COVID-19–associated venous thromboembolism portends worse survival ☆,☆☆,★

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ABSTRACT

Patients with coronavirus disease 2019 (COVID-19) seem to be at high risk for venous thromboembolism (VTE) development, but there is a paucity of data exploring both the natural history of COVID-19–associated VTE and the risk for poor outcomes after VTE development. This investigation aims to explore the relationship between COVID-19–associated VTE development and mortality. A prospectively maintained registry of patients older than 18 years admitted for COVID-19–related illnesses within an academic health care network between March and September 2020 was reviewed. Codes from the tenth revision of the International Classification of Diseases for VTE were collected. The charts of those patients with a code for VTE were manually reviewed to confirm VTE diagnosis. There were 2,552 patients admitted with COVID-19–related illnesses. One hundred and twenty-six patients (4.9%) developed a VTE. A disproportionate percentage of patients of Black race developed a VTE (70.9% VTE v 57.8% non-VTE; $P = .012$). A higher proportion of patients with VTE expired during their index hospitalization (22.8% VTE v 8.4% non-VTE; $P < .001$). On multivariable logistic regression analysis, VTE was independently associated with mortality (odds ratio = 3.17; 95% confidence interval, 1.9–5.2; $P < .001$). Hispanic/Latinx ethnicity was associated with decreased mortality (odds ratio = 0.45; 95% confidence interval, 0.21–1.00; $P = .049$). Hospitalized patients of Black race with COVID-19 were more prone to VTE development, and patients with COVID-19 who developed in-hospital VTE had roughly nearly threefold higher odds of mortality. Further emphasis should be placed on optimizing COVID-19 anticoagulation protocols to reduce mortality in this high-risk cohort.

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1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), emerged in December 2019 and quickly developed into a pandemic. Disease severity can range from asymptomatic clinical presentations to multi-organ system failure and death. As investigators study this complex virus, certain
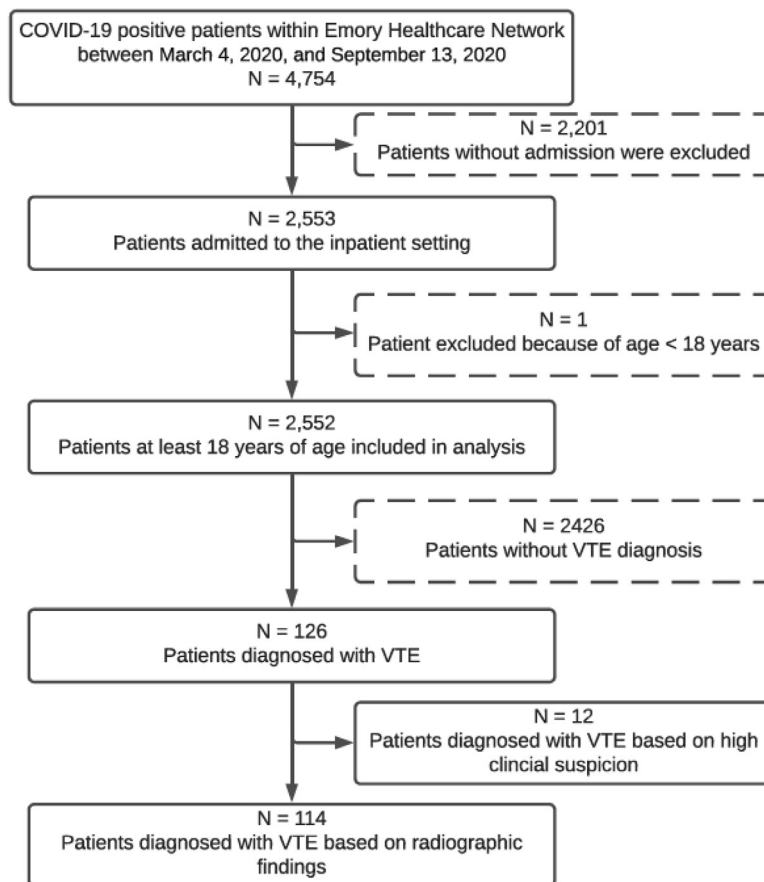
Fig. 1 – Flowchart illustrating delineation of venous thromboembolism (VTE) cohort. COVID-19, coronavirus disease 2019.

characteristics of COVID-19 infection appear to place patients at higher risk for complications and death.

One aspect of COVID-19 that has garnered increased attention is its associated hypercoagulable state; many investigators have reported higher than expected rates of arterial and venous thromboembolic events (VTEs) [1–4]. Because hospitalized patients with COVID-19 seem to be at high risk for VTEs, various health care institutions supported early anticoagulation strategies in hospitalized patients, albeit with sparse data to guide these protocols [5–8].

There is a paucity of published data regarding both the natural history of COVID-19–associated VTEs and the risk for poor outcomes with VTE development. Our primary goal was to estimate the incidence of VTEs in our large academic health care network. In addition, we aimed to explore the relationship between COVID-19–associated VTEs and mortality.

2. Methods

This study was approved by our institution's Institutional Review Board (IRB 00000601). All patients older than 18 years who were admitted to one of four hospitals within our large academic health care network between March 4, 2020 and September 13, 2020 for COVID-19–related illnesses were identified from a prospectively maintained database within the institution's Corporate Data Warehouse. This administrative database houses demographic patient information that was used for analysis, including but not limited to age, birth sex, race, ethnicity, insurance status, high-risk comorbidities as identified by the Centers for Disease Control and Prevention, hospital length of stay, and in-hospital mortality. Codes from the tenth revision of the International Classification of Diseases (ICD-10) were used to capture incident VTE development. Any patient requiring care within an intensive care unit (ICU) during any part of their hospital stay were included in the ICU cohort. Any patient not treated within an ICU during their hospital stay were included in the ward cohort. Vulnerable populations, including prisoners, pregnant women, and minors, were excluded from the study.

While reviewing the initial dataset, it was noted that the use of ICD-10 codes for VTE provided many false positives for in-hospital VTE development. Therefore, to validate VTE events, we manually reviewed all COVID-19 admissions with a documented ICD-10 code for VTE to obtain a more accurate in-hospital VTE incidence. Patients were defined as having an in-hospital VTE based on the following criteria: radiographic findings confirming VTE diagnosis and documentation of high clinical suspicion for VTE per the physician of record. Although 114 (90.5%) of the 126 patients with VTE were diagnosed by radiographic findings, only 12 (9.5%) of 126 patients in the VTE cohort were diagnosed based on high clinical suspicion (Fig. 1). COVID-19 admissions within the study period with ICD-10 codes for VTE without either radiographic

evidence of, or high clinical suspicion for, VTE were included in the overall analysis within the non-VTE cohort.

Statistical analysis was completed using R programming (The R Project for Statistical Computing) and SAS (SAS Institute). Chi-square tests and analysis of variance tests were used to assess categorical variables and t-tests were used to analyze continuous variables. Logistic regression models were used to perform univariable and multivariable analyses for the outcomes of both development of VTE and mortality.

3. Results

Between March 4, 2020 and September 13, 2020, there were 2,552 patients admitted with a COVID-19–related illness to one of four hospitals within an academic health care network. One hundred and twenty-six patients (4.9%) were diagnosed with a VTE during their index hospital stay. Although roughly one-third of all COVID-19 admissions required at least a portion of their care in an ICU, 70 (55.6%) of the 126 patients in the VTE cohort were treated in an ICU. The median age of patients in the VTE cohort was not significantly different from the median age of patients in the non-VTE cohort (60.4 years VTE v 58.4 years non-VTE; $P = .214$). Female sex at birth comprised just over half of both the VTE and non-VTE cohorts (50.4% VTE v 50.1% non-VTE; $P = 1.0$). Of note, although patient ethnicity was not statistically significantly different between the cohorts, patients who developed a VTE were more often of Black race (70.9% VTE v 57.8% non-VTE; $P = .012$). There was no significant difference in insurance status/type between the two cohorts: Medicare (40.3% VTE v 43.4% non-VTE), Medicaid (5.5% VTE v 4.7% non-VTE), private insurance (39.1% VTE v 38.6% non-VTE), and uninsured/self-pay (12.7% VTE v 11.8% non-VTE) status (Table 1).

The profiles of comorbidities of the two cohorts were largely similar. VTE occurrence was found to be associated with a history of neurocognitive disorder (33.1% VTE v 24.7% non-VTE; $P = .043$) and congestive heart failure (37.8% VTE v 25.2% non-VTE; $P = .002$). Of note, cancer (12.0% VTE v 13.4% non-VTE; $P = .754$), cerebrovascular disease (16.8% VTE v 22.0% non-VTE; $P = .161$), and tobacco use (29.8% VTE v 29.1% non-VTE; $P = .957$) were not associated with VTE development (Table 1). ABO blood type was not appreciably different between patients who developed a VTE and those who did not.

Although hospital length of stay did not differ for patients who required ICU care (12.0 days VTE v 9.9 days non-VTE; $P = .118$), patients who developed a VTE had overall longer hospital stays (13.8 days VTE v 8.8 days non-VTE; $P < .001$). Patient discharge disposition, which included acute care transfer, post-acute care transfer, home, home with home health care, discharge against medical advice, hospice, and death, was also significantly different, although largely driven by patient mortality (Table 1).

Patients in the VTE cohort had higher mean C-reactive protein levels (125.7 VTE v 88.9 non-VTE; $P < .001$). Patients with VTE had higher mean partial thromboplastin times (61.1 VTE v 38.5 non-VTE; $P < .001$) and higher mean international normalized ratio (INR) levels (1.4 VTE v 1.3 non-VTE; $P = .001$). Patients who developed a VTE had statistically significantly higher mean D-dimer levels (9,184.9 VTE v 2,812.9 non-VTE;

$P < .001$). There were no significant differences in maximum creatinine (2.2 VTE v 2.6 non-VTE; $P = .166$), maximum fibrinogen (614.2 VTE v 644.1; $P = .204$), and maximum platelet (339.0 v 359.2; $P = .128$) levels between the two cohorts.

A univariable analysis was completed to determine risk factors associated with VTE development. This demonstrated that Black race (odds ratio [OR], 1.63; 95% confidence interval (CI), 1.03–2.58; $P = .023$), congestive heart failure (OR, 1.82; 95% CI, 1.26–2.64; $P < .001$), and ICU status (OR, 2.68; 95% CI, 1.87–3.85; $P < .001$) were each associated with VTE development. Multivariable logistic regression analysis with VTE development as the outcome of interest was completed using backward elimination method with significance evaluated at the 0.2 alpha level. ICU status (adjusted odds ratio [aOR], 2.57; 95% CI, 1.77–3.73; $P < .001$) and history of congestive heart failure (aOR, 1.65; 95% CI, 1.09 to 2.51; $P < .18$) were both independently associated with VTE development (Table 2).

To evaluate the impact of COVID-19–associated VTE development on mortality, we performed further analyses with mortality as the outcome of interest. A higher proportion of patients with VTE died during their index hospitalization (22.8% VTE v 8.4% non-VTE; $P < .001$). Univariable analysis demonstrated that non-Hispanic/non-Latinx ethnicity (85.0% expired v 78.1% alive; $P = .004$), median patient age (70.9 years expired v 56.9 years alive; $P < .001$), ICU status (82.9% of expired patients in ICU v 17.1% of expired patients on the ward; $P < .001$), and VTE development (13.0% expired v 3.9% alive; $P < .001$) were all associated with mortality. On multivariable logistic regression, older age (aOR 1.05; 95% CI, 1.04–1.07; $P < .001$), VTE development (aOR, 3.17; 95% CI, 1.93–5.21; $P < .001$), and ICU status (aOR, 12.41; 95% CI, 8.76–17.56; $P < .001$) were all independently associated with mortality (Table 3). Of note, Hispanic/Latinx ethnicity (OR, 0.45; 95% CI, 0.21–1.00; $P = .049$) was associated with decreased odds of mortality (Fig. 2).

4. Discussion

Current studies report higher than anticipated rates of VTE development in patients with COVID-19. Before the COVID-19 pandemic, VTE rates for critically ill patients ranged from 5% to 15% [9–11]. For those patients with COVID-19 requiring ICU admission, early publications reported VTE rates ranging from 20% to 69% [3–4,12–14]. To date, VTE development among ward patients with COVID-19 has not been well characterized [15]. In addition, a paucity of data exists regarding the risk factors for increased VTE development in patients with COVID-19.

To address the emerging documentation of increased VTE rates secondary to COVID-19, institutions globally began implementing aggressive anticoagulation protocols in hospitalized patients with COVID-19. Several clinical trials have explored the efficacy and safety of low- and full-dose anticoagulation in patients with COVID-19. For example, a national observational cohort study of veterans with COVID-19 demonstrated that early implementation of prophylactic anticoagulation resulted in reduced 30-day mortality rates [16]. In addition, multiple international trials were conducted to compare the outcomes of patients with COVID-19 on low-dose versus full-dose anticoagulation; these studies include the Accelerating COVID-19 Therapeutic Interventions and

Table 1 – Characteristics of all COVID-19 admissions, as delineated by venous thromboembolism status.			
Admitted patients with COVID-19 (n = 2,552)	Without VTE (n = 2,426)	With VTE (n = 126)	P value
Demographics			
Age, y, mean (SD)	58.4 (17.5)	60.4 (16.8)	.216
Male sex at birth, n (%)	1211 (49.9)	63 (49.6)	1.000
Race, n (%)			.012
Black	1401 (57.8)	90 (70.9)	
White	607 (25.0)	24 (18.9)	
Other	417 (17.2)	13 (10.2)	
Ethnicity, n (%)			.313
Hispanic/Latinx	246 (10.1)	12 (9.4)	
Non-Hispanic	1906 (78.6)	106 (83.5)	
Not reported	273 (11.3)	9 (7.1)	
Insurance status, n (%)			.930
Medicaid	134 (5.5)	6 (4.7)	
Medicare	977 (40.3)	55 (43.3)	
Private	948 (39.1)	49 (38.6)	
Uninsured/self-pay	307 (12.7)	15 (11.8)	
Not reported	59 (2.4)	2 (1.6)	
Comorbidities, n (%)			
History of VTE	12 (0.5)	4 (3.1)	.177
Hypertension	1,723 (71.1)	96 (75.6)	.317
Hyperlipidemia	1,159 (47.8)	56 (44.1)	.470
Type 1 diabetes mellitus	114 (4.7)	6 (4.7)	1.000
Type 2 diabetes mellitus	1,065 (43.9)	57 (44.9)	.903
Chronic kidney disease	667 (27.5)	35 (27.6)	1.000
Cerebrovascular disease	408 (16.8)	28 (22.0)	.161
Neurocognitive disorder	598 (24.7)	42 (33.1)	.043
Obesity (body mass index >30)	798 (32.9)	45 (35.4)	.622
Coronary artery disease	645 (26.6)	37 (29.1)	.598
Congestive heart failure	612 (25.2)	48 (37.8)	.002
Asthma	355 (14.6)	16 (12.6)	.612
Chronic obstructive pulmonary disease	229 (9.4)	12 (9.4)	1.000
Obstructive sleep apnea	312 (12.9)	24 (18.9)	.068
Tobacco use	722 (29.8)	37 (29.1)	.957
Cancer	292 (12.0)	17 (13.4)	.754
Liver disease	376 (15.5)	23 (18.1)	.508
Hospital factors			
Hospital length of stay, d, mean (SD)	8.8 (9.6)	13.8 (14.81)	< .001
In-hospital mortality, n (%)	203 (8.4)	29 (22.8)	< .001
Discharge disposition, n (%)			< .001
Acute care transfer	3 (0.1)	0 (0.0)	
Against medical advice	28 (1.2)	0 (0.0)	
Expired	214 (8.8)	33 (26.0)	
Home	1,544 (63.7)	56 (44.1)	
Home with home health care	318 (13.1)	18 (14.2)	
Hospice	46 (1.9)	4 (3.1)	
Post-acute care transfer	272 (11.2)	16 (12.6)	
Abbreviations: COVID-19, coronavirus disease; SD, standard deviation; VTE, venous thromboembolism.			

Vaccines-4 (ACTIV-4) trial; Randomized, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP); and Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTAC) trial. All of the aforementioned trials were stopped early in COVID-19 ICU patients because of concern for potential harm of anti-coagulation in this population. However, in non-ICU patients, findings suggest that full-dose anticoagulation can improve patient outcomes, such as a decreased need for end-organ support, including mechanical ventilation [17]. Although several of the early studies evaluating VTE in this patient population analyzed the impact of heparin use on mortality,

few studies have explored the relationship between VTE and mortality itself [18–21]. Clearly defining such a relationship could alter decision-making paradigms in the management of this high-risk patient population.

In our multicenter academic health care network, 2,552 patients were admitted with COVID-19 during a 8-month period. One hundred and twenty-six of these 2,552 patients, roughly 1 in every 20, were diagnosed with a VTE. Although ICD-10 codes were used for data abstraction to define those who had VTE during their index COVID-19 hospital encounter, manual chart review was completed to confirm the VTE di-agnosis. Roughly 67% of these 2,552 patients did not require

Table 2 – Variables associated with in-hospital venous thromboembolism development in COVID-19 admissions.

Covariate	cOR (95% CI)	cOR P value	aOR (95% CI)	aOR P value
Demographics				
Sex at birth				
Female	1.03 (0.72–1.47)	.876	—	—
Male	—	—	—	—
Race			—	—
Black	1.63 (1.03–2.58)	.038	1.54 (0.97–2.46)	.068
Other	0.56 (0.13–2.39)	.431	0.52 (0.12–2.24)	.376
Unknown	0.77 (0.36–1.63)	.497	0.76 (0.52–1.12)	.477
White	—	—	—	—
Ethnicity				
Hispanic/Latinx	0.80 (0.42–1.51)	.493	—	—
Unknown	0.56 (0.13–2.39)	.139	—	—
Non-Hispanic/non-Latinx	—	—	—	—
Insurance				
Medicaid	0.98 (0.41–2.30)	.956	—	—
Private insurance	1.06 (0.67–1.67)	.800	—	—
Uninsured/self-pay	1.06 (0.36–3.12)	.920	—	—
Medicare	—	—	—	—
Comorbidities				
Hypertension	1.25 (0.82–1.89)	.296	—	—
Hyperlipidemia	0.85 (0.59–1.21)	.362	0.76 (0.52–1.52)	.170
Type 2 diabetes mellitus	1.06 (0.74–1.51)	.768	—	—
Chronic kidney disease	1.06 (0.71–1.57)	.784	0.74 (0.47–1.16)	.186
Congestive heart failure	1.82 (1.26–2.64)	.001	1.65 (1.09–2.51)	.018
Cancer	1.06 (0.62–1.81)	.835	—	—
Tobacco abuse	0.98 (0.66–1.45)	.925	—	—
Hospital factors				
ICU status	2.68 (1.87–3.85)	<.001	2.57 (1.77–3.73)	<.001

Abbreviations: aOR, adjusted odds ratio; cOR, crude odds ratio; COVID-19, coronavirus disease; ICU, intensive care unit.

Table 3 – Predictors of mortality after COVID-19 admission.

Covariate	Adjusted odds ratio (95% CI)	P value
Demographics		
Age	1.05 (1.04–1.07)	< .001
Race		
UnknownOtherBlackWhite	1.91 (0.96–3.80)1.05 (0.48–2.31)0.82 (0.58–1.17)—	.282.907.282—
Ethnicity		
UnknownHispanic/LatinxNon-Hispanic/Non-Latinx	1.20 (0.66–2.17)0.45 (0.21–1.00)—	.545.049—
Insurance		
Uninsured/self-payPrivate insuranceMedicaidMedicare	0.76 (0.25–2.32)0.66 (0.47–0.93)1.01 (0.45–2.24)—	.626.017.983—
Comorbidities		
Hyperlipidemia	0.68 (0.49–0.94)	.019
Type 1 diabetes mellitus	1.57 (0.82–3.00)	.175
Chronic kidney disease	1.63 (1.19–2.25)	.003
Cerebrovascular disease	1.66 (1.17–2.35)	.004
Neurocognitive disorder	1.24 (0.90–1.72)	.188
Liver disease	1.92 (1.36–2.73)	< .001
Hospital factors		
Intensive care unit status	12.41 (8.76–17.56)	< .001
Venous thromboembolism	3.17 (1.93–5.21)	< .001

ICU level of care ("ward cohort"). Although a disproportionate percentage of patients in the VTE cohort were Black (70.9%) compared with the non-VTE cohort (57.8%), there were no statistically significant differences in median age, sex at birth, or ethnicity between the VTE and non-VTE cohorts. Patients in the VTE cohort had higher mean D-dimer (9,184.9 v 2,812.9) and C-reactive protein (125.7 v 88.9) levels. Those who developed VTE during their index COVID-19 hospital encounter also stayed in the hospital on average 5 days longer than those who did not develop VTE. Patients in the VTE cohort had significantly higher mortality rates, with an absolute difference in mortality of 14.4%. On multivariable
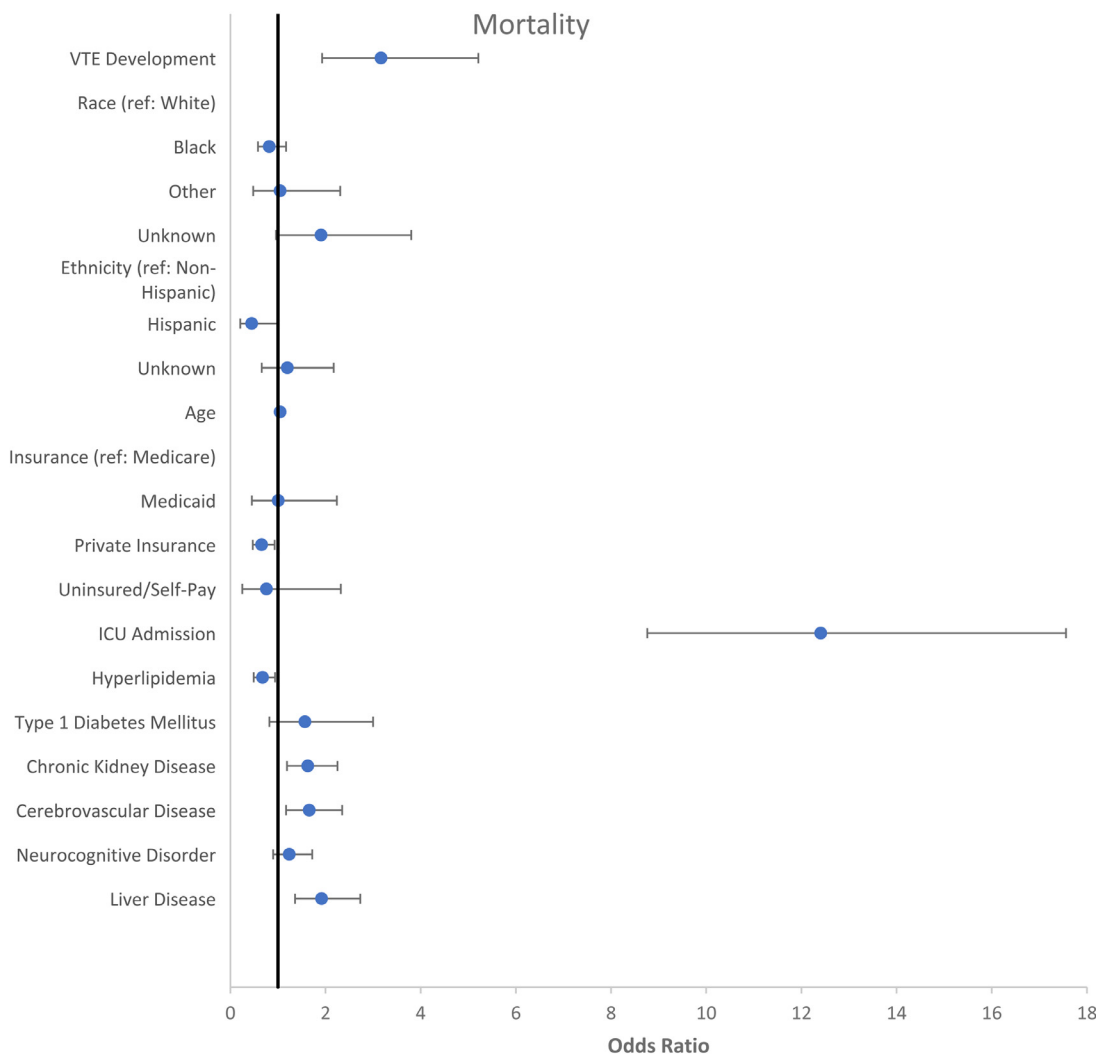
Fig. 2 – Forest plot demonstrating risk factors associated with mortality on multivariable analysis. ICU, intensive care unit; VTE, venous thromboembolism.

analysis, VTE was found to be independently associated with mortality, with an adjusted odds ratio of 3.17.

In reviewing our experience, we noted three things. First, our in-hospital COVID-19 VTE rate (4.9%) was comparable with or lower than that in other centers [10–13]. Our institution employed tiered anticoagulation protocols shortly after the first known COVID-19 hospitalizations in our state and this may account, in part, for our low COVID-19–associated VTE incidence rates. Second, our COVID-19–related death rates are lower than those reported in many of the large reviews [22,23]. These lower mortality rates are also reflected in published data from our institution's critical care team, who postulated that the delayed inception and peak of COVID-19 cases in our state may have allowed our institution to establish more consensus-driven clinical protocols before the influx of admissions [24]. Third, despite these lower mortality rates within our institution, we found that VTE development was independently associated with mortality. This finding suggests a need for targeted anticoagulation strategies for high-risk patients in this population.

Historically, based on large population studies, patients who develop VTE have a 30-day mortality rate of 3.0%, far exceeding the 30-day mortality rate for patients who do not develop a VTE (0.4%) [25]. Clearly, VTE complicates other pre-existing comorbidities and puts patients at increased risk for mortality. In our cohort, patients with COVID-19 who developed a VTE had an in-hospital mortality rate of 22.8%, compared with an in-hospital mortality rate of 8.4% for patients with COVID-19 who did not develop a VTE. Even in an at-risk population with evidence of increased hypercoagulability, VTE drastically alters mortality rates, stressing the importance of prophylaxis, early diagnosis, and rapid treatment.

Although there is the potential for bleeding complications with anticoagulation, studies have demonstrated that therapeutic anticoagulation is achievable in COVID-19 patients with low bleeding rates [20,26]. Of the 126 patients with COVID-19 who developed VTE in our health care network, 5 had documented bleeding complications. Four of these patients were able to resume anticoagulation before discharge. Two additional patients exhibited symptomatology similar to

disseminated intravascular coagulation; these presentations were attributed to COVID-19 coagulopathy rather than to anticoagulation therapy. Considering the high rate of mortality in patients with COVID-19 who develop VTE, early anticoagulation strategies in high-risk patients may be lifesaving.

We found an independent association of ICU admission and prehospitalization history of congestive heart failure with VTE development. In our study, any patient requiring care within an ICU during their hospital stay were included in the ICU cohort. A temporal relationship cannot be established, as VTE development may have occurred at any point during a patient's hospitalization, and not all patients were admitted directly to the ICU on presentation to the hospital. Patients requiring ICU admission were inherently more sick; consequently, it is feasible that VTE development may have occurred as a sequela of their critical illness. However, it is also feasible that VTE development itself contributed to or represented a marker of clinically significant critical illness in the patient with COVID-19, considering the association between VTE occurrence and mortality in this COVID-19 cohort.

Our reported sample size allowed for a more comprehensive analysis of risk factors for VTE and mortality than a single-center review; however, a multi-institutional analysis is needed to confirm our findings. Also, our study is a retrospective chart review, which poses its own limitations, given variability in chart documentation. In addition, as is the current standard of care in our institution, routine surveillance for VTE was not performed. Our VTE rates may represent an underestimation of the overall incidence of VTE in this patient population. As mentioned, tiered anticoagulation protocols were implemented within the first month of COVID-19 hospitalizations in our state, which could have theoretically altered the normal pathophysiologic course of the virus and further underestimated the overall untreated incidence of VTE in patients with COVID-19. Well-known risk factors for VTE, such as history of malignancy, tobacco use, and cerebrovascular disease, were not associated with increased rates of VTE in our cohort. This may be due in part to the early and aggressive implementation of anticoagulation protocols in our institution.

In addition to VTE rates and the impact of VTE on mortality, our descriptive analysis also builds on other important findings published in the current literature. Early studies at the beginning of the pandemic showed increased rates of COVID-19 infection, hospitalization, and death among patients of Black race [27,28]. Our study found that Black patients appear to have disproportionately higher rates of incident VTE, as well. If Black patients with COVID-19 are more prone to VTE development, and if there is an independent association between VTE and COVID-19 mortality, further investigation should be aimed toward determining whether early anticoagulation strategies should be refined further to improve the management of high-risk subgroups who remain at disproportionately higher risk of negative sequelae or death with COVID-19 infection. Interestingly, although more patients of Black race developed VTE, Black race was not found to be independently associated with mortality when adjusting for other covariates of interest. Also of note, Hispanic/Latinx ethnicity was associated with decreased odds of mortality; however, the upper limit of the 95% CI was 1.00 (OR = 0.45; 95% CI, 0.21–1.00). Our study included only 258 patients who identified as His-

panic/Latinx, or 10.1% of the total study population. A larger sample size would improve our ability to discern whether there is in fact an association between Hispanic/Latinx ethnicity and improved survival in this COVID-19 cohort.

5.　　Conclusions

Patients of Black race who are diagnosed with COVID-19 are more prone to VTE development and patients with COVID-19 who develop VTE during their hospital stay have nearly three-fold increased odds of mortality. Further emphasis should be placed on understanding which patients with COVID-19 are at increased risk of VTE development and developing models for prophylactic and therapeutic anticoagulation protocols as an effort to reduce mortality in this high-risk cohort.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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