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Risk of posthospital venous thromboembolism in patients with COVID-19 varies by SARS-CoV-2 period and vaccination status

Tracking no: ADV-2022-008984R1

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Abstract:

Conflict of interest: No COI declared

COI notes:

Preprint server: No;

Author contributions and disclosures: N.R. and A.P. conceived of and designed the study, analyzed the data, and wrote the first draft of the manuscript. All authors participated in analyzing the data and critical revision of the manuscript.

Non-author contributions and disclosures: Yes; The authors thank Mei Lee and Wei Tao from the Kaiser Permanente Division of Research for their assistance in data collection. Funding for this project was provided by the National Heart, Lung, and Blood Institute (R01HL126130).

Agreement to Share Publication-Related Data and Data Sharing Statement: Data sharing can be facilitated by an email to corresponding author

Clinical trial registration information (if any):

Risk of posthospital venous thromboembolism in patients with COVID-19 varies by SARS-CoV-2 period and vaccination status

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Ambulatory patients with COVID-19 have a low risk of developing venous thromboembolism (VTE); whereas hospitalization is associated with a higher risk, necessitating thromboprophylaxis.[1,2] The use of extended thromboprophylaxis following COVID-19 hospitalization is controversial, and risk stratification tools are needed to better predict who may benefit. We report the 90-day incidence of VTE following hospitalization, stratified by COVID-19 surge period and vaccination status among adults tested for SARS-CoV-2.

We performed a retrospective cohort study of 63,920 adult Kaiser Permanente Northern California members who were hospitalized within 30-days of SARS-CoV-2 polymerase chain reaction testing from 12/1/2020 to 2/28/2022. If multiple SARS-CoV-2 tests were performed, the index date was the first date with a positive result or the first date with a negative result if all tests were negative. Based on the predominant SARS-CoV-2 variant circulating in California, we defined the pre-Delta period from 12/15/2020 to 5/31/2021, Delta (B.1.617.2) period from 6/1/2021 to 11/30/2021 and Omicron (B.1.1529) period from 12/1/2021 to 2/28/2022. We excluded subjects who were asymptomatic at the time of SARS-CoV-2 testing, had a history of VTE, or received anticoagulation in the prior year.

We assessed the incidence and timing of VTE within 90-days of hospital discharge using a combination of diagnosis codes, new anticoagulant prescriptions, and encounters for VTE with a centralized anticoagulation service.[3,4] We stratified patients by the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE VTE) score to assess VTE risk

in hospitalized patients for extended thromboprophylaxis (low/moderate [0–3] and high [4+] risk).[5] COVID-19 vaccination was defined as the receipt of two doses of a mRNA vaccine (BNT162b2 [Pfizer-BioNTech] or m-RNA-1973 [Moderna]) or one dose of the Ad.26.COV2.S [Janssen] vaccine 14 or more days prior to viral testing. Multivariable Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for 90-day post-hospital VTE. The Kaiser Permanente Northern California institutional review board approved the study and waived informed consent.

Of the 63,290 hospitalized patients tested for SARS-CoV-2 (mean [SD] age 59 [20] years; 36,438 [56%] women), there were 10,084 (15.9%) unvaccinated patients with COVID-19 and 3,443 (5.4%) subjects with COVID-19 vaccine breakthrough infections (Table 1). 90-day post-hospital VTE incidence among SARS-CoV-2 negative patients (Table 2) was 0.7% and did not vary across the three variant periods (P = .86). The incidence of post-hospital VTE was higher in both unvaccinated (1.6%) and vaccinated (1.2%) patients with COVID-19 compared to SARS-CoV-2 negative patients (P <.001). Time from hospital discharge to VTE diagnosis was shorter in patients with COVID-19 (12 days [IQR 5,23]) compared to SARS-CoV-2 negative patients (22 days [IQR 9,40]; P < .001) and did not differ by surge period in COVID-19 patients (P = .245).

During the pre-Delta period, there was a higher incidence of VTE events in unvaccinated cases (1.3%) compared to SARS-CoV-2 negative cases (0.7%; P = .001), and vaccine breakthrough hospitalizations were rare with only one 90-day post-hospital VTE event (1/33 [3.0%]; P = .11). During the Delta surge period, 90-day post-hospital VTE was higher among both unvaccinated (2.1%) and vaccinated COVID-19 patients (1.7%) compared to SARS-CoV-2 negative patients (0.7%; P = .001 for both). However, during the Omicron period, VTE incidence in vaccine breakthrough (0.9%) and SARS-CoV-2 negative patients (0.7%) were similar but was higher in unvaccinated patients as compared to SARS-CoV-2 negative patients (1.3%; p < .001).

With multivariable regression, the adjusted HR for 90-day post-hospital VTE during the Delta surge period was 2.2 (95% CI 1.3 – 3.6; P = 0.002) for vaccinated COVID-19 patients and 4.1 (95% CI 3.1 – 5.3; P < .001) for unvaccinated COVID-19 patients compared to SARS-CoV-2 negative patients (Table 2). The HRs during the Omicron surge period were 1.5 (95% CI, 1.0 – 2.3; P = .083) and 2.2 (95% CI, 1.4 – 3.4; P < .001) for vaccinated and unvaccinated COVID-19 patients, respectively.

When examining patients with low/moderate IMPROVE VTE risk score during the Delta period, we again found higher 90-day post-hospital VTE incidence in both vaccinated (1.6% [16/1,000]) and unvaccinated COVID-19 patients (2.1% [76/3,699]) compared to SARS-CoV-2 negative patients (0.6% [86/14,117]; P < .001). However, during the Omicron period, post-hospital VTE incidence was similar in vaccinated COVID-19 and SARS-CoV-2 negative patients with low/moderate IMPROVE VTE risk (0.7% [17/2,327] vs 0.6% [83/14,835]; P = .313) but higher in unvaccinated COVID-19 patients (1.3% [20/1,579]; P < .05 for both).

We found that the incidence of 90-day post-hospital VTE was higher in both unvaccinated and vaccinated COVID-19 patients compared to SARS-CoV-2 negative patients, and, notably, that unvaccinated COVID-19 patients had a higher risk of post-hospital VTE as compared to patients with COVID-19 vaccine breakthrough infections. When examined by study period, COVID-19 patients had a higher incidence of VTE in the Delta period compared to either the pre-Delta or Omicron period. Moreover, patients with vaccine breakthrough infections during the Omicron period had a risk of post-hospital VTE that was not significantly above the baseline risk for hospitalized SARS-CoV-2 negative patients, while unvaccinated COVID-19 patients had a significantly higher risk. Increased incidence of post-hospital VTE in COVID-19 patients

persisted when examining the subset of patients with low/moderate IMPROVE VTE risk scores. This finding was consistent across study periods in unvaccinated COVID-19 patients but only in the Delta period among COVID-19 vaccine breakthrough patients.

Clinical risk factors associated with post-hospital VTE in COVID-19 patients include advanced age, prior VTE, intensive care unit stay, chronic kidney disease and cardiovascular disease.[6] Our results suggest that SARS-CoV-2 variant and vaccination status may be independent risk factors for post-hospital VTE in patients with COVID-19. While there are no prospectively validated risk assessment models in patients with COVID-19, the IMPROVE VTE score has been externally validated in hospitalized COVID-19 patients.[7,8] The MICHELLE trial used the IMPROVE VTE score and D-dimer levels to identify high-risk patients with COVID-19 following hospitalization and randomized them to prophylactic oral anticoagulation or placebo for 35 days.[9] The reduction in major and fatal thromboembolic events in patients on anticoagulation was driven by a reduction in asymptomatic, symptomatic, and fatal pulmonary emboli. However, the trial was conducted during the period prior to SARS-CoV-2 Delta variant predominance and widespread COVID-19 vaccination.

There are limitations to our findings. Residual confounding may persist despite multivariable modeling given the retrospective nature of our analysis. In addition, we excluded patients with a history of VTE, potentially impacting post-hospital VTE incidence. D-dimer testing was not routinely performed in patients admitted to the hospital; therefore, we may have not identified all subjects at high risk of post-hospital VTE using a more dynamic risk assessment. The strengths of our study include evaluation of only symptomatic events and a large diverse cohort with a relatively high vaccination rate, allowing cross group comparisons of an infrequent event.

Our data support continued re-evaluation of the risks and benefits of antithrombotic treatments with ongoing surges of novel SARS-CoV-2 variants. We eagerly await the publication of ongoing randomized clinical trials (XACT [NCT04640181], ACTIV-4c [NCT04650087], HEAL-COVID [NCT04801940] and others) to assess the benefit of extending thromboprophylaxis in COVID-19 patients post-hospital discharge. Prospective clinical trials are needed to validate the effect of SARS-CoV-2 variant and vaccination status on the incidence of post-hospital VTE, and whether this is reduced by extended thromboprophylaxis.

Acknowledgements: The authors thank Mei Lee and Wei Tao from the Kaiser Permanente Division of Research for their assistance in data collection.

Funding/Support: Funding for this project was provided by the National Heart, Lung, and Blood Institute (R01HL126130).

Author Contributions: N.R. and A.P. conceived of and designed the study, analyzed the data, and wrote the first draft of the manuscript. All authors participated in analyzing the data and critical revision of the manuscript.

Disclosures of Conflict-of-interest: The authors declare no competing financial interests.

Role of the Funder/Sponsor: The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Table 1: Hospitalized Cohort Characteristics			
	SARS-CoV-2 negative **N=50,393**	Vaccinated COVID-19 (+) **N=3,443**	Unvaccinated COVID-19 (+) **N=10,084**
Age, years			
Median (IQR)	62 (42-76)	62 (43-76)	55 (41-67)
Sex			
Female	28,795 (57.1)	1,904 (55.3)	5,092 (50.5)
Male	21,598 (42.9)	1,539 (44.7)	4,992 (49.5)
Race/ethnicity			
African American	3,980 (7.9)	337 (9.8)	1,168 (11.6)
Asian	8,819 (17.5)	516 (15.0)	1,325 (13.1)
Hispanic	9,514 (18.9)	928 (27.0)	3,246 (32.2)
White	24,609 (48.8)	1,416 (41.1)	3,653 (36.2)
Missing/other	3,471 (6.9)	246 (7.1)	692 (6.9)
Body mass index			
Healthy weight	14,342 (28.5)	772 (22.4)	1,269 (12.6)
Overweight	15,721 (31.2)	1,014 (29.5)	2,661 (26.4)
Obese	17,599 (34.9)	1,521 (44.2)	5,568 (55.2)
Underweight	1,396 (2.8)	64 (1.9)	87 (0.9)
Missing	1,335 (2.7)	72 (2.1)	499 (5.0)
Median (IQR)	28 (24-32)	29 (25-34)	31 (27-37)
Comorbidities			
Hypertension	22,634 (44.9)	1,695 (49.2)	4,448 (44.1)
Diabetes	12,473 (24.8)	1,147 (33.3)	3,095 (30.7)
Chronic kidney disease	10,699 (21.2)	832 (24.2)	1,421 (14.1)
COPD	11,981 (23.8)	873 (25.4)	2,333 (23.1)
Congestive heart failure	8,098 (16.1)	448 (13.0)	694 (6.9)
Malignancy	6,790 (13.5)	397 (11.5)	581 (5.8)
Leukemia/lymphoma/myeloma	1,193 (2.4)	110 (3.2)	115 (1.1)
Peripheral vascular disease	18,058 (35.8)	1,318 (38.3)	2,163 (21.5)
Rheumatologic disease	1,342 (2.7)	120 (3.5)	166 (1.7)
Transplant	679 (1.4)	129 (3.8)	97 (1.0)
Interstitial lung disease	1,361 (2.7)	94 (2.7)	211 (2.1)
History of smoking	21,895 (43.5)	1,612 (46.8)	3,776 (37.5)
Lab test setting			
Outpatient	23,427 (46.5)	1,795 (52.1)	6,045 (60.0)
Inpatient	26,966 (53.5)	1,648 (47.9)	4,039 (40.1)
ICU level of care	4,103 (8.1)	236 (6.9)	918 (9.1)
IMPROVE VTE Score (IQR)	1 (0,1)	1 (0,1)	1 (0,1)
Hospital length of stay, days (IQR)	2 (0,4)	3 (1,5)	4 (2,7)
COVID-19 period			
Pre-Delta	20,644 (41.0)	33 (1.0)	4,738 (47.0)
Delta	14,531 (28.8)	1,029 (29.9)	3,736 (37.1)
Omicron	15,218 (30.2)	2,381 (6.92)	1,610 (16.0)
Vaccine type	N=27,984	N=3,443	
Pfizer/BioNTech	15,691 (56.1)	2,042 (59.3)	
Moderna	10,764 (38.5)	1,010 (29.3)	
Janssen	1,527 (5.5)	391 (11.4)	

Data represent no. (%) unless otherwise specified.

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; VTE, venous thromboembolism

Table 2: Unadjusted and adjusted 90-day post-hospital VTE incidence by SARS-CoV-2 positivity and study period (n=63,920)					
SARS-CoV-2 Period	SARS-CoV-2 (-) n=50,393	Vaccinated COVID-19 (+) n=3,443		Unvaccinated COVID-19 (+) n=10,084	
	(Reference)	Unadjusted	Adjusted HR (95% CI)	Unadjusted	Adjusted HR (95% CI)
Pre-Delta n=25,415	0.7% (144/20,644)	3.0% (1/33)	2.9 (0.4, 20.9)[a]	1.3% (60/4738)	2.1 (1.6, 2.8)[b]
Delta n=19,296	0.7% (100/14,531)	1.7% (17/1029)	2.2 (1.3, 3.6)[c]	2.1% (79/3736)	4.1 (3.1, 5.3)[d]
Omicron n=19,209	0.7% (99/15,218)	0.9% (22/2381)	1.5 (1.0, 2.3)[e]	1.3% (21/1610)	2.2 (1.4, 3.4)[f]

VTE, venous thromboembolism; HR, hazard ratio; CI, confidence interval
Hazard ratios with 95% confidence interval and p-values presented for Cox regression of 90-day post-hospital VTE in COVID-19 subgroups relative to SARS-CoV-2 negative patients

a. $P = .287$
b. $P < .001$
c. $P = .002$
d. $P < .001$
e. $P = .083$
f. $P < .001$