Letters

RESEARCH LETTER

Incidence of 30-Day Venous Thromboembolism in Adults Tested for SARS-CoV-2 Infection in an Integrated Health Care System in Northern California

Hospitalization for COVID-19 is associated with high rates of venous thromboembolism (VTE).[1] Whether SARS-CoV-2 infection affects the risk of VTE outside of the hospital setting remains poorly understood. We report on the 30-day incidence of outpatient and hospital-associated VTE following SARS-CoV-2 testing among adult members of the Kaiser Permanente Northern California health plan.

Methods | We performed a retrospective cohort study of 220 588 adult members of the Kaiser Permanente Northern California health plan who were tested for SARS-CoV-2 by polymerase chain reaction from February 25 through August 31, 2020. For participants with multiple SARS-CoV-2 tests, the index date was the first test date with a positive result or the first test date with a negative result if all tests were negative. We characterized study participants by demographic information, comorbidities, testing location, and level of care, excluding participants who were asymptomatic at the time of testing or had received anticoagulation in the prior year. We assessed incidence and timing of 30-day VTE using diagnosis codes, new anticoagulant prescriptions, and VTE encounters with a centralized anticoagulation management service.[2] We identified inpatient anticoagulation based on consecutive-day administration of VTE treatment dosing of oral, intravenous, or subcutaneous anticoagulants. We defined VTE as outpatient events when diagnosed in outpatient or emergency department settings and as hospital-associated events when diagnosed during or after hospitalization. The Kaiser Permanente Northern California institutional review board approved the study and waived informed consent according to the Common Rule. Analyses were performed using SAS, version 9.4 (SAS Institute Inc); 2-sided χ^2 and Kruskal-Wallis tests with $P < .05$ were considered to be statistically significant.

Results | Of the 220 588 patients with symptoms who were tested for SARS-CoV-2 (mean [SD] age, 47.1 [17.3] years; 131 075 [59.4%] women), 26 104 (11.8%) had a positive result (**Table 1**). Within 30 days of testing, a VTE was diagnosed in 198 (0.8%) of the patients with a positive SARS-CoV-2 result and 1008 (0.5%) of patients with a negative result ($P < .001$). Viral testing took place in an outpatient setting for most of the patients (117 of 198; 59.1%) who had a positive SARS-CoV-2 test result and later developed VTE. Of these 117 patients, 89 (76.1%) required subsequent hospitalization. Among those patients who underwent outpatient viral testing, 30-day VTE incidence was higher among those with a positive SARS-CoV-2 result than among those with a negative result (4.7 vs 1.6 cases per 1000 individuals tested; $P < .001$). Compared with patients with a negative SARS-CoV-2 test result, those with a positive result had a higher 30-day incidence of hospital-associated (5.8 vs 3.0 cases per 1000 individuals tested; $P < .001$) but not outpatient VTE (1.8 vs 2.2 cases per 1000 tested; $P = .16$; **Table 2**). Posthospital VTE occurred with similar frequency among participants with positive and negative SARS-CoV-2 test results (1.0 vs 1.1 cases per 1000 tested; $P = .51$). In patients with a positive result, the median (interquartile range) number of days (11 [4-21] vs 11 [1-25]; $P = .67$) from viral testing to anticoagulation was comparable for outpatient and posthospital VTE.

Discussion | The incidence of outpatient VTE among symptomatic patients with positive SARS-CoV-2 test results was similar to that of patients with negative results. In parallel to recent reports, posthospital VTE incidence did not differ by SARS-CoV-2 status and was comparable with that seen in clinical trials of thromboprophylaxis.[3,4] A VTE is a potentially preventable complication of SARS-CoV-2 infection, especially in outpatients with risk factors for thrombosis or severe COVID-19. Ongoing randomized clinical trials will determine whether the risks and benefits of prophylactic anticoagulation in outpatients with COVID-19 will improve clinical outcomes.[5] Recognizing that the timing of outpatient VTE paralleled that of posthospital events, the 30-day duration of outpatient thromboprophylaxis proposed in clinical trials may be sufficient to mitigate virally mediated thromboinflammation.[6]

Limitations of VTE diagnosis include changes in diagnostic testing patterns because of possible infection transmission or recognition of VTE risk with SARS-CoV-2, as well as increased use of empirical anticoagulation and/or anti-inflammatory agents. Our approach to case identification may have missed VTE; however, incidence in hospitalized patients paralleled that identified using natural language processing methods.[1] Lastly, outpatient VTE burden may have been underestimated if diagnostic imaging occurred shortly after hospitalization.

These findings suggest that VTE incidence outside of the hospital is not significantly increased with SARS-CoV-2 infection and argue against the routine use of outpatient thromboprophylaxis outside of clinical trials. Recognizing that COVID-19–associated symptoms and disability may persist for months, clinical trials and additional longitudinal studies are needed to understand the role of outpatient and hospital treatment in 90-day VTE.

Table 1. Characteristics of Participants With Symptoms (n = 220 588) by SARS-CoV-2 and Venous Thromboembolism (VTE) Status

Characteristic	Patients, No. (%)			
	SARS-CoV-2 positive		SARS-CoV-2 negative	
	No VTE (n = 25 906)	VTE (n = 198)	No VTE (n = 193 476)	VTE (n = 1008)
Age, y				
18-29	5925 (23)	14 (7)	34 180 (18)	28 (3)
30-39	5670 (22)	19 (10)	41 102 (21)	47 (5)
40-49	5451 (21)	38 (19)	36 432 (19)	89 (9)
50-59	4682 (18)	48 (24)	33 676 (17)	152 (15)
60-69	2655 (10)	40 (20)	25 593 (13)	245 (24)
70-79	984 (4)	26 (13)	14 382 (7)	234 (23)
≥80	539 (2)	13 (7)	8111 (4)	213 (21)
Median (IQR)	42 (31-55)	56 (45-67)	46 (34-60)	68 (56-78)
Sex				
Women	13 649 (53)	79 (40)	116 837 (60)	510 (51)
Men	12 257 (47)	119 (60)	76 639 (40)	498 (49)
Race/ethnicity				
Asian	3176 (12)	30 (15)	32 310 (17)	116 (12)
Black	1767 (7)	25 (13)	13 857 (7)	105 (10)
Hispanic	13 116 (51)	88 (44)	46 857 (24)	127 (13)
White	5667 (22)	45 (23)	84 398 (44)	615 (61)
Missing/other	2180 (8)	10 (5)	16 054 (8)	45 (4)
BMI				
Underweight	163 (1)	1 (0)	2616 (1)	24 (2)
Healthy weight	4588 (18)	23 (12)	55 413 (29)	256 (25)
Overweight	7963 (31)	56 (28)	62 134 (32)	303 (30)
Obese	12 086 (47)	110 (56)	69 244 (36)	417 (41)
Unknown	1106 (4)	8 (4)	4069 (2)	8 (1)
Median (IQR)	30 (26-34)	31 (28-36)	28 (24-32)	29 (24-34)
Comorbidities				
Hypertension	2563 (10)	98 (49)	25 151 (13)	611 (61)
Diabetes	2672 (10)	71 (36)	18 493 (10)	322 (32)
Chronic kidney disease	901 (3)	28 (14)	11 056 (6)	273 (27)
COPD/asthma	2254 (9)	38 (19)	28 058 (15)	300 (30)
Congestive heart failure	364 (1)	22 (11)	6128 (3)	256 (25)
Liver cirrhosis	69 (0)	3 (2)	1029 (1)	38 (4)
Malignant neoplasm	397 (2)	15 (8)	8592 (4)	298 (30)
Charlson Comorbidity Index score				
0	18 428 (71)	96 (48)	122 256 (63)	264 (26)
1-2	5698 (22)	66 (33)	48 548 (25)	271 (27)
3-4	986 (4)	16 (8)	11 429 (6)	193 (19)
≥5	794 (3)	20 (10)	11 243 (6)	280 (28)
Median (IQR)	0 (0-1)	1 (0-2)	0 (0-1)	2 (0-5)
Smoking status				
Ever	6597 (25)	58 (29)	66 075 (34)	491 (49)
Never	18 367 (71)	131 (66)	124 209 (64)	510 (51)
Unknown	942 (4)	9 (5)	3192 (2)	7 (1)
Test month				
February-April	2068 (8)	46 (23)	28 428 (15)	201 (20)
May	979 (4)	9 (5)	32 579 (17)	235 (23)
June	3354 (13)	25 (13)	28 577 (15)	165 (16)
July	12 185 (47)	70 (35)	61 153 (32)	217 (22)
August	7320 (28)	48 (24)	42 739 (22)	190 (19)

(continued)

Table 1. Characteristics of Participants With Symptoms (n = 220 588) by SARS-CoV-2 and Venous Thromboembolism (VTE) Status (continued)

Characteristic	Patients, No. (%)			
	SARS-CoV-2 positive		SARS-CoV-2 negative	
	No VTE (n = 25 906)	VTE (n = 198)	No VTE (n = 193 476)	VTE (n = 1008)
Laboratory test setting				
Outpatient	22 209 (86)	95 (48)	168 780 (87)	190 (19)
Emergency department	2420 (9)	22 (11)	12 997 (7)	107 (11)
Inpatient	1277 (5)	81 (41)	11 699 (6)	711 (71)
Highest level of follow-up care				
Outpatient/emergency department	23 092 (89)	28 (14)	172 713 (89)	114 (11)
Inpatient	2252 (9)	82 (41)	18 479 (10)	645 (64)
Intensive care unit	562 (2)	88 (44)	2284 (1)	249 (25)

Abbreviations: BMI, body mass index calculated as weight in kilograms divided by height in meters squared; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

Table 2. Incidence of 30-Day Venous Thromboembolism (VTE) Among Participants (n = 220 588) by Diagnosis Location and SARS-CoV-2 Status

Location	No. (rate per 1000 participants)		*P* value[a]
	SARS-CoV-2 positive (n = 26 104)	SARS-CoV-2 negative (n = 194 484)	
All VTE events[b]	198 (7.6)	1008 (5.2)	<.001
Outpatient VTE	47 (1.8)	434 (2.2)	.16
Hospital-associated VTE	151 (5.8)	574 (3.0)	<.001
Inpatient	125 (4.8)	352 (1.8)	<.001
Posthospitalization	26 (1.0)	222 (1.1)	.51
Viral testing			
Outpatient	117 of 24 746 (4.7)	297 of 182 074 (1.6)	<.001
Inpatient	81 of 1358 (59.6)	711 of 12 410 (57.3)	.72

Abbreviation: IQR, interquartile range.

[a] χ^2 test.

[b] Outpatient, occurring in outpatient or emergency department settings; hospital-associated VTE, occurring during or after hospitalization.

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