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Predictors of venous thromboembolism in patients with COVID-19 in an underserved urban population: A single tertiary center experience

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Abstract

Introduction: Venous thromboembolism (VTE) is reported in up to 27% of patients with COVID-19 due to SARS-CoV-2 infection. Dysregulated systemic inflammation and various patient traits are presumed to underlie this anomaly. Optimal VTE prophylaxis in COVID-19 patients has not been established due to a lack of validated models for predicting VTE in this population. Our study aims to address this deficiency by identifying demographic and clinical characteristics of COVID-19 patients associated with increased VTE risk.

Methods: This study is a retrospective analysis of all adult patients (final sample, n = 355) hospitalized with confirmed COVID-19 at Einstein Medical Center Philadelphia between March 1 and April 24, 2020. Demographic and clinical patient data were collected and factors associated with VTE were identified and analyzed using t-tests, multivariable logistic regression, and receiver operating characteristic (ROC) curves.

Results: Thirty patients (8.5%) developed VTE. Patients with VTE had significantly higher D-dimer levels on admission ($P = 0.045$) and peak D-dimer levels ($P < 0.0001$), in addition to higher rates of vasopressor requirements ($P = 0.038$), intubation ($P = 0.003$), and death ($P = 0.023$). Age (OR 1.042), obstructive sleep apnea (OR 5.107), and need for intubation (OR 3.796) were associated with significantly increased odds of VTE. Peak D-dimer level was a good predictor of VTE (AUC 0.806, $P < 0.0001$) and a D-dimer cutoff of >6640 ng/mL had high (>70%) sensitivity and specificity for VTE.

Conclusion: Peak D-dimer level may be the most reliable clinical marker in COVID-19 patients for predicting VTE and future prospective studies should attempt to further validate this.

KEYWORDS

COVID-19, d-dimer, novel coronavirus, predictors, venous thromboembolism

1 | INTRODUCTION

An increased incidence of venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism, has been reported in hospitalized patients with coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] The mechanism underlying this phenomenon remains unclear but suggested explanations include hypercoagulability related to cytokine storm and virally-mediated upregulation of antiphospholipid antibody production.[2–3] Differences in patient traits such as the severity of SARS-CoV-2 infection, preexisting medical conditions, age, race, and ethnicity may also contribute to the development of VTE. Epidemiologic studies have shown that Black and Latino patients have disproportionately worse outcomes from COVID-19 compared to Caucasian or Asian populations.[4] Reported VTE incidence in hospitalized patients with COVID-19 ranges from 3.3% to 27%.[5–6] Serum D-dimer is a marker of clot degradation that can be used in the diagnostic workup of VTE in the general population; however, its utility in COVID-19 patients is confounded by the fact that they often have highly elevated D-dimer levels even in the absence of clinically identified VTE.[1] There is data to suggest that VTE prophylaxis is associated with reduced mortality in patients with severe COVID-19 infection or significant elevations in serum D-dimer levels.[7] However, there are no consensus guidelines on optimal VTE prophylaxis in COVID-19 patients. This is largely due to a lack of validated predictors for identifying patients at the highest risk of developing VTE. This present study is important because it aims to identify demographic and clinical characteristics of COVID-19 patients associated with increased VTE risk.

2 | MATERIALS AND METHODS

2.1 | Study design, participants, and data collection

Our study was a retrospective analysis of all adult patients admitted to Einstein Medical Center Philadelphia from March 1 to April 24, 2020 with COVID-19 diagnosis confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) assays performed on nasopharyngeal swab specimens. This time period was chosen because those dates correspond to the peak of the COVID-19 pandemic that we experienced at our health center. This study was approved by the institutional review board.

2.2 | Statistical analysis

Demographic and clinical variables were presented using descriptive statistics and frequencies. Categorical variables were analyzed with chi-square testing. Independent t-test was used for continuous variables. Mann-Whitney U testing was used to compare differences for skewed variables. Multivariable logistic regression was used to evaluate the factors associated with VTE among patients with COVID-19. Receiver-operating characteristic (ROC) analysis and area under the curve (AUC) were used to analyze the optimal D-dimer cutoff for VTE detection. AUC 0.9 to 1 was defined as excellent accuracy; 0.8–0.9 was good; 0.7–0.8 was fair; 0.6–0.7 was poor; 0.5–0.6 was fail. When the AUC was >0.7, Youden's index identified the cutoff value that maximized sensitivity and specificity. Sensitivities, specificities, and likelihood ratios were calculated. 95% confidence intervals were used and are presented when appropriate. All analyses were performed using IBM SPSS Statistics for Windows, Version 23.0.

3 | RESULTS

The initial sample included 389 patients. After excluding 34 patients who were still admitted at the time of analysis, the final sample included 355 patients (see Figure 1).

3.1 | Demographic and baseline comorbidities data

In the final patient sample, the mean age (±SD) was 66.21 ± 14.21 years, 49% were female, and 71% were Black. Baseline medical comorbidities included hypertension (77%), diabetes mellitus (47%), COPD (13%) and asthma (8%).

3.2 | Mortality and in-hospital complications data

There were 80 (23%) in-hospital deaths and a 64% mortality rate in ICU patients. In total, 30 patients developed VTE which corresponded to a VTE incidence of 8.5%. There was a 13% VTE incidence in ICU patients. Among patients with VTE, 40% died and 50% needed intubation. The overall pharmacologic VTE prophylaxis rate was 84% and all patients who developed VTE were already receiving prophylaxis at the time of VTE diagnosis. Significantly more patients with VTE died (40% vs 21%, $P = 0.023$) and needed vasopressors (40% vs 21%, $P = 0.038$) and intubation (50% vs 23%, $P = 0.003$) compared to patients without VTE (see Table 1). Significantly more patients with VTE received corticosteroids (67% vs 26%, $P < 0.0001$) and tocilizumab (40% vs 10%, $P < 0.0001$) and had higher rates of warfarin use (10% vs 0.3%, $P = 0.002$). Age (OR 1.042, 95% CI 1.004-1.082), obstructive sleep apnea (OSA; OR 5.107 95%, CI 1.141-22.859), and need for intubation (OR 3.796, 95% CI 1.602-8.996) were associated with increased odds of VTE,
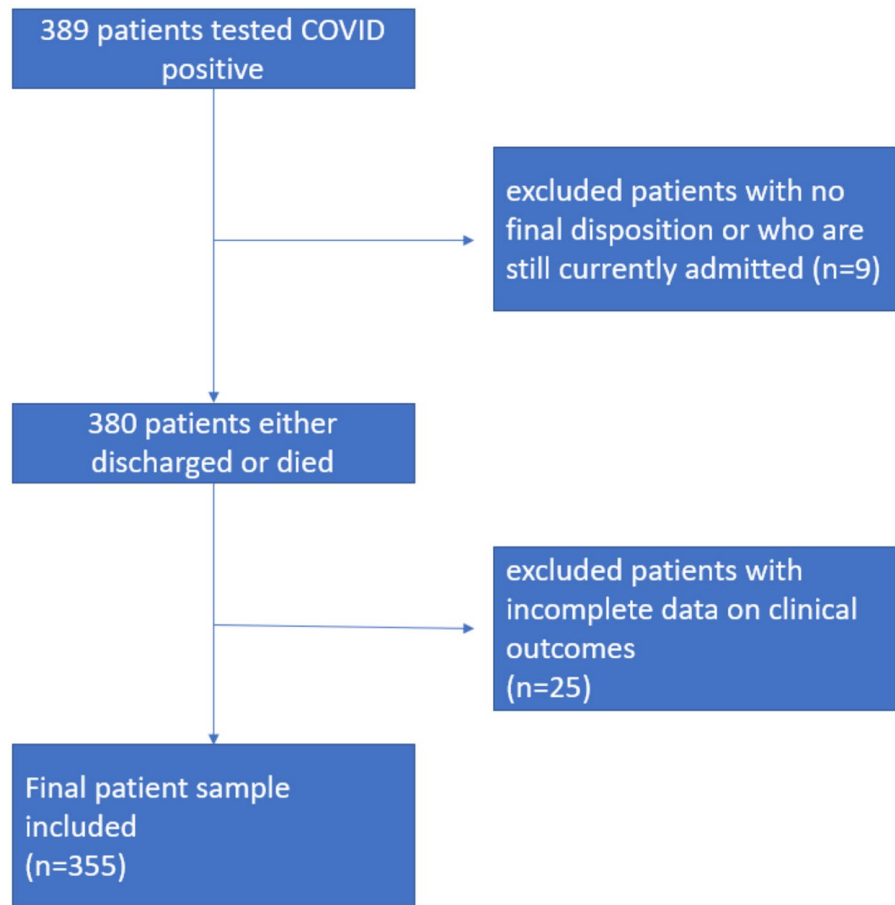
while atrial fibrillation (OR 0.102, 95% CI 0.011-0.942) and chronic kidney disease (CKD; OR 0.179, 95% CI 0.033-0.964) were associated with decreased odds (see Table 2).

3.3 | Biomarkers data

Patients with VTE had significantly higher peak C-reactive protein (CRP; 230 vs 154 mg/L, $P = 0.002$), lactate dehydrogenase (LDH; 496 vs 390 IU/L, $P = 0.004$), admission D-dimer (3220 vs 1690 ng/mL, $P = 0.045$) and peak D-dimer values (12510 vs 2785 ng/mL, $P < 0.0001$) compared to patients without VTE. Peak D-dimer level was a good predictor of VTE (AUC 0.806, 95% CI 0.751-0.854, $P < 0.0001$; see Figure 2) while admission D-dimer level was a poor predictor (AUC 0.625). A serum D-dimer cutoff > 6640 ng/mL was calculated to have a 77% sensitivity, 78% specificity, positive likelihood ratio of 3.45, and negative likelihood ratio of 0.3 for VTE detection.

4 | DISCUSSION

A wide range of VTE incidence has been reported in studies of hospitalized COVID-19 patients.[5–6] Our VTE incidence

of 8.5% was more than double that of a similarly sized New York study with a 3.3% VTE incidence.[5] Our mortality rate was 22.5% while in the New York study it was 10.2%. Despite similar sample sizes, these disparities may be partially due to differences in the racial composition of the samples. Our sample was 71% Black while the New York sample was more heterogenous (ie, 37.4% White, 12.5% Black, 17.0% Asian, 33.1% other). Other studies have reported Black patients accounting for 70% of COVID-19 deaths in Chicago and 40% of COVID-19 deaths in Michigan, while only comprising 30% and 14%, respectively, of those populations.[8] If VTE incidence is a surrogate for poorer outcomes in COVID-19 patients, these statistics suggest that the higher VTE incidence rate seen in our study may be due to the relatively high proportion of Black patients in our sample. The further epidemiologic investigation is required to explain the apparent racial differences in outcomes in COVID-19 patients, though disproportionately higher rates of chronic medical conditions and healthcare disparities in Blacks patients may play a role.

Unregulated inflammation is central to the pathogenesis of hypercoagulability seen in critical illness and sepsis.[9] This occurs via pathways involving immune system dysfunction and cytokine overproduction that promote the activation of prothrombotic mediators. Our observation of significantly higher peak CRP, LDH, admission D-dimer,

TABLE 1 Demographic and clinical characteristics of COVID-19 patients with and without venous thromboembolism (VTE)

Characteristics	With VTE (n=30)	Without VTE (n=325)	P-value
Age (mean ± SD)	70.13 ± 11.52	65.85 ± 14.39	0.114
Female, n (%)	16 (53)	158 (49)	0.704
BMI (mean ± SD)	29.79 ± 6.82	29.71 ± 9.30	0.961
Ethnicity, n (%)			0.475
Black	22 (73)	231 (71)	
White	1 (3)	26 (8)	
Hispanic	2 (7)	36 (11)	
Other	5 (17)	32 (10)	
Comorbidities, n (%)			
COPD	1 (3)	44 (14)	0.150
Asthma	1 (3)	26 (8)	0.715
Obstructive sleep apnea	4 (13)	21 (7)	0.149
Heart failure	4 (13)	56 (17)	0.799
Atrial fibrillation	1 (3)	38 (12)	0.227
Liver cirrhosis	0 (0)	10 (3)	1.000
Diabetes	13 (43)	153 (47)	0.708
Chronic kidney disease	3 (10)	62 (19)	0.323
End stage renal disease on dialysis	3 (10)	38 (12)	1.000
HIV	0 (0)	7 (2)	1.000
Coronary artery disease	4 (13)	73 (23)	0.354
Hypertension	24 (80)	248 (76)	0.822
Lab parameters on admission (median IQR)			
FiO_2% requirement	34 (27-65)	28 (21-36)	0.027
Ferritin	1028 (523-2301)	807 (326-1792)	0.166
Ferritin peak	1730 (879-4792)	1186 (391-3219)	0.069
D-dimer	3220 (883-10725)	1690 (975-3073)	0.045
D-dimer peak	12510 (6135-25000)	2785 (1378-6308)	<0.0001
CRP	166 (86-302)	125 (53-208)	0.091
CRP peak	230 (140-326)	154 (75-233)	0.002
Procalcitonin	0.34 (0.13-2.89)	0.22 (0.09-0.91)	0.068
Procalcitonin peak	0.40 (0.16-7.31)	0.32 (0.10-1.44)	0.051
LDH	496 (404-645)	390 (282-530)	0.004
LDH peak	703 (594-866)	499 (346-667)	<0.0001
Troponin	0.05 (0.02-0.18)	0.03 (0.01-0.10)	0.117
BNP	38 (10-161)	72 (14-528)	0.231
COVID-19 treatment, n (%)			
Hydroxychloroquine	22 (73)	194 (60)	0.173
Steroids	20 (67)	83 (26)	<0.0001
Tocilizumab	12 (40)	31 (10)	<0.0001
Pharmacologic VTE prophylaxis	30 (100)	270 (83)	0.007
Home medications, n (%)			
Warfarin	3 (10)	1 (0.3)	0.002
Heparin/LMWH	0 (0)	13 (4)	0.613

(Continues)

T A B L E 1 (Continued)

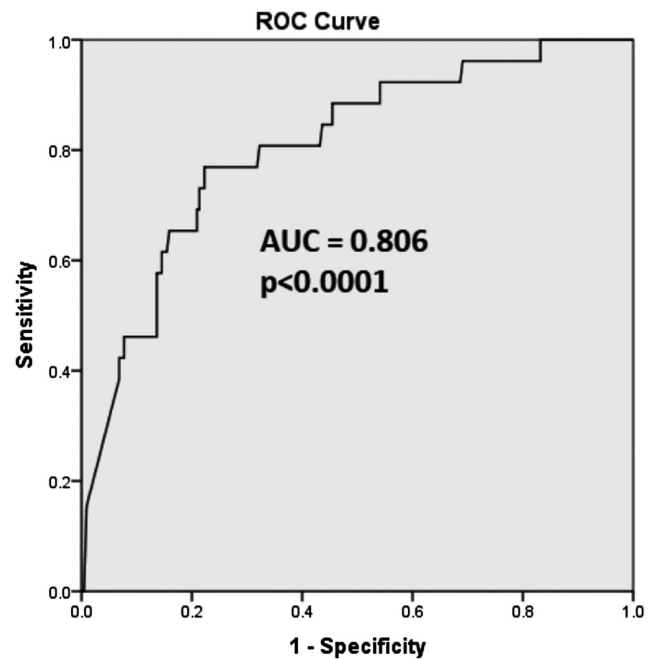| Characteristics	With VTE (n=30)	Without VTE (n=325)	P-value
Antiplatelets	8 (27)	134 (41)	0.172
Clinical outcomes, n (%)			
Inpatient death	12 (40)	68 (21)	0.023
Need for CRRT/HD	8 (27)	48 (15)	0.112
Need for vasopressors	12 (40)	69 (21)	0.038
Need for intubation	15 (50)	74 (23)	0.0

Abbreviations: BMI, body mass index (kg/m^2); BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; HD, hemodialysis; IQR, inter-quartile range; LDH, lactate dehydrogenase; LMWH, low molecular weight heparin.

T A B L E 2 Multivariable logistic regression analysis showing factors associated with venous thromboembolism in patients with COVID-19

Characteristics	Odds ratio (95% CI)	P-value
Age	1.042 (1.004-1.082)	0.029
Male	Referent	
Female	1.181 (0.500-2.790)	0.704
BMI	1.002 (0.950-1.057)	0.938
Black	Referent	
White	0.726 (0.080-6.587)	0.776
Hispanic	0.702 (0.135-3.661)	0.674
Others	2.244 (0.678-7.429)	0.186
Diabetes	1.033 (0.427-2.499)	0.942
Coronary artery disease	0.428 (0.115-1.595)	0.206
Heart failure	1.033 (0.275-3.884)	0.962
Hypertension	0.803 (0.268-2.406)	0.695
COPD	0.150 (0.018-1.237)	0.078
Atrial fibrillation	0.102 (0.011-0.942)	0.044
Obstructive sleep apnea	5.107 (1.141-22.859)	0.033
Asthma	0.417 (0.048-3.590)	0.426
Chronic kidney disease	0.179 (0.033-0.964)	0.045
Need for intubation	3.796 (1.602-8.996)	0.002

Abbreviations: BMI, body mass index (kg/m^2); COPD: chronic obstructive pulmonary disease.

F I G U R E 2 Receiver-operating characteristic (ROC) analysis of the accuracy of peak serum D-dimer level for diagnosis of venous thromboembolism (VTE). AUC of 0.806 (95% CI 0.751-0.854, $P < 0.0001$) corresponds to good accuracy (defined as AUC of 0.8–0.9) for predicting VTE

and peak D-dimer levels in patients with VTE is consistent with this. We also observed that VTE was associated with significantly higher usage of corticosteroids, tocilizumab, and vasopressors, in addition to a greater need for intubation and higher mortality rates. Cumulatively, these findings suggest that a more robust inflammatory state in the serum of COVID-19 patients contributes to higher VTE incidence and that COVID-19 patients who develop VTE have more advanced disease states, require more aggressive medical therapy, and have poorer outcomes compared to those without VTE.

There were no significant differences in age, gender, ethnicity, BMI, or pre-existing medical comorbidities (see Table 1) when comparing COVID-19 patients who did and did not develop VTE. This suggests that the baseline pre-hospitalization characteristics of the two groups did not have an appreciable effect on the development of VTE. However, multivariable regression analysis conducted on the patients who developed VTE identified several characteristics (ie, age, OSA, and need for intubation) that were significantly associated with VTE (see Table 2). A significant association between increasing age and VTE is not unexpected as age is a known risk factor for VTE in the general population; this is attributed to a direct relationship between increasing age and increased coagulation activity, decreased fibrinolysis,

and increasing likelihood of comorbid conditions that confer their own increased risk of VTE.[10] Rationalizing the association between OSA and VTE in COVID-19 is less straightforward. A 2012 study from Taiwan of over 10 000 patients observed a 3-fold increase in VTE incidence among patients with OSA independent of other comorbidities.[11] A proposed explanation for this finding is that a hypercoagulable state exists in OSA patients due to chronic, intermittent hypoxia driving the production of reactive oxygen species and other prothrombotic mediators. The connection between VTE and the need for intubation in COVID-19 patients is at least partially explained by the sedation and immobilization inherent with intubation. Interestingly, atrial fibrillation was associated with decreased VTE risk after multivariable regression analysis; however, only one patient who developed VTE had known atrial fibrillation at baseline so it is difficult to infer any significance from this finding.

A key finding was that peak D-dimer level, as opposed to the level at the time of admission, was associated with significantly more VTE ($P < 0.0001$ vs. 0.045). Because low D-dimer level on admission does not rule out the possibility of developing VTE, this finding suggests that COVID-19 progression plays a larger role in VTE incidence than the initial disease status. Furthermore, this suggests that there is value in trending D-dimer levels throughout the hospital stay, particularly in patients with a worsening clinical condition. A caveat to this finding is that elevated D-dimer level is not highly specific for VTE and can be seen in other systemic inflammatory conditions, including disseminated intravascular coagulation, myocardial infarction, and sepsis, among others.[12]

In concordance with this finding, our analysis demonstrated that peak D-dimer level was a good predictor of VTE, while admission D-dimer was a poor predictor. We calculated an optimal D-dimer cutoff of > 6640 ng/mL for VTE detection. There are multiple possible reasons for such a high cutoff. First, the upper limit of normal for our laboratory's D-dimer assay is 490 ng/mL, so adopting a higher cutoff to predict VTE in COVID-19 patients is reasonable given the relatively low specificity of D-dimer for VTE. In addition, a higher D-dimer cutoff is necessary given the massive amounts of background inflammation in the serum of patients hospitalized with COVID-19. Furthermore, there is data to suggest that patients who are older and/or Black have higher D-dimer levels at baseline[13], which is consistent with our sample containing predominantly Black and older patients.

Limitations of our study include the fact that our patient sample was predominantly Black, which might restrict the generalizability of our results to other patient populations. The sample size used in our analysis (final n = 355) might have been too small to generalize our findings to larger patient populations. Our laboratory uses a serum D-dimer assay with an upper limit of 25 000 ng/mL, which might have

influenced the results because some patients could have had even higher D-dimer levels. The relatively low VTE event rate might have underestimated the predictive value of D-dimer. Lower extremity venous Dopplers and CT scans were not routinely performed unless clinically indicated, which might have underestimated the VTE incidence. Our analysis of D-dimer levels did not involve stratification based on COVID-19 severity, so the cutoff we calculated might not apply to patients who were less sick; less sick patients might have had even lower D-dimer cutoffs.

In conclusion, COVID-19 patients with VTE had higher mortality rates and need for vasopressors and intubation compared to patients without VTE. Age, OSA, and need for intubation were associated with a significantly increased VTE incidence. Peak, but not admission, D-dimer level was a good predictor of VTE in COVID-19 patients. Further research is needed to establish a consensus for using serum D-dimer level to predict VTE in COVID-19 patients as well as to optimize an ideal VTE prophylaxis regimen in this patient population.

CONFLICTS OF INTEREST

None of the authors has any conflicts of interest to disclose.

DISCLOSURE STATEMENT

There was no monetary or material support for this research investigation.

AUTHOR CONTRIBUTIONS

Wrote the manuscript, analyzed data, primary research/study designer: Drew H. Barnes; *Analyzed data, primary research/study designer*: Kevin Bryan Lo; *Collected data*: Ruchika Bhargav, Fahad Gul, Eric Peterson, Grace Salacup, Jerald Pelayo, Jeri Albano. *Offered guidance on study design and manuscript*: Zurab Azmaiparashvili, Janani Rangaswami, Gabriel Patarroyo-Aponte; *Primary research/study designer*: Andres Mora Carpio.

ETHICS STATEMENT

This material is the authors' own original work, which has not been previously published elsewhere.

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