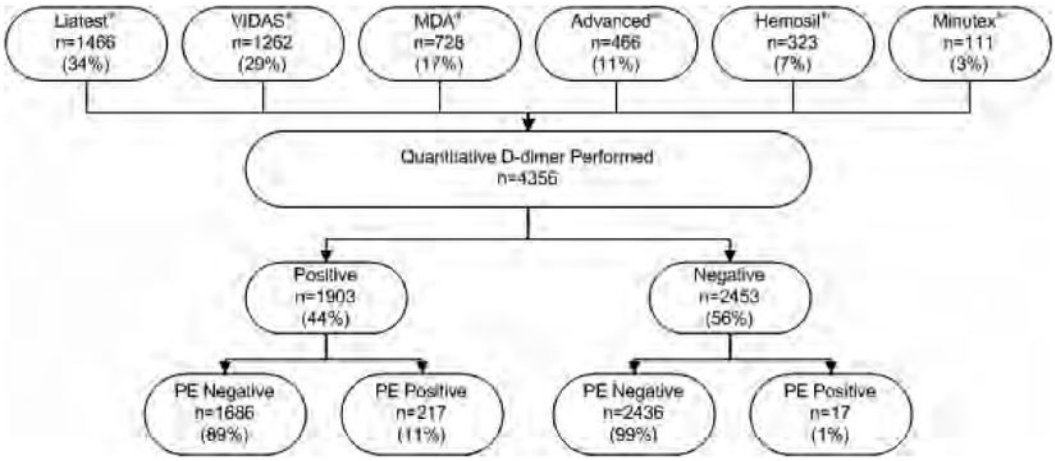

Figure 1.
Study enrollment. PE = pulmonary embolism.

Table 1
Predictors Included in Final Multivariable Model

Predictor	Categories
Age (yr) *	<30, 30–39, 40–49, 50–59, 60–69, 70–79, ≥80
Antiplatelet drug use †	Yes/no
Anxiety	Yes/no
BMI	<25.0, 25.0–29.9, 30.0–34.9, ≥35.0
CAD	Yes/no
Cerebrovascular disease ‡	Yes/no
CHF	Yes/no
Cocaine use	Yes/no
Connective tissue disease	Systemic lupus erythematosis, rheumatoid arthritis, other
Diabetes mellitus	Yes/no
D-dimer assay	Advanced, Biopool, Hemosil, Liatest, MDA, Vidas
Estrogen replacement therapy	Yes/no
Family history of VTE	Yes/no
Sex	Female, male
Hemodialysis	Yes/no
Hemoptysis	Yes/no
Hypertension	Yes/no
Lung disease	Asthma, COPD, other
Malignancy	Active, inactive
Pregnancy	First trimester, second trimester, third trimester, ≤4 weeks postpartum
Sickle cell disease or trait	Yes/no
Smoking	Yes/no
Thrombophilia	Yes/no
Immobility	Generalized, limb, neurologic
Race	Asian, Black or African American, Hispanic, white, other
Surgery	Abdominal, chest, orthopedic, other
Trauma	Yes/no
Travel	Yes/no
Warfarin use	Yes/no
VTE history	None, under treatment, not under treatment

BMI = body mass index; CAD = coronary artery disease (a history of angina, myocardial infarction, or coronary artery revascularization procedure); CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; VTE = venous thromboembolism (deep vein thrombosis or PE).

* Age was considered categorical, although a separate analysis was also performed where age was included in the model as an ordinal variable.

† Antiplatelet drugs include aspirin, ticlopidine, and clopidogrel.

‡ Cerebrovascular disease includes any history of stroke or transient ischemic attack.

Table 2
Characteristics of Enrolled Patients

Characteristic	Total, *n* (%)	D-dimer Negative, *n* (%)	D-dimer Positive, *n* (%)	Ratio of False- to True-positive D-dimers
Enrolled	4,356 (100)	2,453 (56)	1,903 (44)	7.8
Female	2,930 (67)	1,320 (45)	1,610 (55)	9.5
Age (yr)				
<30	605 (14)	373 (62)	232 (38)	14.5
30–39	961 (22)	642 (67)	319 (33)	8.4
40–49	954 (22)	619 (65)	335 (35)	8.6
50–59	798 (18)	468 (59)	330 (41)	6.3
60–69	507 (12)	217 (43)	290 (57)	8.1
70–79	328 (8)	100 (30)	228 (70)	6.4
≥80	203 (5)	34 (17)	169 (83)	5.8
Race/ethnicity				
Black or African American	1,474 (34)	753 (51)	721 (49)	8.2
Hispanic	238 (5)	155 (65)	83 (35)	40.5
White	2,500 (57)	1,454 (58)	1,046 (42)	6.9
Other	144 (3)	91 (63)	53 (37)	9.6
Pretest probability of PE*				
Low (<15%)	3,224 (74)	1,206 (37)	2,018 (63)	14.1
Intermediate (15%–40%)	933 (21)	561 (60)	372 (40)	5.6
High (>40%)	191 (4)	132 (69)	59 (31)	1.5
BMI				
<25	1,517 (35)	871 (57)	646 (43)	9.4
25–29.9	1,240 (28)	695 (56)	545 (44)	7.5
30–34.9	790 (18)	447 (57)	343 (43)	7.4
≥35	809 (19)	440 (54)	369 (46)	6.4
Cocaine use	68 (2)	31 (46)	37 (54)	17.5
Family history of PE	538 (12)	331 (62)	207 (38)	4.9
Immobility				
General	243 (6)	71 (29)	172 (71)	4.9
Limb	73 (2)	21 (29)	52 (71)	3.3
Neurologic	26 (1)	8 (31)	18 (69)	8.0
Hemoptysis	116 (3)	45 (39)	71 (61)	10.8
Medication use				
Antiplatelet	652 (15)	290 (44)	362 (56)	6.9
Estrogen	400 (9)	249 (62)	151 (38)	5.3
Warfarin	178 (4)	84 (47)	94 (53)	5.7
Past medical history				
Anxiety	548 (13)	335 (61)	213 (39)	10.2
CAD	416 (10)	152 (37)	264 (63)	10.5
Cerebrovascular disease	151 (3)	67 (44)	84 (56)	15.8

Characteristic	Total, *n* (%)	D-dimer Negative, *n* (%)	D-dimer Positive, *n* (%)	Ratio of False- to True-positive D-dimers
CHF	287 (7)	99 (34)	188 (66)	8.0
Connective tissue disease				
Rheumatoid arthritis	76 (2)	30 (39)	46 (61)	22.0
Systemic lupus erythematosis	53 (1)	22 (42)	31 (58)	9.3
Other connective tissue disease	26 (1)	11 (42)	15 (58)	4.0
Diabetes	556 (13)	243 (44)	313 (56)	9.4
Hemodialysis	38 (1)	12 (32)	26 (68)	25
Hypertension	1,503 (35)	696 (46)	807 (54)	7.9
Lung disease				
Asthma	478 (11)	292 (61)	186 (39)	15.9
COPD	273 (6)	107 (39)	166 (61)	10.1
Malignancy				
Active	203 (5)	59 (29)	144 (71)	4.5
Inactive	211 (5)	95 (45)	116 (55)	7.3
Sickle cell disease or trait	15 (0)	1 (7)	14 (93)	13.0
Thrombophilia	45 (1)	24 (53)	21 (47)	4.3
VTE				
Under treatment	118 (3)	56 (47)	62 (53)	2.9
Not under treatment	258 (6)	118 (46)	140 (54)	4.6
Pregnancy				
First trimester	18 (0)	8 (44)	10 (56)	—[†]
Second trimester	31 (1)	7 (23)	24 (77)	—
Third trimester	23 (1)	1 (4)	22 (96)	—
Postpartum	65 (1)	19 (29)	—	—
Smoking	1,635 (38)	905 (55)	730 (45)	11.0
Surgery				
Abdominal	72 (2)	18 (25)	54 (75)	5.8
Chest	34 (1)	10 (29)	24 (71)	11.0
Orthopedic	49 (1)	15 (31)	34 (69)	2.8
Other	37 (1)	11 (30)	26 (70)	—
Trauma	36 (1)	17 (47)	19 (53)	8.5
Travel	398 (9)	261 (66)	137 (34)	6.2

BMI = body mass index; CAD = coronary artery disease (a history of angina, myocardial infarction, or coronary artery revascularization procedure); CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; PE = pulmonary embolism; VTE = venous thromboembolism (deep vein thrombosis or PE).

[*] Pretest probability determined by treating physician.

[†] No patients who had D-dimer performed were diagnosed with PE.

Table 3

Multivariable Analysis of Factors Associated With Positive D-dimer Results

	OR	95% CI	Adjusted Risk Ratio*	95% CI	p-value
Female	1.22	1.04–1.42	1.12	1.03–1.21	0.01
Age (yr)					
30–39	0.93	0.73–1.18	0.96	0.84–1.09	0.54
40–49	1.09	0.86–1.39	1.05	0.92–1.18	0.48
50–59	1.33	1.03–1.71	1.16	1.01–1.30	0.03
60–69	2.58	1.92–3.47	1.55	1.39–1.70	<0.0001
70–79	4.54	3.20–6.46	1.84	1.67–1.98	<0.0001
≥80	10.49	6.63–16.61	2.11	1.98–2.21	<0.0001
Race/ethnicity					
Black or African American	1.48	1.26–1.73	1.23	1.14–1.33	<0.0001
Hispanic	1.02	0.75–1.40	1.01	0.84–1.19	0.88
Other	1.09	0.74–1.60	1.05	0.84–1.27	0.67
BMI					
25–29.9	1.10	0.92–1.31	1.05	0.96–1.15	0.29
30–34.9	1.07	0.88–1.31	1.04	0.93–1.15	0.50
≥35	1.16	0.95–1.43	1.09	0.97–1.20	0.15
Cocaine use	2.02	1.20–3.38	1.40	1.11–1.66	0.008
Family history of PE	0.96	0.78–1.18	0.98	0.86–1.09	0.70
Immobility					
General	2.34	1.70–3.22	1.50	1.31–1.66	<0.0001
Limb	2.76	1.56–4.89	1.57	1.26–1.82	0.001
Neurologic	3.05	1.24–7.51	1.61	1.12–1.96	0.02
Hemoptysis	2.01	1.33–3.04	1.40	1.16–1.62	0.001
Medication use					
Antiplatelet drug	1.09	0.88–1.35	1.05	0.93–1.18	0.41
Estrogen	1.22	0.96–1.55	1.12	0.98–1.25	0.10
Warfarin	0.57	0.38–0.85	0.70	0.52–0.91	0.006
Past medical history					

	OR	95% CI	Adjusted Risk Ratio*	95% CI	p-value
Anxiety	0.82	0.67–1.01	0.89	0.78–1.00	0.06
CAD	1.22	0.93–1.59	1.12	0.96–1.28	0.15
Cerebrovascular disease	0.71	0.48–1.06	0.81	0.62–1.03	0.09
CHF	1.23	0.91–1.65	1.12	0.95–1.30	0.18
Connective tissue disease					
Rheumatoid arthritis	1.80	1.07–3.00	1.33	1.04–1.61	0.03
Systemic lupus erythematosis	2.09	1.15–3.80	1.42	1.08–1.71	0.02
Other connective tissue disease	1.50	0.63–3.57	1.23	0.75–1.68	0.37
Diabetes mellitus	1.05	0.84–1.31	1.03	0.90–1.16	0.66
Hemodialysis	2.24	1.06–4.72	1.45	1.03–1.80	0.03
Hypertension	1.02	0.87–1.21	1.01	0.91–1.12	0.80
Lung disease					
Asthma	0.83	0.67–1.03	0.90	0.78–1.02	0.09
COPD	1.02	0.75–1.37	1.01	0.84–1.18	0.92
Malignancy					
Active	2.58	1.84–3.63	1.55	1.36–1.72	<0.0001
Inactive	1.09	0.79–1.50	1.05	0.87–1.23	0.60
Sickle cell disease or trait	24.17	3.08–189	2.18	1.62–2.28	0.002
Thrombophilia	1.20	0.61–2.36	1.11	0.74–1.48	0.59
VTE					
Under treatment	1.60	0.99–2.60	1.27	0.99–1.53	0.06
Not under treatment	1.41	1.07–1.87	1.20	1.04–1.36	0.02
Pregnancy					
First trimester	2.65	0.99–7.05	1.54	1.00–1.94	0.05
Second trimester	7.31	3.04–17.61	1.95	1.61–2.14	<0.0001
Third trimester	51.25	6.79–386	2.25	1.93–2.30	0.0001
Postpartum	4.18	2.33–7.47	1.76	1.48–1.97	<0.0001
Smoking	1.13	0.98–1.30	1.07	0.99–1.15	0.10
Surgery					
Abdominal	3.47	1.93–6.25	1.68	1.38–1.91	<0.0001
Chest	2.69	1.21–5.98	1.55	1.11–1.89	0.02

	OR	95% CI	Adjusted Risk Ratio*	95% CI	p-value
Orthopedic	2.20	1.12–4.33	1.45	1.06–1.77	0.02
Other	3.24	1.00–10.44	1.64	1.00–2.05	0.05
Trauma	0.71	0.33–1.53	0.81	0.46–1.24	0.38
Travel	0.85	0.67–1.08	0.91	0.78–1.04	0.19

Reference groups: age = <30 years; race = white; BMI = <25.

BMI = body mass index; CAD = coronary artery disease (a history of angina, myocardial infarction, or coronary artery revascularization procedure); CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; PE = pulmonary embolism; VTE = venous thromboembolism (deep vein thrombosis or PE).

*Adjusted according to method of Zhang and Yu.[14] RR = OR/(1 – P_0) + (P_0 × OR), where RR = risk ratio, OR = odds ratio, and P_0 = the incidence of the outcome of interest in nonexposed subjects.

Table 4

Multivariable Analysis of Factors Associated With False-positive D-dimer Results

	OR	95% CI	Adjusted Risk Ratio*	95% CI	p-value
Female	1.36	1.15–1.60	1.20	1.09–1.31	0.002
Age (yr)					
30–39	0.92	0.72–1.17	0.96	0.83–1.08	0.50
40–49	1.06	0.83–1.36	1.03	0.90–1.17	0.64
50–59	1.26	0.97–1.65	1.13	0.98–1.28	0.08
60–69	2.46	1.82–3.34	1.53	1.35–1.69	<0.0001
70–79	4.27	2.97–6.14	1.81	1.63–1.96	<0.0001
≥80	9.54	5.97–15.26	2.09	1.94–2.19	<0.0001
Race/ethnicity					
Black or African American	1.46	1.24–1.71	1.23	1.13–1.32	<0.0001
Hispanic	1.11	0.81–1.52	1.06	0.88–1.24	0.53
Other	1.12	0.75–1.66	1.06	0.84–1.29	0.57
BMI					
25–29.9	1.09	0.91–1.30	1.05	0.95–1.15	0.36
30–34.9	1.04	0.85–1.28	1.02	0.91–1.14	0.72
≥35	1.09	0.88–1.35	1.05	0.93–1.17	0.44
Cocaine use	2.14	1.26–3.60	1.46	1.14–1.75	0.005
Family history of PE	0.91	0.73–1.13	0.95	0.82–1.07	0.38
Immobility					
General	2.18	1.57–3.05	1.49	1.28–1.69	<0.0001
Limb	2.38	1.31–4.34	1.53	1.16–1.84	0.004
Neurologic	2.89	1.16–7.25	1.63	1.09–2.04	0.02
Hemoptysis	2.07	1.35–3.16	1.45	1.18–1.69	0.008
Medication use					
Antiplatelet drug	1.07	0.86–1.33	1.04	0.91–1.18	0.57
Estrogen	1.13	0.88–1.45	1.07	0.93–1.22	0.35
Warfarin	0.63	0.41–0.97	0.74	0.54–0.98	0.04
Past medical history					

	OR	95% CI	Adjusted Risk Ratio*	95% CI	p-value
Anxiety	0.82	0.67–1.03	0.89	0.78–1.02	0.08
CAD	1.31	1.0–1.72	1.17	1.00–1.34	0.05
Cerebrovascular disease	0.75	0.51–1.12	0.83	0.64–1.07	0.16
CHF	1.21	0.89–1.64	1.12	0.93–1.31	0.22
Connective tissue disease					
Rheumatoid arthritis	1.87	1.12–3.15	1.38	1.07–1.68	0.02
Systemic lupus erythematosis	2.06	1.12–3.79	1.44	1.07–1.77	0.02
Other connective tissue disease	1.56	0.60–4.04	1.27	0.72–1.80	0.36
Diabetes mellitus	1.10	0.88–1.37	1.06	0.92–1.20	0.42
Hemodialysis	2.41	1.14–5.12	1.53	1.08–1.91	0.02
Hypertension	1.07	0.90–1.27	1.04	0.93–1.16	0.45
Lung disease					
Asthma	0.87	0.69–1.08	0.92	0.79–1.05	0.20
COPD	1.02	0.76–1.39	1.01	0.84–1.20	0.87
Malignancy					
Active	2.50	1.75–3.57	1.57	1.35–1.77	<0.0001
Inactive	1.07	0.77–1.49	1.04	0.85–1.24	0.70
Sickle cell disease or trait	25.78	3.26–204	2.32	1.70–2.44	0.002
Thrombophilia	1.30	0.62–2.71	1.16	0.73–1.60	0.48
VTE					
Under treatment	1.21	0.71–2.06	1.11	0.81–1.41	0.49
Not under treatment	1.32	0.98–1.78	1.16	0.99–1.33	0.07
Pregnancy					
First trimester	2.89	1.08–7.69	1.63	1.05–2.06	0.04
Second trimester	7.71	3.20–18.55	2.07	1.69–2.28	<0.0001
Third trimester	55.38	7.34–417	2.40	2.05–2.45	<0.0001
Postpartum	4.57	2.57–8.19	1.87	1.57–2.10	<0.0001
Smoking	1.20	1.03–1.39	1.11	1.02–1.20	0.004
Surgery					
Abdominal	3.27	1.79–5.99	1.71	1.36–1.99	<0.0001
Chest	3.09	1.35–7.08	1.67	1.18–2.04	0.01

	OR	95% CI	Adjusted Risk Ratio*	95% CI	p-value
Orthopedic	2.08	1.03–4.23	1.44	1.02–1.83	0.04
Other	3.80	1.18–12.31	1.78	1.10–2.20	0.03
Trauma	0.80	0.36–1.75	0.87	0.49–1.34	0.57
Travel	0.81	0.63–1.05	0.88	0.75–1.03	0.11

Reference groups: age = <30 years; race = white; BMI = <25.

BMI = body mass index; CAD = coronary artery disease (a history of angina, myocardial infarction, or coronary artery revascularization procedure); CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; PE = pulmonary embolism; VTE = venous thromboembolism (deep vein thrombosis or PE).

*Adjusted according to method of Zhang and Yu.[14] RR = OR/(1 – P_0) + (P_0 × OR), where RR = risk ratio, OR = odds ratio, and P_0 = the incidence of the outcome of interest in non-exposed subjects.