Prevalence and Predictors of Venous Thromboembolism or Mortality in Hospitalized COVID-19 Patients

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Abstract

Background We aimed to identify the prevalence and predictors of venous thromboembolism (VTE) or mortality in hospitalized coronavirus disease 2019 (COVID-19) patients.

Methods A retrospective cohort study of hospitalized adult patients admitted to an integrated health care network in the New York metropolitan region between March 1, 2020 and April 27, 2020. The final analysis included 9,407 patients with an overall VTE rate of 2.9% (2.4% in the medical ward and 4.9% in the intensive care unit [ICU]) and a VTE or mortality rate of 26.1%. Most patients received prophylactic-dose thromboprophylaxis. Multivariable analysis showed significantly reduced VTE or mortality with Black race, history of hypertension, angiotensin converting enzyme/angiotensin receptor blocker use, and initial prophylactic anticoagulation. It also showed significantly increased VTE or mortality with age 60 years or greater, Charlson Comorbidity Index (CCI) of 3 or greater, patients on Medicare, history of heart failure, history of cerebrovascular disease, body mass index greater than 35, steroid use, antirheumatologic medication use, hydroxychloroquine use, maximum D-dimer four times or greater than the upper limit of normal (ULN), ICU level of care, increasing creatinine, and decreasing platelet counts.

Conclusion In our large cohort of hospitalized COVID-19 patients, the overall in-hospital VTE rate was 2.9% (4.9% in the ICU) and a VTE or mortality rate of 26.1%. Key

Keywords
- COVID-19
- D-dimer
- hospitalized
- mortality
- venous thromboembolism

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predictors of VTE or mortality included advanced age, increasing CCI, history of cardiovascular disease, ICU level of care, and elevated maximum D-dimer with a cutoff at least four times the ULN. Use of prophylactic-dose anticoagulation but not treatment-dose anticoagulation was associated with reduced VTE or mortality.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic quickly led to high rates of morbidity and mortality globally, with reported rates of elevated thrombotic events, the majority of which represent venous thromboembolism (VTE).[1] Inpatient rates of VTE vary (1.7–46%),[1–3] with significant mortality presumed to be secondary to VTE.[2,3] These data are evidenced by postmortem studies showing classic macro-vessel disease and pulmonary microthrombi, suggesting in situ fatal pulmonary embolism (PE).[4,5]

Predictors of VTE in COVID-19 inpatients include D-dimer, sepsis-induced coagulopathy score, lymphocyte count, and prothrombin time; these are known from generally smaller cohorts.[6] A clear mechanism for the increased thrombosis rates has yet to be elucidated. Thus, optimal thromboprophylaxis strategies in high-risk COVID-19 inpatients remain unclear. While reduced VTE events and mortality have been noted with full-dose anticoagulation compared with the low-dose one,[3,7] more recent studies have found either no benefit between prophylactic and therapeutic anticoagulation or that in-hospital mortality was 2.3 times greater with preemptive treatment-dose anticoagulation from the time of hospital admission.[8,9]

With limited data in large populations of hospitalized COVID-19 patients to date, as well as conflicting data on predictors of VTE or mortality, we assessed the prevalence and predictors of VTE or mortality in hospitalized COVID-19 patients.

Methods

Study Design, Setting, and Population

This retrospective cohort study included adult patients with a diagnosis of COVID-19, aged 18 years and older, and hospitalized in one of 13 acute care hospitals across a multihospital integrated health care network in the New York metropolitan region between March 1, 2020 and April 27, 2020. Diagnosis was confirmed by a positive result on at least one polymerase chain reaction test during hospitalization. Patients were excluded if they were on the obstetrics service, or if an outcome of death or discharge had not been reached by April 30, 2020. Patients with a length of stay less than 8 hours were excluded as they did not meet the definition of inpatient stay. VTE events less than 8 hours were also excluded as those events were unlikely to be hospital-acquired. Patients were excluded if there was no baseline creatinine or platelet value, if baseline medications were not recorded, or if a Charlson Comorbidity Index (CCI) score could not be calculated. Transfers between in-system hospitals were considered as a single visit. For patients with multiple hospitalizations for COVID-19, only the first hospitalization was considered. Our system policy that went into effect on April 7, 2020 at the height of the pandemic recommended standard prophylactic-dose low-molecular-weight heparin (LMWH) for hospitalized COVID-19 patients with CrCl >15 mL/min and intermediate doses of LMWH for COVID-19 inpatients with a body mass index (BMI) >30. The study was performed with institutional review board approval and waiver of informed consent.

Data Source

Data were obtained from the enterprise inpatient electronic health record (Sunrise Clinical Manager, Allscripts, Chicago, Illinois, United States). Data and outcomes were tracked until April 30, 2020.

Outcomes

The primary outcome of interest was a composite of first VTE event or in-hospital death. The rationale for the combined primary outcome was that death is a competing endpoint for VTE, with a large proportion of inpatient deaths attributed to undiagnosed VTE.[5] Indeed, autopsy data in hospitalized patients with COVID-19 suggested that approximately 60% and up to 100% of thrombotic events including PE and pulmonary arterial thrombosis may not be suspected before death, indicating that thrombotic mechanisms play a major role in mortality.[4,5]

VTE event and date were defined by new acute deep venous thrombosis (DVT) or new appearance of PE. DVT was defined as deep vein incompressibility (where compression could be performed) or appearance of echogenic luminal material on color Doppler/duplex.[10] PE diagnosis was confirmed by filling defect on computed tomography pulmonary angiography. For all VTE imaging performed by the Department of Radiology, the presence or absence of VTE was prospectively entered as a discrete variable by the interpreting radiologist during the original clinical interpretation of the report beginning on April 7, 2020 or by manual consensus review of the radiology reports by two attending radiologists prior to April 7, 2020. For all point-of-care ultrasound imaging for DVT, two radiologists reviewed the extracted clinical notes documenting results. Only cases with a definitive diagnosis of DVT based on point-of-care ultrasound were recorded as positive.

Covariates

We collected data on patient demographics, comorbidities, home/hospital medications, baseline laboratory results, and intensive care unit (ICU) admission. All covariates were measured at baseline, except for in-hospital anticoagulation,

D-dimer levels, and ICU level of care. Baseline was defined as the interval from the start of hospital care until 48 hours postadmission. Start of hospital care was defined as the earliest event of registration, admission to the hospital, or admission to the ICU.

We used patient-reported race and ethnicity to categorize patients into one of five groups: White, Black, Asian, Other/Multiracial, and Unknown/Declined. We identified the following comorbidities by *International Statistical Classification of Disease and Related Health Problems, Tenth Revision (ICD-10)* coding: cancer, coronary artery disease (CAD), hypertension, asthma, chronic obstructive pulmonary disease (COPD), diabetes, chronic liver disease, peripheral arterial disease (PAD) or peripheral vascular disease (PVD), cerebrovascular disease, hyperlipidemia, end-stage renal disease (ESRD), or chronic kidney disease (CKD). We calculated the CCI as a measure of total comorbidity burden. Smoking history was categorized as active/former smoker, never smoker, or unknown smoker. BMI was categorized as less than or equal to 35, greater than 35, or unknown.

Baseline laboratory results included the first creatinine and platelet results within 48 hours of admission. Maximum D-dimer included the highest D-dimer during hospitalization for patients without VTE or highest D-dimer prior to VTE for patients with VTE. Maximum D-dimer was categorized as normal to less than 4 times the upper limit of normal (ULN), 4 to 6 times the ULN, >6 times the ULN, and unknown. The ULN for D-dimer was 239 ng/mL.

Inpatient medications included anticoagulants, antiplatelets, steroids, intravenous immunoglobulin (IVIG), biologics, rheumatologic anti-inflammatories, immunosuppressants, antivirals, angiotensin converting enzyme (ACE)/angiotensin receptor blockers (ARBs), azithromycin, hydroxychloroquine (HCQ), chloroquine, famotidine, statins, and antacids/antihistamines. Medications started within 48 hours of admission were considered baseline medications.

Home medications included anticoagulants and antiplatelets. Thromboprophylaxis was classified as none, treatment dose, or prophylaxis dose per ►**Supplementary Table S1** (available in the online version). We defined in-hospital thromboprophylaxis at treatment dose only if treatment-dose anticoagulation was started more than 24 hours prior to the endpoint (VTE/death vs. discharged alive or transferred). This definition excluded patients merely with high clinical suspicion for VTE (but no objective testing). We also conducted a sensitivity analysis that included treatment-dose anticoagulation irrespective of a time cutoff. For patients diagnosed with a VTE, the highest dose prior to the first diagnosed VTE was used in all analyses. For patients not diagnosed with a VTE, the highest anticoagulant dose prior to discharge (deceased or alive) was used.

A patient was considered to have been admitted to the ICU only if there was a recorded date/time of ICU level of care (defined as use of vasopressors, ventilation, or admission to a named ICU). ICU-attributable VTE had to occur at least 2 hours after start of ICU level care; VTE within 2 hours was considered attributable to non-ICU.

Data Analysis

For each categorical factor, the chi-square test was used to examine the association between that factor and the composite outcome of VTE or death. For each continuous factor, logistic regression was used to examine the association between that factor and VTE/death.

Factors that were significantly associated with VTE/death in the univariable analysis ($p < 0.10$), or specified a priori, were included in a multivariable logistic regression model to examine the joint effects of those factors on VTE/death. Factors specified for inclusion a priori were those that literature strongly associated with VTE, including cancer, heart failure, PVD/PAD, CVD, CKD or ESRD, antiplatelet medications (either at home or started within 48 hours of admission), home anticoagulants, in-hospital anticoagulants, age, and CCI. Backward elimination was then used to remove factors that did not contribute information to the model.

All analyses were performed with SAS version 9.4 (SAS institute, Cary, North Carolina).

Results

As shown in ►**Fig. 1**, in total 11,265 patients were considered. After 1,858 exclusions, 9,407 patients met the criteria. Of those, 63.8% were >60 years, 13.0% had BMI ≥35, 59.3% were males, 38.3% were white, and 21.2% were Hispanic (►**Table 1**). CCI ≥5 in 46.4% of patients, and Medicare was the most frequent insurance (47.3%). For past medical history, 7.7% of patients had cancer, 59.9% hypertension, 12.8% CAD, 8.2% heart failure, 4.0% PAD/PVD, 2.6% VTE, 5.9% cerebrovascular disease, 20.7% hyperlipidemia, 2.5% chronic liver disease, 8.4% asthma, 6.1% COPD, 36.1% diabetes, and 8.3% CKD/ESRD. Also, 7.4% of patients were on treatment-dose home anticoagulation compared with 2.9% on prophylactic dose and 65.5% with no home anticoagulation. Further, 29.8% of patients were on hospital or home antiplatelet therapy. ICU admission was recorded for 19.7% of patients. Also, 18.6% of patients were on treatment-dose hospital thromboprophylaxis compared with 71.0% prophylactic dose, and 10.4% with no initial hospital anticoagulant thromboprophylaxis. Finally, 76 patients (0.81%) received their first treatment dose anticoagulants within 24 hours of a VTE without initial objective testing.

VTE Rate

VTE was diagnosed in 274 (2.9%) patients. Of these, 170 (62.0%) had at least 1 DVT, 85 (31.0%) had at least 1 PE, and 19 (6.9%) had concurrent DVT and PE. ICU level of care was associated with a greater rate of VTE (4.9%; 91/1,854) than non-ICU (or unknown ICU timing) (2.4%; 183/7,553) ($p < 0.001$). The VTE rate was 3.3% in males compared with 2.3% in females ($p = 0.003$). The VTE rate varied significantly by maximum D-dimer ($p < 0.001$). A maximum D-dimer >6 times ULN was associated with a VTE rate of 9.3% (226/2,432) compared with 1.9% (10/522) for 4 to 6 times ULN and 0.4% (16/3,860) for 4 times the ULN.

Of the 274 patients who had at least one VTE, 28 (10.2%) did not receive any anticoagulation prior to diagnosis, 180

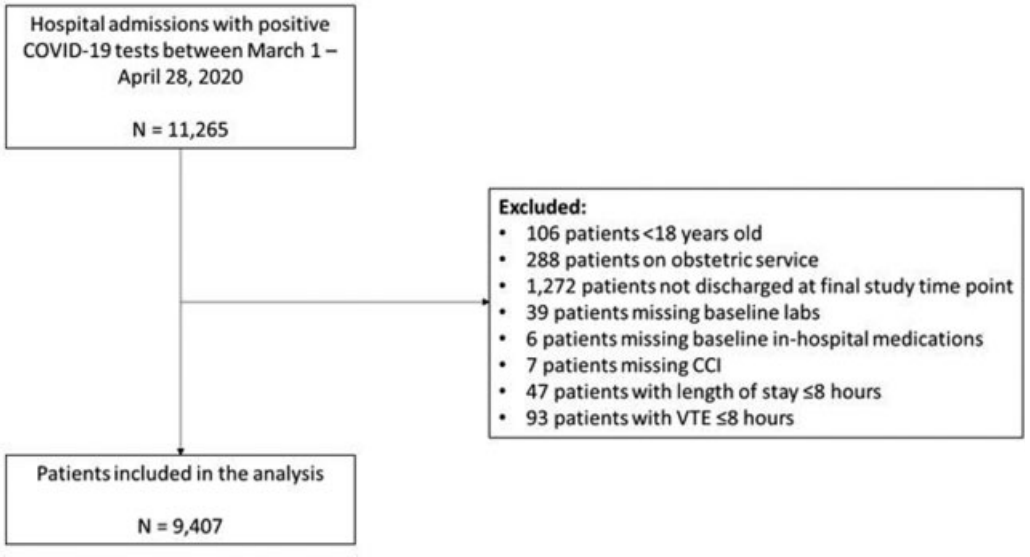

Fig. 1 Patient population. CCI, Charlson Comorbidity Index; COVID-19, coronavirus disease 2019; VTE, venous thromboembolism.

(65.7%) received only prophylactic dose, and 66 (24.1%) received treatment dose prior to diagnosis.

VTE or Mortality—Univariable Analysis

Overall VTE or mortality rate was 26.1% (►**Table 2**). Univariable analysis showed that the VTE or mortality rate was 27.8% in males and 23.7% in females ($p < 0.001$), and higher in ICU patients (68.3%) than in non-ICU patients (15.3%) ($p < 0.001$). Maximum D-dimer >6 times ULN was associated with a VTE or mortality rate of 55.7% compared with 29.9% for 4 to 6 times ULN and 11.4% for <4 times ULN (11.4%) ($p < 0.001$). Patients with VTE or mortality had significantly higher baseline creatinine (2.1 for VTE vs. 1.5 for mortality; $p < 0001$) and significantly lower platelet counts (214.5×10^9 for VTE vs. 230.6×10^9 for mortality; $p < 0.001$) than patients without VTE or mortality.

VTE or mortality was lowest with CCI 0 (7.1%) compared with CCI 1–2 (11.4%), CCI 3–4 (21.6%), and CCI ≥5 (38.7%) ($p < 0.001$). VTE was also lower in patients with a history of asthma ($p < 0.001$). VTE or mortality was significantly higher with history of cancer, hypertension, CAD, heart failure, PAD or PVD, VTE, cerebrovascular disease, hyperlipidemia, COPD, diabetes, and CKD/ESRD (each $p < 0.001$).

Most in-hospital treatment regimens for COVID-19 were associated with increased rates of VTE or mortality, including steroids, IVIG, anti-inflammatories, immunosuppressants, azithromycin, and chloroquine (each $p < 0.03$). ACE/ARB and antacids/antihistamines were associated with decreased VTE or mortality (each $p < 0.001$). There were no significant differences in VTE or mortality with statins, famotidine, HCQ, antivirals, or biologics.

Home anticoagulation and antiplatelet use were associated with higher VTE or mortality than no anticoagulation or antiplatelet use ($p < 0.001$). The use of hospital thromboprophylaxis at prophylactic doses (but not treatment doses) was associated with a lower VTE or mortality than no anticoagulation (19.1% for VTE vs. 30.5% for mortality; $p < 0.001$).

VTE or Mortality—Multivariable Analysis

Multivariable analysis (►**Table 3**) showed a significant reduction in VTE or mortality with black race compared with white race (odds ratio [OR]: 0.68, 95% CI: 0.57–0.81), history of hypertension (OR: 0.79, 95% CI: 0.67–0.93), ACE/ARB use (OR: 0.75, 95% CI: 0.62–0.92), and decreasing platelet counts (OR: 0.93 per $50{,}000 \times 10^9$ units, 95% CI: 0.90–0.96). Initial thromboprophylaxis with prophylactic-dose anticoagulation compared with no anticoagulation revealed a reduction in VTE or mortality (OR: 0.55, 95% CI: 0.44–0.69). The use of treatment-dose anticoagulation for thromboprophylaxis did not reveal a significant reduction in VTE or mortality (OR: 0.83, 95% CI: 0.69–1.11). The 76 patients who received their first treatment dose of anticoagulant within 24 hours of a VTE event did not change these conclusions (data not shown).

Multivariable analysis showed a significant increase in VTE or mortality with advanced age (60–75 years vs. 18–59 years [OR: 1.4, 95% CI: 1.12–1.76], >75 years vs. 18–59 years [OR: 3.33, 95% CI: 2.56–4.33]); CCI 3–4 versus CCI 0 (OR: 2.34, 95% CI: 1.54–3.55); CCI ≥5 versus CCI 0 (OR: 4.99, 95% CI: 3.22–7.75); Medicare versus commercial insurance (OR: 1.39, 95% CI: 1.14–1.68); history of heart failure (OR: 1.37, 95% CI: 1.12–1.68); history of cerebrovascular disease (OR: 1.37, 95% CI: 1.08–1.74); BMI >35 versus ≤35 (OR: 1.38, 95% CI: 1.12–1.70); steroid use (OR: 1.68, 95% CI: 1.45–1.94); antirheumatic medication use (OR: 1.87, 95% CI: 1.34–2.62); HCQ use (OR: 1.16, 95% CI: 1.00–1.34); maximum D-dimer 4 to 6 times ULN versus 4 times the ULN (OR: 2.1, 95% CI: 1.61–2.74) and >6 times ULN versus <4 times ULN (OR: 5.28, 95% CI: 4.46–6.25); ICU level of care (OR: 9.77, 95% CI: 8.32–11.46); and increasing creatinine (OR: 1.03 per 0.5 units, 95% CI: 1.02–1.05).

Discussion

Our study of more than 9,400 COVID-19 inpatients in a multihospital health system revealed two main findings. First, the overall in-hospital symptomatic VTE rate was

Table 1 Patient demographics

Demographic	No. (%)
Total	9,407 (100%)
Age, y	
18–59	3,407 (36.2%)
60–75	3,365 (35.8%)
75+	2,635 (28.0%)
BMI	
Unknown	2,029 (21.6%)
≤35	6,154 (65.4%)
> 35	1,224 (13.0%)
CCI	
0	850 (9.0%)
1–2	1,968 (20.9%)
3–4	2,222 (23.6%)
5+	4,367 (46.4%)
Sex	
Female	3,827 (40.7%)
Male	5,580 (59.3%)
Race	
Asian	812 (8.6%)
Black	1,995 (21.2%)
Other	2,583 (27.5%)
Unknown	413 (4.4%)
White	3,604 (38.3%)
Ethnicity	
Hispanic or Latino	1,992 (21.2%)
Not Hispanic or Latino	6,814 (72.4%)
Other/unknown	601 (6.4%)
Insurance	
Commercial	2,810 (29.9%)
Medicaid	1,901 (20.2%)
Medicare	4,445 (47.3%)
Other	102 (1.1%)
Self-pay	149 (1.6%)
Medical history	
No cancer	8,680 (92.3%)
Cancer	727 (7.7%)
No hypertension	3,774 (40.1%)
Hypertension	5,633 (59.9%)
No CAD	8,207 (87.2%)
CAD	1,200 (12.8%)
No heart failure	8,634 (91.8%)
Heart failure	773 (8.2%)
No PAD or PVD	9,028 (96.0%)
PAD or PVD	379 (4.0%)
No/unknown VTE	9,160 (97.4%)
VTE	247 (2.6%)
No cerebrovascular disease	8,856 (94.1%)
Cerebrovascular disease	551 (5.9%)
No hyperlipidemia	7,457 (79.3%)
Hyperlipidemia	1,950 (20.7%)
No chronic liver disease	9,168 (97.5%)
Chronic liver disease	239 (2.5%)
No asthma	8,620 (91.6%)
Asthma	787 (8.4%)
No COPD	8,836 (93.9%)
COPD	571 (6.1%)
No diabetes	6,009 (63.9%)
Diabetes	3,398 (36.1%)
No ESRD or CKD	8,624 (91.7%)
ESRD or CKD	783 (8.3%)
Tobacco	
Active/former smoker	1,880 (20.0%)
Never smoker	6,952 (73.9%)
Unknown smoking history	575 (6.1%)
D-dimer maximum	
Unknown	2,577 (27.4%)
Normal to <4× ULN	3,876 (41.2%)
4–6× ULN	522 (5.5%)
> 6× ULN	2,432 (25.9%)
ICU	
No	7,225 (76.8%)
Yes	1,854 (19.7%)
Unknown timing	328 (3.5%)
Treatment/medication	
Hospital anticoagulation	
None	979 (10.4%)
Prophylaxis dose	6,675 (71.0%)
Treatment dose	1,753 (18.6%)
Home anticoagulation	
Unknown	2,274 (24.2%)
None	6,166 (65.5%)
Prophylaxis dose	273 (2.9%)
Treatment dose	694 (7.4%)
Home or hospital antiplatelet	
None	4,531 (48.2%)
Present	2,804 (29.8%)
NA	2,072 (22.0%)

Table 1 (*Continued*)

Hospital steroids	
None	6,868 (73.0%)
Present	2,539 (27.0%)
Hospital IVIG	
None	9,380 (99.7%)
Present	27 (0.3%)
Hospital biologic	
None	9,298 (98.8%)
Present	109 (1.2%)
Hospital rheumatologic anti-inflammatory	
None	9,089 (96.6%)
Present	318 (3.4%)
Hospital immunosuppressant	
None	8,944 (95.1%)
Present	463 (4.9%)
Hospital antiviral	
None	9,066 (96.4%)
Present	341 (3.6%)
Hospital ACE/ARB	
None	8,183 (87.0%)
Present	1,224 (13.0%)
Hospital azithromycin	
None	5,007 (53.2%)
Present	4,400 (46.8%)
Hospital HCQ	
None	3,242 (34.5%)
Present	6,165 (65.5%)
Hospital chloroquine	
None	9,391 (99.8%)
Present	16 (0.2%)
Hospital famotidine	
None	8,227 (87.5%)
Present	1,180 (12.5%)
Hospital statin	
None	6,283 (66.8%)
Present	3,124 (33.2%)
Hospital antacid/antihistamine	
None	8,928 (94.9%)
Present	479 (5.1%)

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; HCQ, hydroxychloroquine; ICU, intensive care unit; IVIG, intravenous immunoglobulin; NA, not applicable; PAD, peripheral arterial disease; PVD peripheral vascular disease; ULN, upper limit of normal, VTE, venous thromboembolism.

Table 2 Univariable predictors of VTE or mortality

Predictor	No VTE or mortality, No. (%)	VTE or mortality, No. (%)	*p*-Value
Total	6,951 (73.9%)	2,456 (26.1%)	
Age, y			
18–59	3,004 (88.2%)	403 (11.8%)	<0.001
60–75	2,473 (73.5%)	892 (26.5%)	
75+	1,474 (55.9%)	1,161 (44.1%)	
BMI			
Unknown	1,382 (68.1%)	647 (31.9%)	<0.001
≤35	4,624 (75.1%)	1,530 (24.9%)	
>35	945 (77.2%)	279 (22.8%)	
CCI			
0	790 (92.9%)	60 (7.1%)	<0.001
1–2	1,744 (88.6%)	224 (11.4%)	
3–4	1,742 (78.4%)	480 (21.6%)	
5+	2,675 (61.3%)	1,692 (38.7%)	
Sex			
Female	2,921 (76.3%)	906 (23.7%)	<0.001
Male	4,030 (72.2%)	1,550 (27.8%)	
Race			
Asian	590 (72.7%)	222 (27.3%)	<0.001
Black	1,537 (77.0%)	458 (23.0%)	
Other	2,016 (78.0%)	567 (22.0%)	
Unknown	312 (75.5%)	101 (24.5%)	
White	2,496 (69.3%)	1,108 (30.7%)	
Ethnicity			
Hispanic or Latino	1,565 (78.6%)	427 (21.4%)	<0.001
Not Hispanic or Latino	4,936 (72.4%)	1,878 (27.6%)	
Other/unknown	450 (74.9%)	151 (25.1%)	
Insurance			
Commercial	2,368 (84.3%)	442 (15.7%)	<0.001
Medicaid	1,572 (82.7%)	329 (17.3%)	
Medicare	2,811 (63.2%)	1,634 (36.8%)	
Other	85 (83.3%)	17 (16.7%)	
Self-pay	115 (77.2%)	34 (22.8%)	
Medical history			
No cancer	6,487 (74.7%)	2,193 (25.3%)	<0.001
Cancer	464 (63.8%)	263 (36.2%)	
No hypertension	2,984 (79.1%)	790 (20.9%)	<0.001
Hypertension	3,967 (70.4%)	1,666 (29.6%)	
No CAD	6,181 (75.3%)	2,026 (24.7%)	<0.001
CAD	770 (64.2%)	430 (35.8%)	
No heart failure	6,524 (75.6%)	2,110 (24.4%)	<0.001
Heart failure	427 (55.2%)	346 (44.8%)	
No PAD or PVD	6,727 (74.5%)	2,301 (25.5%)	<0.001
PAD or PVD	224 (59.1%)	155 (40.9%)	
No/unknown VTE	6,800 (74.2%)	2,360 (25.8%)	<0.001
VTE	151 (61.1%)	96 (38.9%)	

Table 2 (*Continued*)

Predictor	No VTE or mortality, No. (%)	VTE or mortality, No. (%)	*p*-Value
No cerebrovascular disease	6,619 (74.7%)	2,237 (25.3%)	<0.001
Cerebrovascular disease	332 (60.3%)	219 (39.7%)	
No hyperlipidemia	5,584 (74.9%)	1,873 (25.1%)	<0.001
Hyperlipidemia	1,367 (70.1%)	583 (29.9%)	
No chronic liver disease	6,773 (73.9%)	2,395 (26.1%)	0.835
Chronic liver disease	178 (74.5%)	61 (25.5%)	
No asthma	6,312 (73.2%)	2,308 (26.8%)	<0.001
Asthma	639 (81.2%)	148 (18.8%)	
No COPD	6,596 (74.6%)	2,240 (25.4%)	<0.001
COPD	355 (62.2%)	216 (37.8%)	
No diabetes	4,550 (75.7%)	1,459 (24.3%)	<0.001
Diabetes	2,401 (70.7%)	997 (29.3%)	
No ESRD or CKD	6,433 (74.6%)	2,191 (25.4%)	<0.001
ESRD or CKD	518 (66.2%)	265 (33.8%)	
Tobacco			
Active/former smoker	1,360 (72.3%)	520 (27.7%)	<0.001
Never smoker	5,518 (79.4%)	1,434 (20.6%)	
Unknown smoking history	73 (12.7%)	502 (87.3%)	
D-dimer maximum			
Unknown	2,075 (80.5%)	502 (19.5%)	<0.001
Normal to <4× ULN	3,433 (88.6%)	443 (11.4%)	
4–6× ULN	366 (70.1%)	156 (29.9%)	
>6× ULN	1,077 (44.3%)	1,355 (55.7%)	
ICU			
No	6,118 (84.7%)	1,107 (15.3%)	<0.001
Yes	588 (31.7%)	1,266 (68.3%)	
Unknown timing	245 (74.7%)	83 (25.3%)	
Treatment/medication			
Hospital anticoagulation			
None	680 (69.5%)	299 (30.5%)	<0.001
Prophylaxis dose	5,398 (80.9%)	1,277 (19.1%)	
Treatment dose	873 (49.8%)	880 (50.2%)	
Home anticoagulation			
Unknown	1,584 (69.7%)	690 (30.3%)	<0.001
None	4,741 (76.9%)	1,425 (23.1%)	
Prophylaxis dose	175 (64.1%)	98 (35.9%)	
Treatment dose	451 (65.0%)	243 (35.0%)	
Home or hospital antiplatelet			
None	3,607 (79.6%)	924 (20.4%)	<0.001
Present	1,857 (66.2%)	947 (33.8%)	
NA	1,487 (71.8%)	585 (28.2%)	
Hospital steroids			
None	5,417 (78.9%)	1,451 (21.1%)	<0.001
Present	1,534 (60.4%)	1,005 (39.6%)	
Hospital IVIG			
None	6,936 (73.9%)	2,444 (26.1%)	0.030
Present	15 (55.6%)	12 (44.4%)	
Hospital biologic			
None	6,872 (73.9%)	2,426 (26.1%)	0.735
Present	79 (72.5%)	30 (27.5%)	
Hospital rheumatologic anti-inflammatory			
None	6,795 (74.8%)	2,294 (25.2%)	<0.001
Present	156 (49.1%)	162 (50.9%)	
Hospital immunosuppressant			
None	6,664 (74.5%)	2,280 (25.5%)	<0.001
Present	287 (62.0%)	176 (38.0%)	
Hospital antiviral			
None	6,700 (73.9%)	2,366 (26.1%)	0.903
Present	251 (73.6%)	90 (26.4%)	
Hospital ACE/ARB			
None	5,974 (73.0%)	2,209 (27.0%)	<0.001
Present	977 (79.8%)	247 (20.2%)	
Hospital azithromycin			
None	3,787 (75.6%)	1,220 (24.4%)	<0.001
Present	3,164 (71.9%)	1,236 (28.1%)	
Hospital HCQ			
None	2,429 (74.9%)	813 (25.1%)	0.099
Present	4,522 (73.3%)	1,643 (26.7%)	
Hospital chloroquine			
None	6,946 (74.0%)	2,445 (26.0%)	<0.001
Present	5 (31.3%)	11 (68.8%)	
Hospital famotidine			
None	6,072 (73.8%)	2,155 (26.2%)	0.616
Present	879 (74.5%)	301 (25.5%)	
Hospital statin			
None	4,653 (74.1%)	1,630 (25.9%)	0.605
Present	2,298 (73.6%)	826 (26.4%)	
Hospital antacid/antihistamine			
None	6,551 (73.4%)	2,377 (26.6%)	<0.001
Present	400 (83.5%)	79 (16.5%)	

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ESRD, end stage renal disease; HCQ, hydroxychloroquine; ICU, intensive care unit; IVIG, intravenous immunoglobulin; NA, not applicable; PAD, peripheral arterial disease; PVD peripheral vascular disease; ULN, upper limit of normal, VTE, venous thromboembolism.

2.9% and significantly higher in the ICU versus medical ward (4.9 vs. 2.4%; $p < 0.001$). Second, the overall VTE or mortality rate of 26.1% was significantly associated with key clinical and laboratory predictors, including advanced age, increasing CCI, ICU care, BMI greater than 35, a history of heart failure or cerebrovascular disease, and maximum D-dimer >4 times (and especially >6 times) ULN for our laboratory. Prophylactic-dose anticoagulation, but not treatment-dose

Table 3 Multivariable predictors of VTE or mortality

	OR	95% CI	*p*-Value
Age, y			
18–59		Reference	
60–75	1.40	(1.12, 1.76)	0.003
>75	3.33	(2.56, 4.33)	<0.001
BMI			
≤35		Reference	
>35	1.38	(1.12, 1.70)	0.003
Unknown	1.33	(1.14, 1.55)	<0.001
CCI			
0		Reference	
1–2	1.46	(0.99, 2.13)	0.054
3–4	2.34	(1.54, 3.55)	<0.001
5+	4.99	(3.22, 7.75)	<0.001
Sex			
Female		Reference	
Male	1.21	(1.06, 1.38)	0.006
Race			
White		Reference	
Asian	1.08	(0.84, 1.38)	0.545
Black	0.68	(0.57, 0.81)	<0.001
Other	0.81	(0.68, 0.96)	0.014
Unknown	0.87	(0.63, 1.22)	0.425
Insurance			
Commercial		Reference	
Medicaid	1.16	(0.93, 1.44)	0.186
Medicare	1.39	(1.14, 1.68)	0.001
Other	1.33	(0.68, 2.62)	0.404
Self-pay	1.14	(0.63, 2.06)	0.668
Medical history			
Hypertension	0.79	(0.67, 0.93)	0.005
Heart failure	1.37	(1.12, 1.68)	0.003
Cerebrovascular disease	1.37	(1.08, 1.74)	0.009
Tobacco			
Never		Reference	
Active/former smoker	1.00	(0.86, 1.17)	1.000
Unknown	15.48	(11.45, 20.92)	<0.001
D-dimer maximum			
Normal–4× ULN		Reference	
4–6x ULN	2.1	(1.61, 2.74)	<0.001
>6x ULN	5.28	(4.46, 6.25)	<0.001
Unknown	1.96	(1.63, 2.34)	<0.001
ICU			
No		Reference	
Unknown	1.42	(1.02, 1.98)	0.036
Yes	9.77	(8.32, 11.46)	<0.001
Treatment/medication			
Steroid use	1.68	(1.45, 1.94)	<0.001
Rheumatologic anti-inflammatory	1.87	(1.34, 2.62)	<0.001
ACE/ARB	0.75	(0.62, 0.92)	0.006
HCQ	1.16	(1.00, 1.34)	0.047
Home anticoagulation			
None		Reference	
Prophylactic dose	1.20	(0.86, 1.67)	0.279
Treatment dose	0.88	(0.69, 1.11)	0.273
Unknown	1.69	(1.42, 2.01)	<0.001
Hospital anticoagulation			
None		Reference	
Prophylactic dose	0.55	(0.44, 0.69)	<0.001
Treatment dose	0.83	(0.65, 1.07)	0.152
Baseline laboratory			
Creatinine (per 0.5 unit increase)	1.03	(1.02, 1.05)	<0.001
Platelet count (per 50,000 unit increase)	0.93	(0.90, 0.96)	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio.
Note: See ►**Table 1**.

anticoagulation, was significantly associated with a decrease in VTE or mortality.

The overall in-hospital symptomatic VTE rate of 2.9% (4.9% in ICU) in our COVID-19 population was slightly higher than VTE rates usually found in medical and ICU wards for patients with sepsis and pneumonia. However, it is also an order of magnitude less than the reported incidence of VTE of 27 to 46% in China and Western Europe without systematic screening.[1,3,11,12] Indeed, the VTE rate of 2.4% in the non-ICU population of our study was more in line with the rates of 3.6 and 1.7% reported in hospitalized COVID-19 populations in New York City health systems during the early part of the pandemic.[2,6] The reasons for the lower VTE rates in U.S. health systems are unclear. Our cohort is much larger than those described previously; we restricted our analysis to capture only clinically evident in-hospital events; we excluded other forms of thrombosis, such as catheter thrombosis, which were included in some studies, and, importantly, our system established early a universal thromboprophylaxis policy for COVID-19 inpatients.[13]

Our analysis revealed a high in-hospital VTE or mortality rate of 26.1%, which is similar to rates of thrombosis and mortality of 30 to 42% in previous studies.[6,14] For our analysis of in-hospital predictors, we combined VTE and mortality because autopsy data in hospitalized patients with COVID-19 suggested that up to approximately 60% of VTE was not suspected before death. These data indicated that thrombotic mechanisms play a major role in mortality and that all-cause mortality and VTE represent competing risks.[5,15] Significant key clinical predictors of in-hospital VTE or mortality included advanced age, especially >75 years (OR: 3.3), a CCI ≥5 (OR:

4.99), history of heart failure or cerebrovascular disease (both with OR: 1.37), BMI ≥35 (OR: 1.38), and ICU level of care (OR: 9.77). Advanced age, history of cardiovascular disease, and obesity have been consistently associated with poor outcomes and increased thrombotic events and mortality in hospitalized COVID-19 patients.[16] Our study is the first to show a nearly fivefold increased risk of VTE or mortality with an elevated CCI ≥5 in this population. Our study showed a nearly 10-fold increased risk of VTE or mortality in critically ill COVID-19 patients. ICU level of care has consistently been a predictor of elevated risk of thromboembolic disease and mortality in this population.[6,17] Other clinical predictors of VTE or mortality included steroid use (OR: 1.68), antirheumatic medication (OR: 1.87), and HCQ use (OR: 1.16), as well as Medicare coverage (OR: 1.39). Black race appeared protective for VTE or mortality, consistent with a previous report that poverty but not race is associated with severe disease.[18] Causal mechanisms for these associations warrant further study.

Elevated D-dimer, either four to six times ULN (OR: 2.1) or ≥6 times ULN (OR: 5.28), showed a significant correlation with VTE or mortality. Early reports from China suggested elevated D-dimer cutoffs of four and, especially, six times ULN based on local laboratory criteria were strong predictors of mortality in COVID-19 inpatients. This observation has been corroborated in our study and by other groups.[2,3] Highly elevated D-dimer may reflect the hyperinflammatory state and cytokine storm that lead to thromboinflammation.[19] We tested and did not find significant associations between VTE or mortality with other laboratory criteria and coagulation parameters that were previously (but not consistently) shown to be predictors of poor outcomes.[3] Increasing creatinine and decreasing platelet counts were associated with minimal clinical implications for VTE or mortality.

In our study, the use of initial prophylactic-dose anticoagulation compared with no anticoagulation was significantly associated with a 45% reduction in VTE or mortality. This finding is consistent with an older report from China that suggested a 39% reduction with prophylactic-dose anticoagulant therapy versus no anticoagulant therapy COVID-19 inpatients with elevated D-dimer.[3] It is also consistent with a recent New York area study that revealed an in-hospital mortality of 29.1% for ICU patients treated with anticoagulants versus 62.7% in patients without anticoagulants.[3,7] Interestingly, we did not find a significant reduction in VTE or mortality with initial treatment-dose anticoagulation. Some reports suggest advantages of using treatment-dose anticoagulant therapy over prophylactic dose for thromboprophylaxis.[20] More recent reports suggest no significant advantages in reducing thrombotic events or mortality.[7] Ongoing randomized trials are comparing usual prophylactic-dose heparin therapy to escalated or treatment-dose heparin therapy for optimal thromboprophylaxis in hospitalized and critically ill COVID-19 patients, with all-cause mortality as the key endpoint.[21]

Our study has several limitations. Although VTE events were carefully adjudicated by two radiologists, the true VTE rate may be underreported as VTE events may not have had confirmatory imaging studies due to concerns of virus exposure by health care staff. In addition, our institutional policy did not advocate for systematic DVT screening, especially in critically ill patients, which may have underrepresented the true VTE incidence.[11] We also were not able to differentiate in situ versus embolic PE with our dataset. We did not include arterial thromboembolism or device- or catheter-associated thrombosis, which may have underrepresented the true incidence of macro-vessel thrombotic disease. In the absence of autopsy data or from objective exam testing, we recognize that mechanisms other than thrombotic ones may have contributed to mortality. However, the overall lower rates of VTE in our data and other recent regional data may point to either an ascertainment bias seen in previous reports of the incidence of COVID-19-induced coagulopathy or in different clinical manifestations of different COVID-19 genotypes. Data collection with critically ill patients may have been fragmented due to limited history and may explain why key clinical data were unavailable in patients with worse outcomes. We could not rule out hidden confounders when attempting to develop our multivariable model. A last potential limitation is that the primary outcome of the composite of VTE or death was analyzed as a binary outcome, using logistic regression rather than survival analysis, even though the endpoint is actually a "time-until-event" outcome. However, from a clinical and practical perspective, the goal of treatment for hospitalized COVID-19 patients is to improve the patient's condition and discharge that patient alive. The length of time it takes to achieve that outcome is not of paramount interest, and thus the use of the binary outcome is reasonable.

Despite these limitations, our analysis has several strengths. It represents a very large in-hospital dataset of hospitalized COVID-19 patients, with over 9,400 patients, allowing more precise estimates of VTE and mortality than previous studies. The VTE events were carefully and systematically adjudicated by experienced radiologists, allowing for greater specificity. We used a centralized COVID-19 database, which was available soon after the pandemic struck our system, that allowed for uniformity of data definitions of both clinical and laboratory factors. The high rate of our combined outcome of VTE and mortality allowed us to adequately assess significant associations with independent variables in the univariable and multivariable analyses.

Conclusion

Our study of over 9,400 hospitalized COVID-19 patients found an overall in-hospital VTE rate of 2.9% (4.9% in ICU) and an overall VTE or mortality rate of 26.1%. Key predictors of VTE or mortality included advanced age, increasing CCI, history of cardiovascular disease, ICU level of care, and elevated maximum D-dimer with a cutoff of at least four times ULN. Use of prophylactic-dose anticoagulation (vs. no anticoagulation) but not treatment-dose anticoagulation was associated with a reduction of VTE or mortality. Our results support universal in-hospital thromboprophylaxis using standard prophylactic-dose anticoagulants for hospitalized COVID-19 patients, with potential to use individual clinical and laboratory parameters to develop a predictive score for VTE and mortality to tailor individualized thromboprophylaxis strategies in high-risk subgroups.

One-Sentence Summary

Key predictors of venous thromboembolism (VTE) or mortality in a large hospitalized coronavirus disease 2019 (COVID-19) population support universal prophylactic-dose thromboprophylaxis with potential to use individual clinical and laboratory parameters to develop a predictive score for individualized thromboprophylaxis strategies in high-risk subgroups.

What is known about this topic?

- Hospitalized COVID-19 patients have considerable rates of venous thromboembolism and thromboembolism-associated mortality.
- Optimal thromboprophylaxis strategies in high-risk COVID-19 inpatients remain unclear.
- Reduced VTE events and mortality have been noted with full-dose anticoagulation compared with the low-dose one.

What does this paper add?

- Identification of key predictors of venous thromboembolism or mortality in a large hospitalized COVID-19 population.
- Universal prophylactic-dose thromboprophylaxis should be considered in hospitalized patients with COVID-19.
- Individual clinical and laboratory parameters may be used to develop a predictive score for individualized thromboprophylaxis strategies in high-risk subgroups.

Note

The data that support the findings of this study are available on request from http://COVID19@northwell.edu. The data are not publicly available due to restrictions as it could compromise the privacy of research participants. This was performed at Northwell Health.

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Conflict of Interest

A.C.S.: consultant for Janssen, Bayer, Bristol Meyers Squibb, Boehringer Ingelheim, the ATLAS Group, and research grants from Janssen and Boehringer Ingelheim. S.L.C.: consultant for Infervision, educational honorarium from Siemens Healthineers, and research funding from the Association of University Radiologists GE Radiology Research Academic Fellowship (GERRAF) and Siemens Healthineers. None of the other authors reported any conflicts of interest.

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