Letters

RESEARCH LETTER

Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System

Patients with coronavirus disease 2019 (COVID-19) are at increased risk of thrombosis.[1] However, studies have been limited in size, did not report all thrombotic events, and focused on patients with severe disease hospitalized in intensive care units (ICUs). We assessed the incidence of, and risk factors for, venous and arterial thrombotic events in all hospitalized patients with COVID-19 at a large health system consisting of 4 hospitals in New York City.

Methods | This study included consecutive patients aged at least 18 years, admitted to a hospital affiliated with NYU Langone Health between March 1 and April 17, 2020, who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using reverse transcriptase–polymerase chain reaction of patient sputum or nasopharyngeal or oropharyngeal swabs. This study was approved by the NYU Grossman School of Medicine Institutional Review Board, which waived the need for informed consent.

Screening for thrombotic events is not standard; diagnoses were made during routine clinical care. Thrombotic events included both venous (deep vein thrombosis [DVT] and pulmonary embolism [PE]) and arterial (myocardial infarction [MI], ischemic stroke, and other systemic thromboembolism). Low-dose (prophylaxis) anticoagulation was used in most patients. As described previously,[2] an open-source natural-language processing tool called simpleNLP, with sensitivity and specificity greater than 95%, searched clinical notes and radiology reports for thrombotic events. Additional chart reviews were performed on echocardiograms, presumptive diagnoses, and diagnostic codes for thrombotic end points. All findings were confirmed by manual chart review. Covariate information was obtained

Table 1. Incidence of Thrombotic Events in Hospitalized Patients With COVID-19

	PE	DVT	Stroke	MI	Other thromboembolism[a]	Any thrombotic event[b]	No thrombotic event
All hospitalized patients (ICU and non-ICU) (n = 3334)							
Events, No. (%)	106 (3.2)	129 (3.9)	54 (1.6)	298 (8.9)	32 (1.0)	533 (16.0)	2801 (84.0)
All-cause mortality, No. (%)[c]	40 (37.7)	36 (27.9)	20 (37)	153 (51.3)	11 (34.4)	230 (43.2)	587 (21.0)
Critical illness, No. (%)[d]	56 (52.8)	81 (62.8)	32 (59.3)	127(42.6)	19 (59.4)	261 (49.0)	634 (22.6)
D-dimer, median (IQR), ng/mL							
Initial[e]	1717 (418-9810)	833 (401-7396)	760 (385-2627)	546 (325-1152)	541 (394-3232)	628 (342-2282)	361 (228-622)
Maximum[f]	10 000 (3329-10 000)	10 000 (4788-10 000)	3247 (1230-10 000)	2058 (586-7615)	3977 (1875-10 000)	3952 (939-10 000)	657 (323-2351)
ICU patients (n = 829)[g]							
Events, No. (%)	52 (6.2)	78 (9.4)	31 (3.7)	115 (13.9)	18 (2.2)	244 (29.4)	585 (70.6)
All-cause mortality, No. (%)[c]	33 (63.5)	25 (32.1)	13 (41.9)	86 (10.4)	9 (50)	146 (59.8)	305 (52.1)
D-dimer, median (IQR), ng/mL							
Initial[e]	1748 (398-10 000)	650 (392-6602)	649 (372-2158)	638 (317-2248)	648 (394-4078)	648 (356-3147)	414 (268-768)
Maximum[f]	10 000 (5273-10 000)	10 000 (6451-10 000)	5876 (2503-10 000)	5762 (2059-10 000)	8549 (2584-10 000)	7973 (2035-10 000)	3608 (1567-9723)
Non-ICU patients (n = 2505)							
Events, No. (%)	54 (2.2)	51 (2.0)	23 (0.9)	183 (7.3)	14 (0.6)	289 (11.5)	2216 (88.5)
All-cause mortality, No. (%)[c]	7 (13.0)	11 (21.6)	7 (30.4)	67 (2.7)	2 (14.3)	84 (29.1)	282 (12.7)
D-dimer, median (IQR), ng/mL							
Initial[e]	1685 (439-7748)	947 (451-7615)	1958 (569-3247)	504 (329-10125)	522 (402-2420)	603 (340-1962)	351 (218-588)
Maximum[f]	7463 (2128-10 000)	6146 (2992-10 000)	760 (547-3595)	854 (396-3881)	1912 (904-3977)	1808 (506-6895)	496 (280-1019)

Abbreviations: COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; ICU, intensive care unit; IQR, interquartile range; MI, myocardial infarction; PE, pulmonary embolism.

SI conversion factor: To convert D-dimer to nmol/L, multiply values by 5.476.

[a] Defined as acute limb ischemia, upper extremity arterial thrombosis, renal and splenic infarcts, and portal vein thrombosis.

[b] Patients could have more than 1 type of thrombotic event.

[c] Defined as death or transfer to hospice as of June 1, 2020.

[d] Defined as mechanical ventilation or transfer to the ICU.

[e] D-dimer values were obtained within 24 hours of admission and were available in 2637 patients (644 ICU patients and 1993 non-ICU patients).

[f] During the course of hospitalization, maximum D-dimer values were available in 2915 patients (770 ICU patients and 2144 non-ICU patients).

[g] ICU patients included anyone who required any ICU stay during their admission.

Table 2. Adjusted Hazard Ratios for Any Thrombosis, Venous Thrombosis, and Arterial Thrombosis in Hospitalized Patients With COVID-19 (N = 3334)

		Thrombosis					
		Any		Venous		Arterial	
Variable	No.	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age, y							
18-44	529	1 [Reference]		1 [Reference]		1 [Reference]	
45-54	469	1.36 (0.94-1.96)	.10	0.95 (0.57-1.59)	.84	1.97 (1.19-3.25)	.01
55-64	714	1.61 (1.14-2.26)	.01	1.41 (0.89-2.24)	.15	1.65 (1.01-2.71)	.05
65-74	756	1.37 (0.96-1.97)	.08	0.83 (0.49-1.41)	.50	1.91 (1.16-3.15)	.01
≥75	866	1.62 (1.13-2.33)	.01	0.49 (0.27-0.87)	.02	2.71 (1.65-4.43)	<.001
BMI							
<18.5	43	1.52 (0.83-2.78)	.17	0.43 (0.05-3.32)	.42	1.78 (0.94-3.40)	.08
18.5-25	613	1 [Reference]		1 [Reference]		1 [Reference]	
26-30	1019	0.99 (0.78-1.25)	.91	1.16 (0.78-1.73)	.47	0.89 (0.67-1.20)	.45
31-40	936	0.90 (0.69-1.16)	.41	1.14 (0.74-1.75)	.56	0.81 (0.59-1.12)	.21
>40	207	1.18 (0.79-1.78)	.42	0.99 (0.50-1.99)	.99	1.01 (0.59-1.73)	.98
Male sex	2014	0.71 (0.52-0.96)	<.001	1.71 (1.21-2.42)	<.001	1.40 (1.11-1.77)	.004
Current smoker	799	1.51 (1.25-1.83)	.74	1.27 (0.88-1.84)	.20	0.86 (0.67-1.10)	.22
Race/ethnicity[a]							
Non-Hispanic White	1444	1 [Reference]		1 [Reference]		1 [Reference]	
Asian	238	1.08 (0.77-1.50)	.66	0.82 (0.46-1.45)	.50	1.24 (0.83-1.85)	.29
Hispanic	49	1.91 (1.15-3.18)	.01	2.01 (0.81-5.00)	.13	1.84 (0.98-3.44)	.06
Non-Hispanic African American	509	0.93 (0.71-1.23)	.62	0.97 (0.60-1.55)	.89	0.99 (0.70-1.38)	.93
Other/multiracial	905	1.10 (0.88-1.36)	.40	0.89 (0.61-1.28)	.52	1.20 (0.92-1.57)	.17
Unknown	189	1.37 (0.97-1.95)	.07	1.37 (0.8-2.33)	.25	1.57 (1.03-2.39)	.04
Comorbidities[b]							
History of myocardial infarction	195	1.43 (1.01-2.03)	.05	0.86 (0.32-2.30)	.76	1.32 (0.90-1.93)	.16
Congestive heart failure	279	1.27 (0.93-1.74)	.13	1.02 (0.43-2.43)	.96	1.30 (0.92-1.85)	.14
Hypertension	1676	0.94 (0.78-1.14)	.52	0.83 (0.58-1.17)	.28	0.99 (0.78-1.25)	.92
Diabetes	1246	0.90 (0.74-1.10)	.31	0.79 (0.55-1.15)	.22	0.97 (0.77-1.23)	.81
Hyperlipidemia	1285	0.88 (0.72-1.08)	.23	0.69 (0.47-1.02)	.06	0.88 (0.69-1.13)	.32
Coronary artery disease	617	1.52 (1.22-1.90)	<.001	0.93 (0.59-1.46)	.75	2.00 (1.54-2.60)	<.001
Initial D-dimer, ng/mL[c]							
<230	619	1 [Reference]		1 [Reference]		1 [Reference]	
230-499	1028	1.17 (0.85-1.60)	.35	1.25 (0.7-2.21)	.45	1.01 (0.7-1.46)	.95
500-1999	690	1.92 (1.4-2.64)	<.001	2.63 (1.49-4.64)	.001	1.52 (1.05-2.19)	.03
2000-4999	157	2.82 (1.87-4.27)	<.001	4.71 (2.26-9.82)	<.001	1.98 (1.23-3.2)	.01
5000-9999	64	5.55 (3.57-8.62)	<.001	14.25 (7.21-28.19)	<.001	2.95 (1.63-5.32)	<.001
≥10 000	79	7.09 (4.69-10.71)	<.001	32.63 (17.2-61.89)	<.001	2.33 (1.32-4.11)	.004
No D-dimer measured	697	1.85 (1.34-2.55)	<.001	2.51 (1.44-4.39)	.001	1.47 (1.00-2.16)	.05

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; COVID-19, coronavirus disease 2019.

SI conversion factor: To convert D-dimer to nmol/L, multiply values by 5.476.

[a] Race and ethnicity were identified by the patient and recorded in the medical chart. Asian group includes Chinese, Asian, Asian–unspecified, Asian Indian, Bangladeshi, Filipino, Pakistani, Vietnamese, Japanese, Korean. Other/multiracial group includes other race, Pacific Islander, Native American (American Indian/Eskimo/Aleutian), and Native Hawaiian.

[b] In addition to the variables listed in the table, we also adjusted for peripheral vascular disease; cerebrovascular disease; chronic obstructive pulmonary disease; kidney disease; cancer; malignancy; and atrial fibrillation.

[c] D-dimer values were included if obtained within 24 hours of admission.

from chart review, and mortality was defined as in-hospital death or discharge to hospice as of June 1, 2020.

We investigated risk factors for thrombotic events and conducted competing risk survival analyses. For the end point of mortality, competing risk was discharge; for the end point of thrombosis, competing risks were death or discharge. Variables were included in the models because of their known association with the outcome of interest and statistical differences on multivariable testing, including age, sex, race/ethnicity, body mass index, smoking, comorbidities, and D-dimer levels.

Statistical analyses were conducted using Rstudio (R version 3.5.1). A 2-tailed $P < .05$ was considered statistically significant.

Results | Among 3334 consecutive hospitalized COVID-19 patients, the median age was 64 (interquartile range, 51-75) years; 39.6% were female. Any thrombotic event (patients

could have more than 1) occurred in 533 (16.0%) patients; 207 (6.2%) were venous (3.2% PE and 3.9% DVT) and 365 (11.1%) were arterial (1.6% ischemic stroke, 8.9% MI, and 1.0% systemic thromboembolism; **Table 1**). Following multivariable adjustment, age, sex, Hispanic ethnicity, coronary artery disease, prior MI, and higher D-dimer levels at hospital presentation were associated with a thrombotic event (**Table 2**).

All-cause mortality was 24.5% and was higher in those with thrombotic events (43.2% vs 21.0%, $P < .001$) (Table 1). After multivariable adjustment, a thrombotic event was independently associated with mortality (adjusted hazard ratio, 1.82; 95% CI, 1.54-2.15; $P < .001$). Both venous (adjusted hazard ratio, 1.37; 95% CI, 1.02-1.86; $P = .04$) and arterial (adjusted hazard ratio, 1.99; 95% CI, 1.65-2.40; $P < .001$) thrombosis were associated with mortality ($P = .25$ for interaction).

Among 829 ICU patients, 29.4% had a thrombotic event (13.6% venous and 18.6% arterial). Among 2505 non-ICU patients, 11.5% had a thrombotic event (3.6% venous and 8.4% arterial).

Discussion | In patients with COVID-19 hospitalized in a large New York City health system, a thrombotic event occurred in 16.0%. D-dimer level at presentation was independently associated with thrombotic events, consistent with an early coagulopathy.

Prior studies varied regarding the precise incidence of thrombosis; however, all suggested a heightened risk in patients with COVID-19.[3,4] This analysis found variation by clinical setting and type of thrombosis event. While thrombosis is observed in other acute infections[5] (eg, 5.9% prevalence during the 2009 influenza pandemic),[6] the thrombotic risk appears higher in COVID-19. Thrombosis in patients with COVID-19 may be due to a cytokine storm, hypoxic injury, endothelial dysfunction, hypercoagulability, and/or increased platelet activity.

This study has several limitations. A diagnosis of thrombosis may be underestimated because imaging studies were limited due to concerns of transmitting infection or competing risk of death. Type of MI was not confirmed with cardiac catheterization. Clinical practice changed over the study period, with increased awareness of thrombotic events and use of anticoagulation, which may affect the incidence of thrombosis.

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