Comparative Frequency of Venous Thromboembolism in Patients Admitted to the Hospital with SARS-CoV-2 Infection versus Community-acquired Pneumonia

To the Editor:

Severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 in Wuhan, Hubei, China, to be the agent causing coronavirus disease (COVID-19) (1). COVID-19 was officially classified as a pandemic by the World Health Organization on March 11, 2020. As of June 2021, the World Health Organization reported more than 174 million cases and more than 3.7 million deaths related to COVID-19 worldwide (2).

Thrombosis has emerged as a potentially important feature of COVID-19. Abnormal markers of hypercoagulability have been reported, including elevated D-dimer, elevated fibrinogen concentrations, elevated factor VIII concentrations, elevated sepsis-induced coagulopathy scores, and thrombocytopenia (3). Early in the pandemic, multiple inpatient and autopsy studies suggested the possibility of an increased prevalence of venous thromboembolism (VTE) in patients with COVID-19 (4–7). A meta-analysis of VTE among inpatients with COVID-19 suggested an overall incidence of 17%, although comparative data are lacking (8).

Multiple studies have identified infection as a risk factor for VTE in patients treated in both the inpatient and outpatient settings (9–11). A prospective study of 113 intensive care unit (ICU) patients determined the prevalence of VTE in ICU patients with sepsis to be 37% (12). Recently, infection was identified as being among the risk factors most predictive of VTE among hospitalized patients (13).

Prior reports of VTE incidence in COVID-19 have not included appropriate comparison groups, limiting capacity to infer the presence of a distinctive thrombophilia associated with SARS-CoV-2 infection. In addition, failure to measure and adjust for rates of testing has limited the security of inferences regarding the incidence of VTE in COVID-19. The uncertainties regarding optimal clinical management and infection control, especially early in the pandemic, likely affected rates of clinical testing, thus underestimating the true incidence of VTE. To address these knowledge gaps, we compared the incidence of VTE among inpatients with COVID-19 with the incidence of VTE among patients with community-acquired pneumonia (CAP) admitted to the same hospitals. We also compared rates of testing for VTE among patients with COVID-19 and patients with CAP.

Methods

This was a retrospective cohort study of all patients admitted to the 23 hospitals of the Intermountain Healthcare system between January 1, 2020, and December 31, 2020, who had a positive test result for SARS-CoV-2 by polymerase chain reaction or antigen test. Intermountain Healthcare is a 23-hospital not-for-profit healthcare system in the Intermountain West. Sequential patients identified by searching all admissions with a positive SARS-CoV-2 test result 7 days before admission and 90 days after admission constituted the study cohort. The median time from admission to positive SARS-CoV-2 polymerase chain reaction test result was 23 hours (interquartile range, −1 to 180 h). The control group included patients with a diagnosis of CAP identified from January 1, 2017, to June 20, 2019, from 16 of the 23 hospitals (14). Lower extremity (LE) Doppler ultrasound, ventilation–perfusion ($\dot{V}/\dot{Q}$) scan, or computed tomography pulmonary angiography (CTPA) performed as clinically indicated 7 days before through 90 days after the index admission date were used to assess VTE. A random sample of 50 charts was reviewed, and accuracy was confirmed in all 50 charts. Positive test results were identified using a validated natural language processing algorithm (15).

Multivariable logistic regression analysis was used to compare the study group and the control group. All analyses were performed using STATA version 17.0 (StataCorp). The analyses controlled for age, sex, ICU versus general hospital ward admission, and probability of VTE as measured by the UTAH score (16). The first UTAH score during the hospitalization was used. A two-tailed $P < 0.05$ was considered statistically significant.

A subanalysis of which test result was first positive among the patients with positive findings for VTE was done for CTPA, $\dot{V}/\dot{Q}$ scan, and LE Doppler for each of the COVID-19 and CAP groups. Comparison of proportions was performed with the chi-square test with 95% confidence interval. A second subanalysis was done of the first positive test result of the patients who underwent more than one imaging modality for CTPA, $\dot{V}/\dot{Q}$ scan, and LE Doppler for patients with COVID-19 and patients with CAP. For both subanalyses, a comparison of proportions was performed using a chi-square test with a 95% confidence interval.

Results

Groups of 7,509 patients with COVID-19 (mean age, 57 yr; 50% female) and 4,304 patients with CAP (mean age, 67 yr; 48% female) were compared (Table 1). Thirty-eight percent of patients with COVID-19 and 43% of patients with CAP underwent VTE testing ($P = 0.992$; adjusted odds ratio [OR], 1.00). In the study cohort, 6.2% of patients with COVID-19 had positive test results for VTE compared with 4.0% of patients with CAP in the control group ($P < 0.00001$; adjusted OR, 1.64) (Table 2). The positivity rate for patients with COVID-19 tested for VTE was 16.3%, whereas the positivity rate for patients with CAP tested for VTE was 9.2%. The rate of positive CTPA findings among patients with COVID-19 compared with patients with CAP was 3.2% versus 1.7%, respectively ($P < 0.00001$; adjusted OR, 1.99), and the rate of positive LE Doppler

Table 1. Demographics

	Patients with COVID-19	Patients with CAP
Total patients	7,509	4,304
Average age, yr	57	67
Female sex, *n* (%)	3,862 (51%)	2,061 (48%)
ICU admission, *n* (%)	2,638 (35%)	2,275 (53%)
Average UTAH score	1.21	1.27

Definition of abbreviations: CAP = community-acquired pneumonia; COVID-19 = coronavirus disease; ICU = intensive care unit.

Table 2. Results of testing for venous thromboembolism in patients with COVID-19 and patients with community-acquired pneumonia

	Patients with COVID-19	Patients with CAP	*P* Value	Adjusted Odds Ratio (95% CI)
Any VTE testing, *n* (%)	2,848 (37.9%)	1,802 (42.9%)	0.992	1.00 (0.92–1.09)
VTE positive incidence	463 (6.2%)	169 (3.9%)	<0.00001	1.64 (1.35–1.99)
Average age VTE positive, yr	61	67	—	—
Female VTE positive, *n* (%)	165 (36%)	70 (41%)	—	—
CTPA performed	2,426 (32.3%)	1,446 (33.6%)	0.102	0.93 (0.85–1.01)
CTPA positive	243 (3.2%)	72 (1.7%)	<0.00001	1.99 (1.48–2.67)
V̇/Q̇ performed	49 (0.7%)	93 (2.2%)	<0.00001	0.27 (0.183–0.38)
V̇/Q̇ positive	15 (0.2%)	4 (0.1%)	0.156	2.30 (0.73–7.29)
LE Doppler performed	802 (10.7%)	533 (12.4%)	0.005	0.83 (0.73–0.95)
LE Doppler positive	248 (3.3%)	109 (2.5%)	0.008	1.40 (1.09–1.79)
CTPA first positive test	223 (48%)	67 (40%)	0.057*	—
V̇/Q̇ first positive test	13 (3%)	4 (2%)	0.762*	—
LE Doppler first positive test	227 (49%)	98 (58%)	0.046*	—
Multiple testing modalities performed	420	262	—	—
Positive test with multiple testing modalities	180 (43%)	81 (31%)	—	—
First test CTPA positive	54 (30%)	31 (38%)	0.187*	—
First test V̇/Q̇ positive	3 (2%)	2 (2%)	0.662*	—
First test LE Doppler positive	123 (68%)	48 (59%)	0.154*	—

Definition of abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; COVID-19 = coronavirus disease 2019; CTPA = computed tomography pulmonary angiography; LE = lower extremity; V̇/Q̇ = ventilation–perfusion; VTE = venous thromboembolism.
Data listed are count (percent incidence in the cohort) unless otherwise specified.
*Indicates an unadjusted *P* value. All other *P* values are adjusted.

among patients with COVID-19 compared with patients with CAP was 3.3% versus 2.5%, respectively ($P = 0.008$; adjusted OR, 1.40) (Table 2).

Of the 463 patients with COVID-19 with positive results for VTE, 223 (48%) had CTPA as their first test. Of the 169 patients with CAP with positive results for VTE, 67 (40%) had CTPA as their first test ($P = 0.057$). Two hundred twenty-seven (49%) of the patients with COVID-19 and 98 (58%) of patients with CAP had LE Doppler as their first test ($P = 0.046$).

Of the 420 patients with COVID-19 who underwent multiple testing modalities for VTE, 180 (43%) had a positive test result for VTE. Fifty-four (30%) patients had CTPA as their first positive test result, 123 (68%) patients had LE Doppler as their first positive test result, and 3 (2%) patients had V̇/Q̇ as their first positive test result. Of the 262 patients with CAP who underwent multiple testing modalities for VTE, 81 (31%) had a positive test result for VTE. Thirty-one (38%) patients had a positive CTPA finding for the first test ($P = 0.187$), 48 (59%) patients had LE Doppler as their first positive test result ($P = 0.15$), and 2 (2%) patients had a V̇/Q̇ scan as their first positive test result ($P = 0.66$) (Table 2).

Discussion

We compared the rates of testing for VTE and the observed rates of objectively confirmed venous thromboembolic disease among patients admitted to a 23-hosiptal not-for-profit healthcare system for COVID-19 infection and CAP. The rate of testing did not differ between the study and control groups; however, we observed a higher rate of VTE among patients with COVID-19 than among patients having a diagnosis of CAP. For the individual components of VTE, we observed a higher incidence of both pulmonary embolism and deep vein thrombosis among patients with COVID-19 than among patients with CAP. This observation aligns with former reports that COVID-19 infection is uniquely thrombogenic among hospitalized medical patients. Our estimates may still be underestimates of the true incidence of VTE in COVID-19 because testing was done for clinical indications but suggests that VTE is more common in COVID-19 than in pneumonia caused by pathogens other than SARS-CoV-2.

Although there were concerns early in the pandemic about infection control during radiologic examinations, and although small variations in tests performed were observed, the magnitude of variation was small and seems unlikely to have affected the estimates of VTE burden. Compared with patients with CAP, our patients with COVID-19 overall underwent equal rates of testing for VTE, although less testing for deep vein thrombosis specifically. Of the patients with COVID-19 tested for VTE, 16.3% had positive results, which is above a previously reported positivity rate of 5% among all inpatients, indicating that testing is likely not done frequently enough for patients with COVID-19 and that there may be missed opportunities to diagnose and treat patients for VTE (17).
A limitation of this study is the lack of a central group of radiologists interpreting the VTE studies because they were interpreted by facility-specific radiologists across our system. Published reports of increased rates of VTE among patients with COVID-19 may have influenced the interpretation of the radiologists, because radiologists were not blinded to clinical status, including COVID-19 diagnosis. There is inherent selection bias in this study related to clinical selection of patients for diagnostic testing. The severity of illness was defined by the patient requiring ICU admission or general floor admission during their hospitalization, which was the only delineation for severity of illness and which is also a limitation of this study. Future studies with VTE testing among all inpatients with COVID-19 would

help identify the true incidence as well as potential improved methods to prevent the occurrence of VTE. ■

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