Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

COVID-19 associated Venous Thromboembolism (VTE) burden in Black women: Findings of Veterans Affairs COVID-19 Shared Data

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1. Introduction

Venous Thromboembolism (VTE) is a serious condition with an incidence rate of 110 per 100,000 women [1]. Acute infection such as COVID-19 is a known risk factor for VTE among immobilized or hospitalized patients due to severe illness [2], and VTE prevalence rate is >35 % higher among Blacks than Whites [3]. The previous literature reports an increased risk of COVID-19 associated VTE incidence among pregnant women [4] and women with hormone replacement therapy [5], possibly suggesting additional risk factors for developing VTE after COVID-19 infection in women. However, generalizing sex-specific risk factor effects on VTE incidence has been limited due to a lack of data and large-scale studies on women.

The United States (US) veteran population is a particularly understudied demographic group vulnerable to COVID-19 infection and its complications. Veterans had more underlying physical, mental, and socioeconomic risk factors associated with COVID-19 infection and worse prognosis compared to the general population [6]. The US military service members are racially diverse; this heterogeneity is more pronounced in women service members—over 40 % of new military service enlistees are women of minority background, and these numbers are rapidly increasing.

Furthermore, it remains unknown whether COVID-19 vaccination mitigates COVID-19-related VTE burden among minority women, whose vaccination rate was significantly lower than White women in the US at the time of the study [7]. To address this gap in the current literature, the current study capitalized on the large-scale Veterans Affairs (VA) COVID-19 Shared Resource Data and examined whether there is a race difference in VTE burden associated with COVID-19 among women, stratified by vaccination history.

2. Methods

2.1. Study data

A total of 157,866 women veterans were tested for COVID-19 between February 24, 2021, and September 15, 2021. The study included women veterans with complete data on race, ethnicity and body mass index (BMI), yielding a sample size of 99,163. Of these, 15,654 (15.8 %) women veterans tested positive (including presumed positive) for SARS-CoV-2, and the index point was the date of the first positive test. The study analyzed data stratified by a vaccination history based on receiving at least one dose of the three available COVID-19 vaccines at the VA—Pfizer-BioNTech, Moderna, and Johnson & Johnson's Janssen.

The final study data included 7265 unvaccinated women with COVID-19 infection and 653 vaccinated women with breakthrough COVID-19 infection. All of them had known racial and ethnic backgrounds, complete data on 60-day follow-up VTE, demographics and clinical characteristics, such as age and BMI.

2.2. Study variables

Baseline demographic data include age, race, and ethnicity. Clinical characteristics include BMI, smoking history, pre-existing comorbidities (diabetes, cardiovascular disease (CVD), and chronic obstructive pulmonary disease (COPD)), a personal history of cancer, and prior VTE. The study included a history of pregnancy and hormone therapy with estrogen and/or progesterone for female-specific conditions within the past two years.

The study's primary outcome is VTE incidence within 60 days from an index date —positive COVID-19 testing. VTE was defined as a deep vein thrombosis in either upper or lower extremities as well as pulmonary embolism. Arterial thromboses were excluded.

2.3. Statistical analysis

Stratified by vaccination history, the study used a penalized logistic regression model with FIRTH Maximum Likelihood Estimation (MLE) method, which adequately conducts MLE when an outcome event is a rare event [8]. Covariates included in the model are age, race, ethnicity, BMI, current smoking status, pre-existing comorbidities, a personal history of cancer, and prior VTE. Additionally, the study included female sex-specific conditions such as pregnancy and hormone therapy within the past two years. Odds ratios (OR) and 95 % confidence intervals (CIs)

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were reported. Inclusion of covariates in the final model was determined by statistical significance of variables and Akaike Information Criteria (AIC). A p-value < 0.05 was set as a criterion for statistical significance. All statistical analyses were conducted using SAS 9.4 (SAS Institute, NC).

3. Results

Of 7265 unvaccinated women veterans tested positive for COVID-19 infection, 120 (1.7 %) women veterans had a VTE event within 60 days from the index date. Of these 120 women, 84 (70 %) had new-onset VTE, and 36 (30 %) had a prior history of VTE. One hundred and twenty three unvaccinated women veterans died after COVID-19 infection and VTE was associated with increased mortality risk among unvaccinated women veterans with COVID-19 infection ($p = 0.0004$).

The overall rate of VTE among unvaccinated women veterans with COVID-19 was 1.5 % ($n = 120$). The VTE incidence rate among Black women at 60 days was significantly higher (2.4 %) than White (1.4 %), Hispanic (0.6 %), and women of other races (0.5 %, $p = 0.0083$; Table 1). After adjusting for covariates, unvaccinated Black women veterans were at two times higher risk of VTE after COVID-19 infection than their white counterparts (OR 1.8, 95 % CI 1.2–2.7). Older age, higher BMI, active cancer, and a prior history of VTE were significantly associated with increased risk of VTE at 60 days (Fig. 1). Unvaccinated women veterans with VTE had higher rates of pre-existing diabetes, COPD, and CVD than those without VTE at 60 days (Table 1). However, the statistical significance of the pre-existing comorbidities in association with a 60-day VTE dissipated after adjusting for covariates among unvaccinated women veterans (Fig. 1).

Of the 653 vaccinated women with breakthrough COVID-19 infection, 9 deaths (1.4 %) were reported at 60 days, and none of the deceased experienced VTE before death. Overall VTE rate among vaccinated women with breakthrough COVID-19 infection was 1.8 % ($n = 12$). There was no statistically significant racial difference in 60-day VTE risk when breakthrough women veteran cases were isolated. Among the breakthrough group, mortality was not associated with VTE at 60 days ($p = 0.6769$).

Women veterans with breakthrough COVID-19-related VTE were older, had higher BMI, and rates of pre-existing CVD, as well as a history of VTE than those without VTE incidence at 60 days (Table 1). After adjusting for covariates, older age (OR 1.09, 95 % CI 1.02–1.16), higher BMI (OR 1.08, 95 % CI 1.02–1.15), and a history of VTE (OR 34.9, 95 % CI 6.3–193.3) were significantly associated with VTE risk at 60 days.

Table 1
Baseline demographic and clinical characteristics by VTE occurrence among unvaccinated COVID-19 tested positive women veterans ($n = 7265$) and vaccinated but later infected with COVID-19 (breakthrough cases, $n = 653$).

Covariates		Unvaccinated COVID-19 tested positive women veterans ($n = 7265$)				Vaccinated but later infected with COVID-19 ($n = 653$)			
		Total	VTE ($n = 120$)	No VTE ($n = 7145$)	p-Value[a]	Total	VTE ($n = 12$)	No VTE ($n = 641$)	p-Value[a]
Age		46.78 ± 12.46	56.3 ± 12.0	46.6 ± 12.4	<0.0001	55.0 ± 12.49	62.83 ± 9.17	54.88 ± 12.50	0.0198
Race/ethnicity	White	3591 (49.4 %)	53 (44.1 %)	3538 (49.5 %)	0.0163	347 (53.1 %)	4 (33.3 %)	343 (53.5 %)	0.0596
	Black	2486 (34.2 %)	60 (50.0 %)	2426 (34.0 %)		224 (34.3 %)	8 (66.7 %)	216 (33.7 %)	
	Hispanic	809 (11.1 %)	5 (4.2 %)	804 (11.3 %)		62 (9.5 %)	0 (0.0 %)	62 (9.7 %)	
	Other	379 (5.2 %)	2 (1.7 %)	377 (5.3 %)		20 (3.1 %)	0 (0.0 %)	20 (3.1 %)	
BMI	kg/m2	31.71 ± 6.96	33.4 ± 7.17	31.7 ± 6.96	0.0063	32.09 ± 7.40	37.05 ± 8.00	32.00 ± 7.37	0.0325
Current smoker	Current	1440 (9.2 %)	14 (6.6 %)	1426 (9.2 %)	0.1881	61 (9.3 %)	2 (16.7 %)	59 (9.2 %)	0.3792
Diabetes		1198 (16.5 %)	41 (34.2 %)	1157 (16.2 %)	<0.0001	188 (28.8 %)	6 (50.0 %)	182 (28.4 %)	0.1017
Cardiovascular disease		1132 (15.6 %)	55 (45.8 %)	1077 (15.1 %)	<0.0001	142 (21.8 %)	7 (58.3 %)	135 (21.1 %)	0.0019
COPD		508 (7.0 %)	26 (21.7 %)	482 (6.8 %)	<0.0001	96 (14.7 %)	1 (8.3 %)	95 (14.8 %)	0.5298
Cancer	New	64 (0.9 %)	3 (2.5 %)	61 (0.8 %)	<0.0001	10 (1.5 %)	0 (0.0 %)	10 (1.6 %)	0.3002
	Ongoing	171 (2.4 %)	15 (12.5 %)	156 (2.2 %)		41 (6.3 %)	2 (16.7 %)	39 (6.1 %)	
	Recovered	524 (7.2 %)	13 (10.8 %)	511 (7.2 %)		73 (11.2 %)	0 (0.0 %)	73 (11.4 %)	
	Never	6508 (89.5 %)	89 (74.2 %)	6417 (89.8 %)		529 (81.0 %)	10 (83.3 %)	519 (80.9 %)	
VTE history within 2 years		129 (1.8 %)	36 (30.0 %)	93 (1.3 %)	<0.0001	14 (2.1 %)	5 (41.7 %)	9 (1.4 %)	<0.0001
Pregnancy at index		146 (0.93 %)	1 (0.83 %)	101 (1.41 %)	0.5921	4 (0.61 %)	0 (0.0 %)	4 (0.62 %)	0.7839
Pregnancy within 2 years		608 (3.88 %)	4 (3.33 %)	383 (5.36 %)	0.3268	23 (3.5 %)	0 (0.0 %)	23 (3.6 %)	0.5044
On hormone therapy (estrogens and/or progesterones) within 2 years	In the past 2 years	894 (12.3 %)	13 (10.8 %)	881 (12.3 %)	0.0969	41 (6.3 %)	1 (8.3 %)	40 (6.2 %)	
	New	62 (0.9 %)	0 (0.0 %)	62 (0.8 %)		2 (0.3 %)	0 (0.0 %)	2 (0.3 %)	
	Ongoing	350 (4.8 %)	3 (2.5 %)	347 (4.9 %)		29 (4.4 %)	1 (8.3 %)	28 (4.4 %)	
	Never	5959 (82.0 %)	104 (86.7 %)	5855 (80.6 %)		581 (89.0 %)	10 (83.3 %)	571 (89.1 %)	

Abbreviations. BMI = body mass index; COPD = chronic obstructive pulmonary disease; VTE = Venous Thromboembolism.
[a] Mantel-Haenszel Chi-Square Statistics.

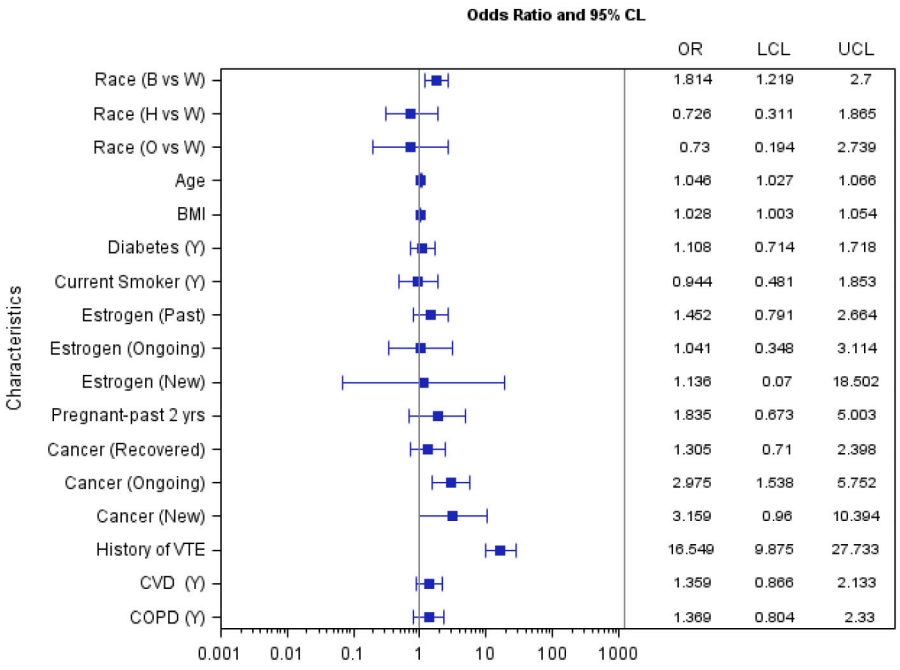

Fig. 1. Odds ratios (OR) and 95 % confidence intervals (CIs) of demographic and clinical characteristics for 60-day VTE risk in unvaccinated women veterans.
Abbreviations. Race B = Black; race H = Hispanic; race O = other race; Y = Yes; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; VTE = Venous Thromboembolism.
Note. The 95 % confidence interval [lower confidence limit (LCL)–upper confidence limit (UCL)] of odds ratios (OR) does not include '1' and is statistically significant under $\alpha = 0.05$.

However, the statistical significance of pre-existing CVD with VTE risk dissipated (p = 0.6022).

Over half (52 %, n = 337) of the women veterans with breakthrough COVID-19 received the Pfizer, 42 % (n = 275) Moderna, and 6 % (n = 41) Johnson and Johnson's Janssen vaccine. The type of vaccination was not associated with risk of increased VTE among the women veterans with breakthrough COVID-19 (p = 0.2451; Table 1).

There was no significant association between pregnancy or hormone therapy and VTE risk at 60 days in either unvaccinated or vaccinated women with COVID-19 infection.

4. Discussion

Black women veterans had a significantly higher risk of developing VTE after COVID-19 infection than their other race counterparts. However, this COVID-19 associated VTE burden among Black women was mitigated by COVID-19 vaccinations. Aside from a significant racial difference, the study findings confirmed that older age, higher BMI, active cancer and VTE history were independently associated with increased VTE risk at 60 days regardless of vaccination status.

A previous study demonstrated that COVID-19 mortality burden in women veterans was similar across race groups [9]. However, the current study found a high VTE risk related to COVID-19 among Black women, and it was associated with increased mortality among the unvaccinated. Women of minority backgrounds may differ in the types of COVID-19 complications that lead to mortality.

Race is associated with a number of factors including socioeconomic status, cultural phenomena, comorbidities, and occasionally genetics in the case of VTE. Racial minority background is significantly associated with baseline characteristics including age, BMI, Diabetes, CVD, prior VTE, and cancer history (Supplementary Tables 1 and 2). While the study addressed a potential bias from confounding effects by employing regressions adjusted for these baseline characteristics, the increased VTE risk may be contributed by not only Black race itself but also other characteristics and factors commonly observed among Black women associated with a higher incidence of VTE, such as prior VTE, CVD, and pregnancy [10].

In this study, VTE incidence was no longer associated with increased mortality risk among the vaccinated group. This indicates COVID-19 vaccination may lower the likelihood of developing VTE and mitigate the risk of VTE-associated death among women of racial and ethnic minority background after COVID-19 infection. However, generalizability of this finding warrants a future study with a larger sample size of vaccinated women of minority backgrounds.

The results of this study highlight the efficacy of the COVID-19 vaccinations in an under-represented and under-studied female population. This may serve as an impetus to improve COVID-19 vaccination efforts and surveillance for COVID-19 associated complications in these women.

In conclusion, the study confirmed a race difference in COVID-19-associated VTE burden among the unvaccinated group using large-scale women veteran population data, all of whom have equal access to VA health care. However, this racial disparity disappears among vaccinated women. Thus, vaccinations may be effective in mitigating COVID-19-associated VTE burden among Black women.

Data sharing statement

Because of the sensitive nature of the data collected for this study, requests to access the dataset are limited to qualified VA-affiliated researchers trained in human subject confidentiality. Protocols may be sent to the VA North Texas Health Care System Institutional Review Board (IRB) at NTXIRBAdmin@va.gov. SAS and R programming code used in the analysis of this study are available from the corresponding author upon reasonable request. All methods were performed in accordance with the relevant guidelines and regulations.

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CRediT authorship contribution statement

Conception and design: H. Jeon-Slaughter, S-H. Choi; Analysis and interpretation of the data: H. Jeon-Slaughter, S-H. Choi, H Nguyen; Drafting of the manuscript: H. Jeon-Slaughter, S-H. Choi, H Nguyen, S. Kanjwal, I. Ibrahim, T. Bat, A. Thomas; Critical revision of the article for important intellectual content. H. Jeon-Slaughter, S-H. Choi, I. Ibrahim, T. Bat, A. Thomas, Statistical experts: H. Jeon-Slaughter, H Nguyen; Obtaining data access and IRB administration: H. Jeon-Slaughter; Data

extraction and assembly of data: H. Jeon-Slaughter, H Nguyen.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2022.07.007.

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