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Venous thromboembolism among patients hospitalized with COVID-19 at Veterans Health Administration Hospitals

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Abstract Patients with coronavirus disease 2019 (COVID-19) are at heightened risk of venous thromboembolic events (VTE), though there is no data examining when these events occur following a COVID-19 diagnosis. We therefore sought to characterize the incidence, timecourse of events, and outcomes of VTE during the COVID-19 pandemic in a national healthcare system using data from Veterans Affairs Administration. (*Am Heart J* 2021;237:1–4.)

Patients with coronavirus disease 2019 (COVID-19) are at heightened risk of thromboembolic events, potentially resulting from propagation of a consumptive coagulopathy due to activation of inflammatory pathways or via endotheliitis.^{1,2} The reported incidence of COVID-19 associated venous thromboembolism (VTE) has varied, likely due to differences in populations studied, settings, patterns of screening, and diagnostic testing. Furthermore, there is no data examining when VTE events occur following a COVID-19 diagnosis. We therefore sought to characterize the incidence, timecourse of events, and outcomes of VTE during the COVID-19 pandemic in a national healthcare system using data from Veterans Affairs (VA) Administration.

Methods

We used the VA Data Warehouse to identify all hospitalized patients with a positive COVID-19 polymerase chain reaction (PCR) between 05/01/2020–08/01/2020. Patients were included if admitted from 48 hours prior to the positive PCR through 21 days following the positive PCR. In the event of multiple positive COVID-19 tests, only the first was considered.

Demographics were obtained using International Classification of Diseases 10th Revision, Clinical Modification (ICD-10) codes at admission (Supplement). The primary outcome was identified using VTE ICD-10 codes after admission through 10/31/2020 at VA hospitals. A propensity score matched, Cox proportional hazard estimate with COVID-19 negative patients was performed using nearest neighbor matching. Event free survival was estimated for COVID-19 positive vs. negative using Kaplan-Meier estimates. An adjusted Cox regression model was used to evaluate the association between COVID-19 and VTE. A P-value <0.05 was considered significant. This study was approved by the Durham VA Medical Center IRB. Analyses were performed using SAS 9.4 (Cary, NC).

Results

During the study period, we found 4,461 hospitalized patients with a positive and 76,929 with negative COVID-19 PCR test(s). The median (25th, 75th percentiles) age of the overall COVID-19 positive cohort was 68 (58, 75) years, 93.3% were male, 52.6% white, 35.7% black, with a median (25th, 75th percentiles) length of stay of 6 (3,14) days (**Table 1**). Among all COVID-19 positive patients, 412 (9.2%) experienced VTE vs. 5,268 (6.8%) of all COVID-19 negative patients ($P<0.0001$). Among 4,314 (96.7% of COVID-19 positive) and 74,398 (96.7% of COVID-19 negative) patients with no prior history of VTE, 305 (7.1%) COVID-19 positive vs. 3,440 (4.6%) COVID-19 negative patients, respectively, experienced VTE ($P<0.0001$). Among COVID-19 positive patients, 67.2% of the VTE events occurred during index hospitalization (vs. 52.3% in COVID-19 negative patients, $P<0.0001$) and 32.7% occurred post-discharge at a median (25th, 75th percentiles) of 16 days (2, 55) vs. 47.7% among COVID-19 negative patients at a median of

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Table 1. Baseline characteristics

	COVID-19 positive (N = 4,461)	COVID-19 negative (N = 76,929)	Total (N = 81,390)	P value
Age (25th, 75th percentiles)	68 (58, 75)	68 (58, 74)	68 (58, 74)	.0005
Gender, n (%)				.8191
Female	298 (6.7)	5207 (6.8)	5505 (6.8)	
Male	4163 (93.3)	71,722 (93.2)	75,885 (93.2)	
Race, n (%)				<.0001
Black	1591 (35.7)	17,316 (22.5)	18,907 (23.2)	
White	2348 (52.6)	52,512 (68.3)	54,860 (67.4)	
Other/Unknown	522 (11.7)	7101 (9.2)	7623 (9.4)	
Prior venous thromboembolism, n (%)				.9850
Yes	147 (3.3)	2531 (3.3)	2678 (3.3)	
No	4314 (96.7)	74,398 (96.7)	78,712 (96.7)	
Anticoagulation prescription, n (%)	482 (10.8)	11,844 (15.4)	12,326 (15.1)	<.0001
Albumin g/dL, n (%)				<.0001
<3.5	2912 (65.3)	29,335 (38.1)	32,247 (39.6)	
3.5-4	931 (20.9)	20,819 (27.1)	21,750 (26.7)	
4+	452 (10.1)	20,767 (27.0)	21,219 (26.1)	
Unavailable	166 (3.7)	6008 (7.8)	6174 (7.6)	
Creatinine mg/dL, n (%)				<.0001
<1	2077 (46.6)	31,889 (41.5)	33,966 (41.7)	
1-1.5	1301 (29.2)	25,617 (33.3)	26,918 (33.1)	
1.5-2	284 (6.4)	5592 (7.3)	5876 (7.2)	
2+	467 (10.5)	6141 (8.0)	6608 (8.1)	
Unavailable	332 (7.4)	7690 (10.0)	8022 (9.9)	
Diabetes, n (%)	1765 (39.6)	26,649 (34.6)	28,414 (34.9)	<.0001
Myocardial Infarction, n (%)	775 (17.4)	17,018 (22.1)	17,793 (21.9)	<.0001
Cerebrovascular Disease, n (%)	448 (10.0)	7962 (10.3)	8410 (10.3)	.5122
Congestive Heart Failure, n (%)	563 (12.6)	12,300 (16.0)	12,863 (15.8)	<.0001
Month of Admission, n (%)				<.0001
April	8 (0.2)	110 (0.1)	118 (0.1)	
May	811 (18.2)	22,415 (29.1)	23,226 (28.5)	
June	1154 (25.9)	27,387 (35.6)	28,541 (35.1)	
July	2325 (52.1)	25,355 (33.0)	27,680 (34.0)	
August	163 (3.7)	1662 (2.2)	1825 (2.2)	
Venous thromboembolism, n (%)				<.0001
Yes	412 (9.2)	5268 (6.8)	5680 (7.0)	
No	4049 (90.8)	71,661 (93.2)	75,710 (93.0)	
Length of Stay (25th, 75th percentiles)	6 (3, 14)	3 (1, 6)	3 (1, 7)	<.0001
Death, n (%)				<.0001
During index inpatient stay	466 (10.4)	1748 (2.3)	2214 (2.7)	
After discharge	300 (6.7)	6955 (9.0)	7255 (8.9)	

27 days (6, 67) (**Figure 1**). Following propensity score matching, the adjusted hazard for VTE associated with a positive COVID-19 test was 1.28 (95% CI 1.10-1.48; P=0.001).

Discussion

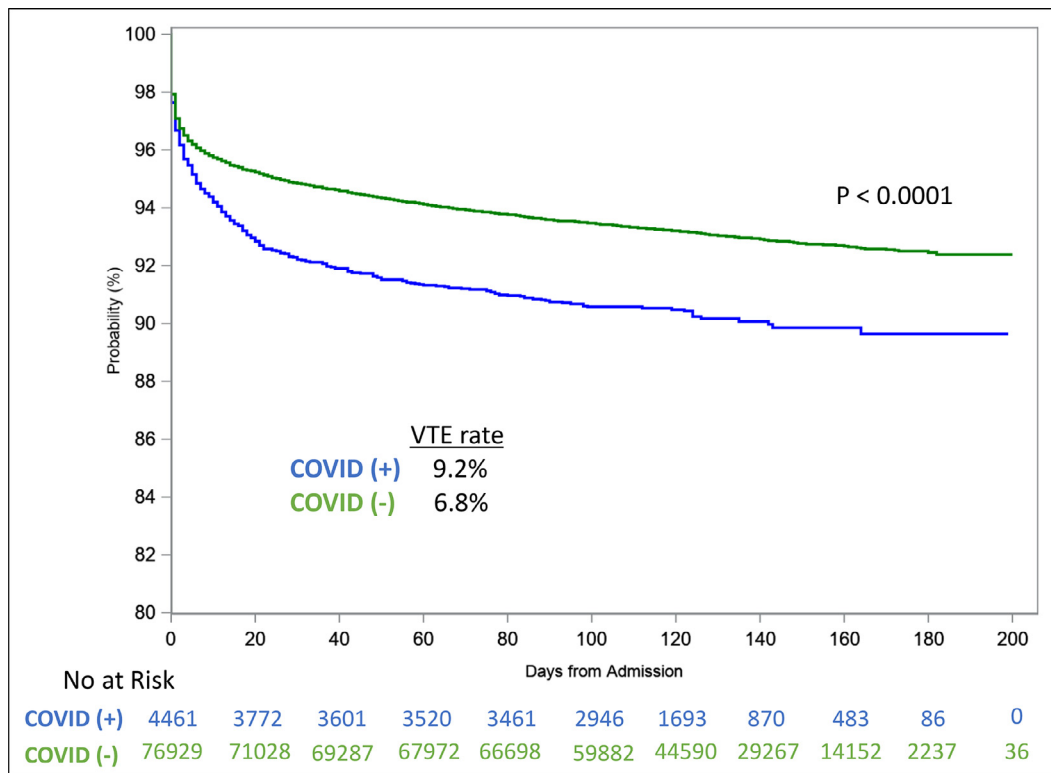
This study of patients at U.S. VA hospitals demonstrates that patients hospitalized with COVID-19, despite thromboprophylaxis, are at increased risk of VTE during admission and following discharge. The rates reported in this large, national sample that includes patients admitted to intensive care, step-down care, and intermediate level care wards are consistent with smaller, regionally-based reports.³ Previous reports have focused on non-critically ill or symptomatic patients.⁴⁻⁶

This analysis adds to the mounting evidence of increased VTE risk in hospitalized patients with COVID-19, and extends our knowledge to now include increased risk following discharge. Furthermore, these results provides additional justification for future randomized controlled trials studying use of antithrombotics in hospitalized and convalescing patients with COVID-19. As stated by professional societies, there is no high quality data to guide thromboprophylaxis in patients with COVID-19.^{7,8}

These results are observational and unmeasured confounders may exist. Furthermore, due to a lack of routine screening in the asymptomatic setting, the true rate of VTE may be underestimated.

The rate of VTE among hospitalized COVID-19 positive patients is high and persists post-discharge justifying

Figure 1



Kaplan-Meier curve for freedom from VTE: COVID-19 positive vs. negative. (+) denotes positive COVID-19 PCR test; (-) denotes negative COVID-19 PCR test

ongoing studies for thromboprophylaxis among patients with COVID-19.

Conflict of interest

Dr J. A Gutierrez discloses the following relationships - Consulting: Janssen Pharmaceuticals and Amgen Inc.

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The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States Government.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.03.010.

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