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COVID-19 and Risk of VTE in Ethnically Diverse Populations

Alan S. Go, MD; Kristi Reynolds, PhD, MPH; Grace H. Tabada, MPH; Priya A. Prasad, PhD, MPH;
Sue Hee Sung, MPH; Elisha Garcia, BS; Cecilia Portugal, MPH; Dongjie Fan, MSPH; Ashok P. Pai, MD;
and Margaret C. Fang, MD, MPH

BACKGROUND: Limited existing data suggest that the novel COVID-19 may increase risk of VTE, but information from large, ethnically diverse populations with appropriate control participants is lacking.

RESEARCH QUESTION: Does the rate of VTE among adults hospitalized with COVID-19 differ from matched hospitalized control participants without COVID-19?

STUDY DESIGN AND METHODS: We conducted a retrospective study among hospitalized adults with laboratory-confirmed COVID-19 and hospitalized adults without evidence of COVID-19 matched for age, sex, race or ethnicity, acute illness severity, and month of hospitalization between January 2020 and August 2020 from two integrated health care delivery systems with 36 hospitals. Outcomes included VTE (DVT or pulmonary embolism ascertained using diagnosis codes combined with validated natural language processing algorithms applied to electronic health records) and death resulting from any cause at 30 days. Fine and Gray hazards regression was performed to evaluate the association of COVID-19 with VTE after accounting for competing risk of death and residual differences between groups, as well as to identify predictors of VTE in patients with COVID-19.

RESULTS: We identified 6,319 adults with COVID-19 and 6,319 matched adults without COVID-19, with mean ± SD age of 60.0 ± 17.2 years, 46% women, 53.1% Hispanic, 14.6% Asian/Pacific Islander, and 10.3% Black. During 30-day follow-up, 313 validated cases of VTE (160 COVID-19, 153 control participants) and 1,172 deaths (817 in patients with COVID-19, 355 in control participants) occurred. Adults with COVID-19 showed a more than threefold adjusted risk of VTE (adjusted hazard ratio, 3.48; 95% CI, 2.03-5.98) compared with matched control participants. Predictors of VTE in patients with COVID-19 included age ≥ 55 years, Black race, prior VTE, diagnosed sepsis, prior moderate or severe liver disease, BMI ≥ 40 kg/m^2, and platelet count > 217 k/μL.

INTERPRETATION: Among ethnically diverse hospitalized adults, COVID-19 infection increased the risk of VTE, and selected patient characteristics were associated with higher thromboembolic risk in the setting of COVID-19.   CHEST 2021; 160(4):1459-1470

KEY WORDS: covid-19; epidemiology; risk factor; VTE

Take-home Points

Study Question: Does the novel COVID-19 independently increase the risk for VTE (DVT or pulmonary embolism)?

Results: Among 12,638 ethnically diverse matched hospitalized adults with and without COVID-19, after accounting for competing risk of death and potential confounders, adults with COVID-19 showed a nearly 3.5-fold higher adjusted risk of experiencing VTE compared with matched adults without evidence of COVID-19 (adjusted hazard ratio, 3.48; 95% CI, 2.03-5.98); older age, Black race, prior VTE, diagnosis of sepsis, pre-existing liver disease, severe obesity, and elevated platelet count were associated with higher risk of VTE in patients with COVID-19.

Interpretation: COVID-19 infection significantly increases the risk of clinically recognized VTE in hospitalized adults, with selected readily available patient characteristics associated with a higher risk of VTE in the setting of COVID-19.

COVID-19 remains a leading cause of death internationally.[1,2] In addition to respiratory and multiorgan failure, thrombosis is an increasing concern, particularly among adults hospitalized with COVID-19. Recent studies have reported that COVID-19 is associated with abnormal coagulation profiles,[3-5] and a recent meta-analysis suggested that it may predispose patients to venous thromboembolic events and other types of thromboembolism, as well as worse outcomes after VTE.[6] However, few data exist about the incidence of VTE associated with COVID-19 in large, ethnically diverse populations. Existing studies have focused primarily on only critically ill patients with COVID-19, with uncertainty about VTE risk compared with appropriate control participants without COVID-19 and after accounting for the competing risk of non-VTE-related death associated with COVID-19.[6] These insights are key to understanding who potentially may benefit from prevention strategies, given that limited evidence exists to help guide which patients with COVID-19 should be offered VTE prophylaxis initially or after hospitalization and at what anticoagulation intensity.[7]

To address these knowledge gaps, we evaluated the rate of VTE among a large, ethnically diverse cohort of adults hospitalized with COVID-19 compared with matched control participants without COVID-19 and also identified predictors of VTE in patients with COVID-19.

Methods

Source Population

The source population was derived from Kaiser Permanente Northern California and Southern California integrated health care delivery systems, which provide comprehensive care that is captured through electronic medical record (EMR) systems covering inpatient, ED, and outpatient settings. Kaiser Permanente Northern California serves > 4.5 million members at 21 hospital-based medical centers, and Kaiser Permanente Southern California serves > 4.6 million members at 15 hospital-based medical centers in California. Their membership is highly representative of their local surroundings and the statewide population with regard to age, sex, and race and ethnicity.[8,9]

Institutional review boards at Kaiser Permanente Northern California and Southern California approved the study (Identifier: 1279252). A waiver of informed consent was obtained because of the nature of this retrospective, data-only study.

Study Sample

The Kaiser Permanente Virtual Data Warehouse and EMR were the primary data sources for patient identification and characterization at participating sites. The Virtual Data Warehouse comprises EMR-based datasets with linked sociodemographic, administrative, pharmacy, laboratory results, and health care use data.[10,11]

We performed a retrospective cohort study of hospitalized adults with COVID-19 and matched hospitalized control participants without evidence of COVID-19 (Fig 1). We first identified adults (age ≥ 18 years) hospitalized at a Kaiser Permanente facility between January 1 and August 31, 2020. We excluded people with missing sex or fewer than 12 months of continuous enrollment and pharmacy benefits before admission to ensure adequate data on covariates.

We identified patients with laboratory-confirmed COVID-19 based on polymerase chain reaction testing for SARS-CoV-2 ascertained through Kaiser Permanente laboratory systems, which also includes results for approved assays from outside laboratories. We assigned each patient's index date as the admission date after the first SARS-CoV-2 test showing positive results within 30 days before or during the index hospitalization.

Medicine (A. S. Go, P. A. Prasad, and M. C. Fang), the Department of Epidemiology and Biostatistics (A. S. Go), University of California, San Francisco, San Francisco, and the Departments of Medicine and of Health Research and Policy (A. S. Go), Stanford University, Palo Alto, CA.

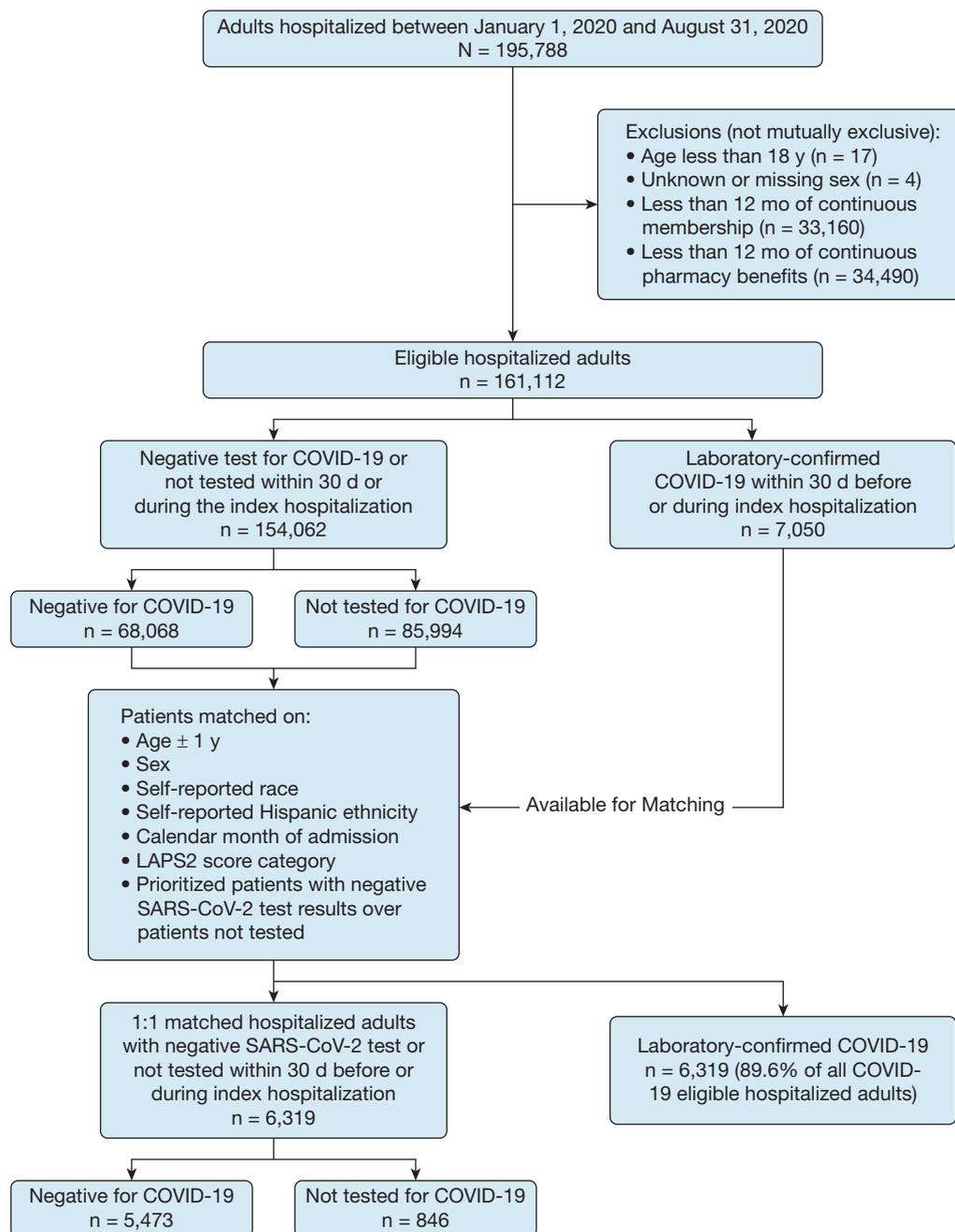**CORRESPONDENCE TO:** Alan S. Go, MD; email: Alan.S.Go@kp.org

Figure 1 – Cohort assembly of hospitalized adults with COVID-19 and matched adults without COVID-19. LAPS2 = Laboratory-Based Acute Physiology Score, version 2.

We next identified a matched cohort of hospitalized adults without evidence of COVID-19 (ie, negative SARS-CoV-2 polymerase chain reaction test results or not having received a test up to 30 days before or during the index hospitalization). If the patient demonstrated negative test results, the hospitalization within 30 days of those results was used as the index hospitalization; if the patient was hospitalized but never underwent SARS-CoV-2 testing, their index date was assigned as the first admission date during the study period. We next performed 1:1 matching between patients with COVID-19 and control participants based on Laboratory-Based Acute Physiology Score, version 2, at admission, age (± 1 year), self-

reported sex, self-reported race and Hispanic ethnicity, and calendar month of index hospitalization. The Laboratory-Based Acute Physiology Score, version 2, is a validated, integrated physiology-based score of severity of illness calculated from multiple laboratory results and vital signs that is highly predictive of short-term mortality.[12]

Outcomes

Censoring occurred at the earliest of a VTE event, death, health plan disenrollment, or completing 30 days of follow-up. The primary outcome was acute VTE (DVT or pulmonary embolism) on or after

index date, which could occur in the inpatient, postdischarge outpatient, or ED setting. We initially searched EMR systems for inpatient encounters with primary or secondary International Classification of Disease, Tenth Revision, diagnosis codes for DVT and pulmonary embolism (codes available on request). Postdischarge ED or outpatient encounters also required evidence of a relevant radiology procedure (eg, chest CT angiography or extremity ultrasound) within 14 days of an encounter with an associated VTE diagnosis code. Given that we demonstrated previously the suboptimal accuracy of VTE diagnosis codes in inpatient, ED, and outpatient settings within participating sites,[13] we developed and validated a rules-based natural language processing algorithm to identify valid acute VTE events from unstructured EMR data within Kaiser Permanente Northern and Southern California. The algorithm was developed and trained on 479 confirmed VTE events, with a positive predictive value of 95% and a negative predictive value of 97% compared with physician adjudication of medical records using standardized diagnostic criteria.[14]

We identified deaths using comprehensive data from health plan databases (including inpatient and ED deaths and proxy reports), state death certificate files, and Social Security Administration Death Master File.[10,15-17] Information on presumed cause(s) of death was unavailable.

Covariates

Demographic characteristics (age, self-reported sex, and self-reported race and Hispanic ethnicity) were collected from EMR data. We ascertained relevant medical history up to 5 years before index date using previously validated approaches based on International Classification of Disease, Ninth and Tenth Revisions, diagnosis and procedure codes, Current Procedure Terminology procedure codes, laboratory results, pharmacy dispensings, and vital sign data.[10,11,18-20] This included cardiovascular conditions (coronary heart disease, acute myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass surgery, heart failure, rheumatic heart disease, atrial fibrillation or flutter, mitral or aortic valvular disease, peripheral artery disease, ischemic stroke, or transient ischemic attack), cardiovascular risk factors (diabetes mellitus, hypertension, dyslipidemia, smoking status), and other medical history (coagulopathy, hypercoagulable hematologic conditions, thrombophilia, chronic lung disease, liver disease, peptic ulcer disease, intracranial hemorrhage, hospitalization for GI hemorrhage, hospitalization for other bleeding, hemiplegia or paraplegia, inflammatory bowel disease, rheumatic disease, cancer, prior mechanical fall, dementia, depression, and substance or alcohol misuse). We also included information on diagnosed sepsis during the index hospitalization based on diagnostic codes. We ascertained

kidney function from the estimated glomerular filtration rate before the index date using the CKD-EPI equation[21] (in milliliters per minute per 1.73 m^2) and serum creatinine concentration on or within 2 days of admission. We also collected preadmission BP, BMI, hemoglobin level, and platelet count, if available, or within 2 days of admission.

We characterized preadmission receipt of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium channel blockers, diuretics, aldosterone receptor antagonists, nonaspirin antiplatelet agents, statins, and other lipid-lowering agents based on data on estimated day supply per dispensed prescription and refill patterns in pharmacy databases using validated methods.[22] Baseline oral anticoagulant use was defined as a dispensed prescription covering any part of the 60 days before or on the index date. Parenteral (heparin, fondaparinux, enoxaparin, dalteparin, and tinzaparin) or oral (warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban) anticoagulant use during the index hospitalization was defined as dispensing during the hospital stay, but before a VTE, if one occurred. Anticoagulant exposure at discharge was characterized as dispensing on or within 7 days after discharge, but before a VTE event, if one occurred during this period.

Statistical Analysis

Analyses were performed using SAS version 9.4 software (SAS Inc.). Baseline characteristics were presented as mean ± SD or median and interquartile range for continuous variables and frequencies with percentages for categorical data. Any missing data were assigned to a missing or unknown category. Given the large sample size, we compared characteristics between matched patients using Cohen's D value[23,24] for continuous variables and Cramér's V[25,26] for categorical variables, with a value of > 0.10 considered potentially significant. We used the Kruskal-Wallis test to compare median values, with $P < .05$ considered significant.

We calculated rates (per 100 person-years) with associated 95% CIs for VTE and death at 30 days, and we compared the cumulative incidence function of VTE by group using Gray's test. Given the concern for competing risk of death that may not be the result of VTE associated with COVID-19, we performed multivariate Fine-Gray subdistribution hazard modeling[27] to account for competing risk of death and potential confounders, with covariates included that significantly differed between groups. Finally, among the subgroup of patients with COVID-19, we conducted a Fine-Gray subdistribution hazard model to identify multivariate predictors of VTE using patient characteristics in Table 1 as candidate predictors.

Results

Baseline Characteristics in Matched Patients

Between January 1 and August 31, 2020, we identified 7,050 eligible hospitalized adults with laboratory-confirmed COVID-19. We matched 6,319 patients with COVID-19 (89.6%) with a hospitalized control group without evidence of COVID-19 based on age, sex, race or ethnicity, level of acute illness severity, and calendar month of hospitalization (Fig 1). Of note, 91.4% of matched patients with COVID-19 were considered to

have severe disease (ie, oxygen saturation < 94% or receipt of high-flow oxygen or mechanical ventilation).[28]

Matched patients were similar at baseline, although patients with COVID-19 were less likely to have cancer and more likely to have sepsis diagnosed during the index hospitalization and to have a higher BMI (Table 1). Among tested patients, those with COVID-19 showed slightly lower median serum creatinine concentration, but higher hemoglobin and platelet counts compared with matched control participants.

TABLE 1] Characteristics of Hospitalized Adults With COVID-19 and Matched Hospitalized Adults Without Evidence of COVID-19

Baseline Characteristic	Overall (N = 12,638)	Patients With COVID-19 (n = 6,319)	Patients Without COVID-19 (n = 6,319)	D or V Value
Age, y	...	...	...	...
Mean ± SD	60.0 ± 17.2	60.0 ± 17.2	60.0 ± 17.2	0.00
Range	18.2-104.3	18.2-103.5	18.2-104.3	...
Age group, y	...	...	...	...
≤ 54	4,747 (37.5)	2,377 (37.6)	2,370 (37.5)	
55-64	2,855 (22.6)	1,430 (22.6)	1,425 (22.6)	
65-74	2,402 (19.0)	1,192 (18.9)	1,210 (19.1)	0.00
75-84	1,716 (13.6)	857 (13.6)	859 (13.6)	
≥ 85	918 (7.3)	463 (7.3)	455 (7.2)	
Women	5,802 (45.9)	2,901 (45.9)	2,901 (45.9)	0.00
Race	...	...	...	...
White	9,340 (73.9)	4,670 (73.9)	4,670 (73.9)	
Black	1,298 (10.3)	649 (10.3)	649 (10.3)	
Asian/Pacific Islander	1,848 (14.6)	924 (14.6)	924 (14.6)	0.00
Other	96 (0.8)	48 (0.8)	48 (0.8)	
Unknown	56 (0.4)	28 (0.4)	28 (0.4)	
Hispanic ethnicity	6,710 (53.1)	3,355 (53.1)	3,355 (53.1)	0.00
Days between COVID-19 test and index hospitalization	...	...	...	...
Mean ± SD	3.3 ± 5.4	3.6 ± 4.8	3.0 ± 5.9	0.10
Median (IQR)	1.0 (0.0-4.0)	2.0 (0.0-6.0)	1.0 (0.0-3.0)	< .001[a]
Not tested	846 (6.7)	0 (0.0)	846 (13.4)	...
Baseline medical history	...	...	...	...
Cardiovascular diseases	...	...	...	...
Coronary heart disease	945 (7.5)	380 (6.0)	565 (8.9)	0.06
Acute myocardial infarction	305 (2.4)	125 (2.0)	180 (2.8)	0.03
Unstable angina	92 (0.7)	32 (0.5)	60 (0.9)	0.03
Percutaneous coronary intervention	747 (5.9)	310 (4.9)	437 (6.9)	0.04
Coronary artery bypass surgery	81 (0.6)	31 (0.5)	50 (0.8)	0.02
Heart failure	1,326 (10.5)	492 (7.8)	834 (13.2)	0.09
Rheumatic heart disease	192 (1.5)	64 (1.0)	128 (2.0)	0.04
Atrial fibrillation or flutter	1,280 (10.1)	528 (8.4)	752 (11.9)	0.06
Mitral or aortic valvular disease	741 (5.9)	259 (4.1)	482 (7.6)	0.08
Peripheral artery disease	738 (5.8)	276 (4.4)	462 (7.3)	0.06
Ischemic stroke or transient ischemic attack	440 (3.5)	184 (2.9)	256 (4.1)	0.03
Cardiovascular risk factors	...	...	...	...
Diabetes mellitus	4,862 (38.5)	2,559 (40.5)	2,303 (36.4)	0.04
Hypertension	6,828 (54.0)	3,315 (52.5)	3,513 (55.6)	0.03
Dyslipidemia	8,100 (64.1)	4,083 (64.6)	4,017 (63.6)	0.01
Former or current smoker	4,868 (38.5)	2,201 (34.8)	2,667 (42.2)	0.08
Other medical history	...	...	...	...
Coagulopathy	1,242 (9.8)	474 (7.5)	768 (12.2)	0.08

(Continued)

TABLE 1] *(Continued)*

Baseline Characteristic	Overall (N = 12,638)	Patients With COVID-19 (n = 6,319)	Patients Without COVID-19 (n = 6,319)	D or V Value
Hypercoagulable condition	278 (2.2)	111 (1.8)	167 (2.6)	0.03
Thrombophilia	99 (0.8)	50 (0.8)	49 (0.8)	0.001
Chronic lung disease	2,898 (22.9)	1,404 (22.2)	1,494 (23.6)	0.02
Moderate or severe liver disease	249 (2.0)	58 (0.9)	191 (3.0)	0.08
Mild liver disease	391 (3.1)	105 (1.7)	286 (4.5)	0.08
Peptic ulcer disease	182 (1.4)	53 (0.8)	129 (2.0)	0.05
Intracranial hemorrhage, nontraumatic	172 (1.4)	60 (0.9)	112 (1.8)	0.04
Intracranial hemorrhage, traumatic	104 (0.8)	43 (0.7)	61 (1.0)	0.02
Hospitalized gastrointestinal hemorrhage	257 (2.0)	77 (1.2)	180 (2.8)	0.06
Hospitalized other bleeding	39 (0.3)	18 (0.3)	21 (0.3)	0.004
Hemiplegia or paraplegia	326 (2.6)	123 (1.9)	203 (3.2)	0.04
Inflammatory bowel disease	163 (1.3)	61 (1.0)	102 (1.6)	0.03
Rheumatic disease	367 (2.9)	161 (2.5)	206 (3.3)	0.02
Cancer	1,132 (9.0)	348 (5.5)	784 (12.4)	0.12
Prior mechanical fall	243 (1.9)	108 (1.7)	135 (2.1)	0.02
Diagnosed dementia	709 (5.6)	403 (6.4)	306 (4.8)	0.03
Diagnosed depression	2,343 (18.5)	997 (15.8)	1,346 (21.3)	0.07
Substance abuse	445 (3.5)	130 (2.1)	315 (5.0)	0.08
Alcohol abuse	826 (6.5)	261 (4.1)	565 (8.9)	0.10
Prior VTE	228 (1.8)	80 (1.3)	148 (2.3)	0.04
Time between prior VTE and index admission, y	...	...	...	...
Mean ± SD	1.6 ± 1.2	1.6 ± 1.2	1.5 ± 1.2	0.11
Median (IQR)	1.3 (0.4-2.6)	1.6 (0.5-2.8)	1.2 (0.4-2.5)	0.42[a]
Sepsis diagnosed during index hospitalization	4,368 (34.6)	3,047 (48.2)	1,321 (20.9)	0.29
Anticoagulant exposure before and during the index hospitalization but before a VTE	...	...	...	...
Baseline oral anticoagulant use	879 (7.0)	309 (4.9)	570 (9.0)	0.08
Parenteral anticoagulant during index hospitalization	8,342 (66.0)	5,269 (83.4)	3,073 (48.6)	0.37
Oral anticoagulant during index hospitalization	852 (6.7)	389 (6.2)	463 (7.3)	0.02
Distribution of anticoagulant use before and after discharge from index hospitalization	...	...	...	...
Oral anticoagulant within 60 d before index date and oral anticoagulant after discharge	694 (5.5)	239 (3.8)	455 (7.2)	
Oral anticoagulant within 60 d before index date, but not after discharge	185 (1.5)	70 (1.1)	115 (1.8)	0.10

(Continued)

TABLE 1] *(Continued)*

Baseline Characteristic	Overall (N = 12,638)	Patients With COVID-19 (n = 6,319)	Patients Without COVID-19 (n = 6,319)	D or V Value
Oral anticoagulant after discharge only	492 (3.9)	316 (5.0)	176 (2.8)	
No anticoagulant use 60 d before index date or after discharge	11,267 (89.1)	5,694 (90.1)	5,573 (88.2)	
Baseline medication use	...	...	...	...
Angiotensin-converting enzyme inhibitor	2,598 (20.6)	1,282 (20.3)	1,316 (20.8)	0.01
Angiotensin II receptor blocker	1,679 (13.3)	883 (14.0)	796 (12.6)	0.02
β-blocker	2,996 (23.7)	1,289 (20.4)	1,707 (27.0)	0.08
Calcium channel blocker	2,188 (17.3)	1,043 (16.5)	1,145 (18.1)	0.02
Diuretic	3,052 (24.1)	1,402 (22.2)	1,650 (26.1)	0.05
Aldosterone receptor antagonist	326 (2.6)	100 (1.6)	226 (3.6)	0.06
Nonaspirin antiplatelet agent	521 (4.1)	210 (3.3)	311 (4.9)	0.04
Statin	5,184 (41.0)	2,602 (41.2)	2,582 (40.9)	0.003
Other lipid-lowering agents	222 (1.8)	100 (1.6)	122 (1.9)	0.01
Vital signs	...	...	...	...
BP, mm Hg	...	...	...	...
Systolic				
≥ 180	2 (0.0)	2 (0.0)	0 (0.0)	
160-179	55 (0.4)	20 (0.3)	35 (0.6)	
140-159	727 (5.8)	283 (4.5)	444 (7.0)	
130-139	1,202 (9.5)	538 (8.5)	664 (10.5)	0.08
121-129	1,769 (14.0)	852 (13.5)	917 (14.5)	
≤ 120	8,864 (70.1)	4,617 (73.1)	4,247 (67.2)	
Missing	19 (0.2)	7 (0.1)	12 (0.2)	
Diastolic	...	...	...	...
≥ 110	1 (0.0)	0 (0.0)	1 (0.0)	
100-109	14 (0.1)	3 (0.0)	11 (0.2)	
90-99	126 (1.0)	35 (0.6)	91 (1.4)	
85-89	232 (1.8)	95 (1.5)	137 (2.2)	0.07
81-84	307 (2.4)	121 (1.9)	186 (2.9)	
≤ 80	11,939 (94.5)	6,058 (95.9)	5,881 (93.1)	
Missing	19 (0.2)	7 (0.1)	12 (0.2)	
BMI, kg/m^2	...	...	...	...
< 18.5	321 (2.6)	107 (1.7)	214 (3.4)	
18.5-25.0	2,614 (20.7)	1,064 (16.8)	1,550 (24.5)	
25.0-25.9	3,805 (30.1)	1,833 (29.0)	1,972 (31.2)	
30.0-39.9	4,425 (35.0)	2,457 (38.9)	1,968 (31.1)	0.13
≥ 40	1,382 (10.9)	809 (12.8)	573 (9.1)	
Unknown	91 (0.7)	49 (0.8)	42 (0.7)	
Laboratory values	...	...	...	...
Preadmission estimated glomerular filtration rate, mL/min/1.73 m^2	...	...	...	...
≥ 90	4,511 (35.7)	2,295 (36.3)	2,216 (35.1)	
60-89	3,962 (31.3)	2,023 (32.0)	1,939 (30.7)	

(Continued)

TABLE 1] *(Continued)*

Baseline Characteristic	Overall (N = 12,638)	Patients With COVID-19 (n = 6,319)	Patients Without COVID-19 (n = 6,319)	D or V Value
45-59	1,160 (9.2)	550 (8.7)	610 (9.6)	
30-44	677 (5.4)	318 (5.0)	359 (5.7)	0.08
15-29	283 (2.2)	111 (1.8)	172 (2.7)	
< 15	125 (1.0)	45 (0.7)	80 (1.3)	
Dialysis or transplant	462 (3.7)	165 (2.6)	297 (4.7)	
Unknown	1,458 (11.5)	812 (12.9)	646 (10.2)	
Serum creatinine on or within 2 d of index hospitalization, mg/dL	...	...	...	...
Mean ± SD	1.3 ± 1.7	1.2 ± 1.6	1.4 ± 1.8	0.15
Median (IQR)	0.8 (0.7-1.1)	0.8 (0.7-1.0)	0.9 (0.7-1.2)	< .001[a]
Missing	1,271 (10.1)	356 (5.6)	915 (14.5)	...
Hemoglobin, g/dL	...	...	...	...
≥ 13.0	4,630 (36.6)	2,791 (44.2)	1,839 (29.1)	
12-12.9	2,412 (19.1)	1,356 (21.5)	1,056 (16.7)	
11-11.9	1,945 (15.4)	956 (15.1)	989 (15.7)	
10-10.9	1,413 (11.2)	576 (9.1)	837 (13.2)	0.24
9-9.9	990 (7.8)	331 (5.2)	659 (10.4)	
< 9	1,133 (9.0)	266 (4.2)	867 (13.7)	
Missing	115 (0.9)	43 (0.7)	72 (1.2)	
Platelet, K/μL	...	...	...	...
Mean ± SD	230.9 ± 100.0	245.8 ± 104.3	216.0 ± 93.1	0.30
Median (IQR)	217.0 (164.0-283.0)	229.0 (172.0-301.0)	206.0 (156.5-263.0)	< .001[a]
Missing	125 (1.0)	46 (0.7)	79 (1.3)	...

Data are presented as No. (%), unless otherwise indicated. IQR = interquartile range.
[a]*P* value using Kruskal-Wallis test.

During the index hospitalization, patients with COVID-19 were more likely to receive parenteral anticoagulant therapy compared with those without evidence of COVID-19, but no difference was found in the receipt of anticoagulants at discharge (Table 1). Compared with matched control participants, patients with COVID-19 had longer median length of stay and were more likely to die during the index hospitalization or be discharged to a skilled nursing facility (Table 2).

COVID-19 and Risk of VTE

During the 30-day follow-up, we observed 1,172 deaths from any cause (817 patients with COVID-19, 355 control participants), with a significantly higher crude rate of death in those with COVID-19 compared with matched control participants (163.7 vs 68.6 per 100 person-years, respectively; *P* < .001).

A total of 313 patients experienced a confirmed VTE during follow-up (160 patients with COVID-19, 153

control participants), with no significant difference in VTE type (Table 3) or timing (COVID-19 patients: median, 2 days [interquartile range, 1.0-2.0 days]; matched control participants: median, 1 day [interquartile range, 1.0-2.0 days]; *P* = .25). In comparing unadjusted cumulative incidence function of VTE, patients with COVID-19 had an unadjusted rate (per 100 person-years) of VTE of 0.025 compared with 0.024 (*P* = .69) in matched control participants during the 30-day follow-up.

However, in multivariable Fine-Gray regression that accounted for competing risk of death and potential confounders (prior VTE, cancer, prior anticoagulant use, BMI, hemoglobin, platelet count, diagnosed sepsis, and receipt of anticoagulation during index hospitalization or at discharge), patients with COVID-19 showed a more than threefold higher adjusted risk of VTE compared with matched patients without evidence of

TABLE 2] Hospital Length of Stay and Discharge Status in Hospitalized Adults With COVID-19 and Matched Hospitalized Adults Without Evidence of COVID-19[b]

Baseline Characteristic	Overall (N = 12,638)	Patients With COVID-19 (n = 6,319)	Patients Without COVID-19 (n = 6,319)	D or V Value
Hospital length of stay, d				
Mean ± SD	8.7 ± 10.7	11.2 ± 12.8	6.2 ± 7.5	0.48
Median (IQR)	5.0 (3.0-9.0)	7.0 (4.0-13.0)	4.0 (3.0-7.0)	< .001[a]
Range	1.0-137.0	1.0-137.0	1.0-125.0	
Discharge status (listed in descending order by frequency)				0.22
Home	7,367 (58.3)	3,641 (57.6)	3,726 (59.0)	
Home health	2,911 (23.0)	1,192 (18.9)	1,719 (27.2)	
Died	1,024 (8.1)	838 (13.3)	186 (2.9)	
Skilled nursing facility	752 (6.0)	432 (6.8)	320 (5.1)	
Hospice	230 (1.8)	70 (1.1)	160 (2.5)	
Against medical advice	62 (0.5)	23 (0.4)	39 (0.6)	
Transferred to other acute inpatient hospital	37 (0.3)	13 (0.2)	24 (0.4)	
Residential facility	35 (0.3)	21 (0.3)	14 (0.2)	
Still in Kaiser Permanente hospital	27 (0.2)	13 (0.2)	14 (0.2)	
Rehabilitation facility	14 (0.1)	4 (0.1)	10 (0.2)	
Nursing home	2 (0.0)	1 (0.0)	1 (0.0)	
Other	9 (0.1)	5 (0.1)	4 (0.1)	
Unknown	168 (1.3)	66 (1.0)	102 (1.6)	

Data are presented as No. (%), unless otherwise indicated. IQR = interquartile range.
[a]P value using Kruskal-Wallis test.
[b]Data in this table reflects the full index hospitalization period, even if it lasted longer than 30 days.

COVID-19 (adjusted hazard ratio [aHR], 3.48; 95% CI, 2.03-5.98).

Finally, among patients with COVID-19, significant multivariable predictors of VTE included age 55 to 64 years (aHR, 1.90; 95% CI, 1.16-3.10 years vs 18-54 years), age 65 to 74 years (aHR, 2.49; 95% CI, 1.52-4.06 years vs 18-54 years), age ≥ 75 years (aHR, 3.32; 95% CI, 1.86-5.92 years vs 18-54 years), Black race (aHR, 1.92; 95% CI, 1.24-2.97 vs White race), prior VTE (aHR, 3.49; 95% CI, 2.83-6.66), moderate or severe liver disease (aHR, 5.95; 95% CI, 2.52-14.07), BMI of ≥

TABLE 3] Distribution of VTE Outcome in Hospitalized Adults With COVID-19 and Matched Adults Without Evidence of COVID-19

VTE Characteristic	Overall (N = 313)	Patients With COVID-19 (n = 160)	Patients Without COVID-19 (n = 153)	P Value
Type of VTE	…	…	…	…
Pulmonary embolism	159 (50.8)	81 (50.6)	78 (51.0)	
Lower extremity DVT	90 (28.8)	51 (31.9)	39 (25.5)	
Upper extremity DVT	43 (13.7)	21 (13.1)	22 (14.4	.31
Mesenteric VTE	15 (4.8)	4 (2.5)	11 (7.2)	
Other or unknown VTE	6 (1.9)	3 (1.9)	3 (1.9)	
VTE timing	…	…	…	…
During index hospitalization	282 (90.1)	148 (92.5)	134 (87.6)	.19
After index hospitalization discharge	31 (9.9)	12 (7.5)	19 (12.4)	

Data are presented as No. (%), unless otherwise indicated.

40.0 kg/m^2 (aHR, 2.02; 95% CI, 1.09-3.74 kg/m^2 vs 18.5-25.0 kg/m^2), platelet count of 217 to 283 K/μL (aHR, 1.70; 95% CI, 1.05-2.77 K/μL vs < 164.0 K/μL), platelet count of > 283 K/μL (aHR, 1.81; 95% CI, 1.13-2.90 K/μL vs < 164.0 K/μL), and having received a diagnosis of sepsis (aHR, 2.68; 95% CI, 1.89-3.79).

Discussion

Among hospitalized adults, COVID-19 was associated independently with a nearly 3.5-fold higher risk of VTE in multivariable analyses that accounted for competing risk of death, a wide range of confounders, and more frequent use of VTE prophylaxis compared with contemporary matched hospitalized control participants. VTE occurred early, and the excess adjusted risk persisted throughout the 30-day follow-up period. The risk of VTE in adults with COVID-19 also was higher with older age, Black race, prior VTE, moderate to severe liver disease, severe obesity, platelet count of > 217 K/μL, and having received a diagnosis of sepsis.

Previous studies exploring VTE in COVID-19 largely have included case reports, case series, or cohorts of only patients with COVID-19 with limited sample size and diversity.[6] In a systematic review of 16 published studies of VTE in patients with COVID-19 from multiple countries, significant heterogeneity was present across studies in terms of sample size, severity of COVID-19, and definition of VTE used, which makes combining results across studies challenging.[6] Across these studied patients with COVID-19, a reported composite VTE risk of 5% in patients not in the ICU and 31% in patients in the ICU was found, for an overall summary estimate of 21% (95% CI, 17%-26%).[6] Bilaloglu et al[29] subsequently examined 3,334 hospitalized patients with COVID-19 in New York and reported 6.2% with clinically recognized VTE. Importantly, however, few published studies have included comparable patients without COVID-19. Helm et al[30] examined 77 patients with COVID-19 with acute respiratory distress syndrome admitted to four French hospitals and a historical propensity-matched cohort of 145 patients with ARDS and reported a higher crude risk of pulmonary embolism in patients with COVID-19 (11.7% vs 2.1%; $P = .01$) with adjusted OR of 9.3 (95% CI, 2.2-40). In contrast, Roberts et al[31] studied 1,877 patients with COVID-19 discharged alive and observed nine VTE events within 42 days after discharge (0.48 per 100 discharges), with no significant association of COVID-19 hospital discharge compared with 18,159 hospital discharges for any medical illness in 2019 at two

London hospitals (OR, 1.6; 95% CI, 0.8-3.1), but this study had limited precision and did not adjust for potential confounders. Our study materially expanded on prior studies to clarify more precisely the short-term risk of VTE associated with hospitalized COVID-19 compared with matched hospitalized patients without COVID-19 derived from a very large, ethnically diverse population receiving care from 36 hospitals that specifically accounted for the impact of competing risk of death. In addition, we provided information on readily available demographic and clinical risk factors for VTE in COVID-19.

The exact mechanisms for why COVID-19 increases VTE risk are not fully delineated, with existing studies having focused primarily on critically ill patients with COVID-19. In fatal COVID-19, widespread alveolar damage, endothelial injury, and severe microangiopathy have been observed.[32] Abnormalities in selected coagulation parameters (eg, D-dimer, fibrin degradation product, fibrinogen, prothrombin time, activated partial thromboplastin time) also seem to be common, with significantly worse abnormalities in these parameters in fatal cases.[3] In addition, a high proportion of selected patients with severe COVID-19 had potentially pathogenic acquired antiphospholipid antibodies.[33,34] Importantly, however, the patterns of derangement in coagulation and inflammatory pathways associated with severe COVID-19 may vary from models described for sepsis-induced coagulopathy or disseminated intravascular coagulation,[35,36] which could have important management implications given the need for robust randomized trial evidence for effective VTE prevention strategies across the spectrum of COVID-19 severity.[37,38]

We studied a carefully matched, demographically diverse cohort with comprehensive longitudinal data through 30 days to facilitate evaluation of the risk of VTE associated with COVID-19 and its severity that extended beyond the index hospitalization. We used a combination of diagnosis codes and a validated natural language processing algorithm applied to EMR data to identify validated acute VTE. We addressed the competing risk of death to evaluate more accurately the excess risk of VTE with COVID-19. Finally, we identified independent predictors of VTE associated with COVID-19 that are readily available clinically.

Our study also had limitations. To maximize generalizability, we included hospitalized adults as control participants if they met matching criteria and did not have a SARS-CoV-2 test performed, but this

only affected 13% of all control participants and if some of these patients had undiagnosed COVID-19, this would bias our results to the null. Given the high rate of anticoagulant use during the index hospitalization in the overall cohort and preferentially higher use in patients with COVID-19, the excess risk associated with COVID-19 may be underestimated. Similarly, our models accounted for the competing risk of death from any cause, and it is possible that there were some deaths resulting from undiagnosed VTE, but this tends to bias results toward the null given the substantially higher rate of death in patients with COVID-19. Given that we studied only hospitalized adults, we were unable to evaluate whether the risk of VTE associated with COVID-19 differs in outpatients with less severe COVID-19. Although our study was performed within integrated health care delivery systems caring for populations that are highly representative of the California-wide population, our results may not completely generalize to all countries and health systems.

Interpretation

In a large, diverse, matched cohort of hospitalized adults, COVID-19 was associated independently with a higher risk of VTE, and several patient characteristics were linked to higher VTE risk in the setting of COVID-19. Randomized trials are needed to identify effective and safe thromboembolism preventive strategies in patients with COVID-19.

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