Title

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Journal

Blood Advances, 6(15)

ISSN

2473-9529

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Publication Date

2022-08-09

DOI

10.1182/bloodadvances.2022007219

Peer reviewed

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COVID-19 and Venous Thromboembolism Risk in Patients With Sickle Cell Disease

Tracking no: ADV-2022-007219R1

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Abstract:
Venous thromboembolism (VTE) is a life threatening complication observed among patients with sickle cell disease (SCD), and also among those with severe COVID-19 infection. Although prior studies show that patients with SCD are at risk of severe COVID-19 illness, it remains unclear if COVID-19 infection further increases VTE risk for this population. We hypothesized that patients with SCD hospitalized for COVID-19 would have higher VTE rates than those hospitalized for other causes. Using electronic health record data from a multisite research network, TriNetX, we identified two groups of patients with SCD hospitalized during 2020: 1) With COVID-19; 2) Without COVID-19. We compared VTE rates using risk ratios estimated based on adjusted Poisson regression model with log link and robust error variances. Of the 281 SCD patients hospitalized with a COVID-19 diagnosis and 4,873 SCD patients hospitalized without a COVID-19 diagnosis, 35 (12.46%) and 418 (8.58%) had incident VTE within 6 months of the index hospitalization. After adjusting for differences in baseline characteristics, no significant differences in VTE rates within 6 months were found between the two groups (adjusted-RR=1.06 (95% Confidence Interval: 0.79-1.41)). These data suggest that hospitalization with COVID-19 does not further increase VTE risk in patients with SCD.

Conflict of interest: No COI declared

COI notes:

Preprint server: No;

Author contributions and disclosures: A.Singh and A.Shet designed research. A.Singh analyzed data. A.B. and T.W. provided critical content expertise. A.Singh, A.B., A.Shet contributed to writing of the manuscript.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: NA

Clinical trial registration information (if any):

COVID-19 and Venous Thromboembolism Risk in Patients With Sickle Cell Disease

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Abstract: 199 words

Word count: 1,404 words

Number of tables: 2

Number of references: 23

Abstract: 200 words limit

Venous thromboembolism (VTE) is a life threatening complication observed among patients with sickle cell disease (SCD), and also among those with severe COVID-19 infection. Although prior studies show that patients with SCD are at risk of severe COVID-19 illness, it remains unclear if COVID-19 infection further increases VTE risk for this population. We hypothesized that patients with SCD hospitalized for COVID-19 would have higher VTE rates than those hospitalized for other causes. Using electronic health record data from a multisite research network, TriNetX, we identified two groups of patients with SCD hospitalized during 2020: 1) With COVID-19; 2) Without COVID-19. We compared VTE rates using risk ratios estimated based on adjusted Poisson regression model with log link and robust error variances. Of the 281 SCD patients hospitalized with a COVID-19 diagnosis and 4,873 SCD patients hospitalized without a COVID-19 diagnosis, 35 (12.46%) and 418 (8.58%) had incident VTE within 6 months of the index hospitalization. After adjusting for differences in baseline characteristics, no significant differences in VTE rates within 6 months were found between the two groups (adjusted-RR=1.06 (95% Confidence Interval: 0.79–1.41)). These data suggest that hospitalization with COVID-19 does not further increase VTE risk in patients with SCD.

Key points (1 to 2):

1. COVID-19 does not exacerbate the already-high risk of venous thromboembolism among hospitalized patients with sickle cell disease

Introduction

Venous thromboembolism (VTE) is the third leading cause of vascular mortality that contributes substantially to annual health care utilization and long-term morbidity[1,2]. Individuals with sickle hemoglobinopathy, i.e., that are either heterozygous or homozygous for a single nucleotide substitution of valine for glutamic acid at the 6th position of the β-globin gene are associated with an increased risk of VTE[3,4]. Epidemiologic studies indicate a 2-4 times higher risk of VTE among patients with sickle cell disease (SCD) compared to patients with other conditions such as asthma that are similar in gender, age and hospitalization frequency. This is particularly concerning as VTE in patients with SCD is independently associated with death[5,6].

VTE is also a life-threatening complication in patients infected with the SARS CoV-2 virus that causes COVID-19[7-11]. The rates of VTE are especially high among COVID-19 patients with sepsis requiring admission to the intensive care unit[12]. Sepsis-associated coagulopathy in patients with COVID-19 results from widespread inflammation that provokes both microvascular and macrovascular thrombosis and leads to multiorgan dysfunction[13]. Prior studies indicate that patients with SCD are at greater risk for severe COVID-19 illness[14,15]. After adjusting for clinical characteristics, our prior analysis suggested that there were no significant differences in VTE outcomes within 14 days of COVID-19 between Black individuals with SCD and those without SCD[14]. However, little is known about the additive risk of VTE due to COVID-19 within the SCD population who have a preexisting thrombosis risk due to a hypercoagulable state[16]. We hypothesized that patients with SCD hospitalized for COVID-19 would have higher VTE rates compared to those hospitalized for other indications. To test this hypothesis, we utilized electronic health record data and made population level comparisons of VTE rates among patients with SCD hospitalized for COVID-19 versus those hospitalized but did not have COVID-19.

Methods

We conducted a retrospective cohort study using data from TriNetX, a research network of electronic health record data from >40 healthcare organizations across the US[17]. Overall, our study population included 70.4% cases from healthcare organizations in the South, 17.8% cases from Midwest, 7% from Northeast and 1.51% from the West. All ages were included in the study. We identified two groups: 1) Patients with SCD hospitalized for COVID-19 or for another diagnosis but tested positive for SARS-CoV-2 (for the sake of brevity referred as Patients with SCD hospitalized with COVID-19) during calendar year 2020; 2) Patients with SCD hospitalized without COVID-19 during 2020. SCD patients were identified using a previously validated algorithm[18,19] that was slightly modified to exclude subjects with ICD code of sickle cell trait to enhace specificity. All types of SCD as specificied by ICD codes were included in the study population (D57.0*, D57.1*, D57.2*, D57.4*, D57.8*) . A table of laboratory values of SCD patients so identified supports that the cohort identified were patients with SCD (Supplement Table 1). COVID-19 cases were identified using the diagnosis codes for COVID-19 infection or a positive SARS-CoV-2 diagnostic test. We considered cases to be hospitalized with COVID-19 if hospitalization occurred within 14-days of COVID-19 diagnosis or a positive result on COVID-19 testing. The comparator group of patients with SCD hospitalized for other indications excluded patients who had COVID-19 at any point in time. The study was exempt from institutional review board approval. It was conducted in accordance with the Declaration of Helsinki.

Index hospitalization: The date of COVID-19 diagnosis and the first hospitalization in year 2020 for patients with SCD hospitalized with COVID-19 and patients with SCD hospitalized without COVID-19, respectively.

Outcome: Venous thromboembolism identified using ICD10 codes (see supplement table 2) within 1 month, 3 months and 6 months of the index event. The ICD10 codes are sensitive to identify thromboembolic events[20,21]. The ICD codes have also previously been used by other

published studies to identify VTE outcomes among individuals with SCD[6,22]. This included pulmonary embolism (PE) and deep vein thrombosis (DVT).

Statistical analysis: We compared demographic and clinical characteristics between the two groups using t-tests or the chi-square test. Poisson regression models with log link and robust error variance were used to estimate the relative risk (RR) and 95% confidence intervals (CI). The outcomes of VTE incidence within 1 month, 3 months and 6 months were modeled separately. The models included baseline characteristics which were significantly different between the two groups as covariates. A p-value of <0.05 was considered as statistically significant. As a sensitivity analysis, we restricted our cohort to those identified as having sickle cell anemia (Hemoglobin SS and $S\beta^0$) and repeated the analysis described above.

Results and Discussion

Our study included 281 SCD patients with COVID-19 and 4,873 SCD patients without COVID-19 hospitalized during year 2020. Patients with SCD hospitalized with COVID-19 were older and a higher proportion of them had a history of hypertension, acute or chronic kidney disease, obesity and prior DVT/PE (Table 1).

Of the SCD patients hospitalized with COVID-19, 20 (7.12%), 28 (9.96%), 35 (12.46%) had an incident VTE within one, three and six months of COVID-19 diagnosis, respectively. In the comparator group, 257 (5.27%), 332 (6.81%), 418 (8.58%) had an incident VTE within one, three and six months of index hospitalization, respectively. There were 13 (4.6%) in the COVID-19 group and 182 (3.7%) in the comparator group who experienced VTE during their index hospitalization. Unadjusted analysis reflected no significant differences in VTE incidence at one month post index event between the two groups (RR=1.35, 95% CI=0.87–2.01, p-value=0.1806), whereas VTE incidence at three months (RR=1.46, 95% CI=1.01–2.11, p-value=0.0420) and six months (RR=1.45, 95% CI=1.05–2.00, p-value=0.0237) after

hospitalization was significantly higher among patients with SCD hospitalized for COVID-19. However, after adjusting for age, history of hypertension, acute or chronic kidney disease, obesity and prior VTE/PE history, there were no significant differences in VTE risk between the SCD COVID-19 and the SCD No COVID-19 group (Table 2). The model estimates showed that age, prior history of VTE/PE and prior history of acute/chronic kidney disease were significantly associated with VTE risk at all time points. The history of prior VTE/PE had a large effect size, which is consistent with the observation of a high VTE recurrence rate in patients with SCD[22]. Similar estimates were observed when restricting our study population to those classified as having sickle cell anemia.

To the best of our knowledge, this is the first study to evaluate VTE risk following COVID-19 in patients with SCD. Overall, these data suggest that for patients with SCD hospitalized with COVID-19 infection, anticoagulation management decisions should be based on individual risk factors, including age, obesity, prior history of acute/chronic kidney disease and most importantly, a prior history of VTE. Interestingly, a substantial proportion of VTE cases in our study population occurred in July (20%), November (22.8%) and December (20%) of 2020 when widespread use of “intermediate dosed” anticoagulation therapy was general clinical practice to prevent VTE in patients with COVID-19[23]. However, the lack of information on both dosage and duration of anticoagulation therapy administration limited our ability to determine the impact of this exposure on study outcomes. Updated clinical anticoagulation management guidelines for individuals hospitalized for COVID 19 suggest that in certain sub groups, therapeutic anticoagulation may improve clinical outcomes[24].Thus additional studies, especially those conducted in patients with SCD affected with COVID-19 could help guide prophylactic and therapeutic anticoagulation management.

The strengths of this study lie in the inclusion of data from multiple health care organizations thereby representing hospital settings within the US which permit some degree of

generalizability. However, certain limitations exist. These include the possibility of missing incident VTE in patients seeking treatment at a different health care institution not part of the TriNetX network. However, over > 70% of our study population had clinical encounters in 2021 at institutions within the TriNetX network suggesting that health care fragmentation and failure to detect new VTE cases was miminal. Importantly, the overall ICD codes have a high sensitivity to identify acute VTE outcomes among hospitalized patients[20,21]. Coding is different for acute versus chronic venous thrombosis. However, the lack of patient identifiers in this administrative database precluded access to and review of imaging studies for VTE diagnosis and therefore we cannot differentiate between prior residual VTE and new onset recurrent VTE,

In conclusion, we did not find significant differences in VTE rates between SCD patients hospitalized with COVID-19 and those hospitalized without COVID-19. These data provide support for the application of current general clinical anticoagulation guidelines for COVID-19 in the general population to patients with SCD. Future prospective studies controlled for anticoagulant therapy exposure may provide more direct evidence to guide antithrombotic management in this unique population.

Authorship

Author contributions

A.Singh and A.Shet designed research; A.Singh analyzed data; A.B. and T.W. provided critical content expertise; A.Singh, A.B., A.Shet contributed to writing of the manuscript.

Conflicts of interest

None of the authors has a relevant conflict of interest.

References

1. Nicholson M, Chan N, Bhagirath V, Ginsberg J. Prevention of Venous Thromboembolism in 2020 and Beyond. *J Clin Med.* 2020;9(8):2467.
2. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. *Am J Prev Med.* 2010;38(4 Suppl):S495-501.
3. Folsom AR, Tang W, Roetker NS, et al. Prospective study of sickle cell trait and venous thromboembolism incidence. *J Thromb Haemost.* 2015;13(1):2-9.
4. Little I, Vinogradova Y, Orton E, Kai J, Qureshi N. Venous thromboembolism in adults screened for sickle cell trait: a population-based cohort study with nested case-control analysis. *BMJ Open.* 2017;7(3):e012665.
5. Naik RP, Streiff MB, Haywood C, Jr., Nelson JA, Lanzkron S. Venous thromboembolism in adults with sickle cell disease: a serious and under-recognized complication. *Am J Med.* 2013;126(5):443-449.
6. Brunson A, Lei A, Rosenberg AS, White RH, Keegan T, Wun T. Increased incidence of VTE in sickle cell disease patients: risk factors, recurrence and impact on mortality. *Br J Haematol.* 2017;178(2):319-326.
7. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine.* 2020;29:100639.
8. Kasinathan S, Mohammad Ashraf H, Minkowitz S, Adeyinka A, Bailey-Correa K. COVID-19 Infection and Acute Pulmonary Embolism in an Adolescent Female With Sickle Cell Disease. *Cureus.* 2020;12(12):e12348.
9. Mahajan P, Dass B, Radhakrishnan N, McCullough PA. COVID-19-Associated Systemic Thromboembolism: A Case Report and Review of the Literature. *Cardiorenal Med.* 2020;10(6):462-469.
10. Rout A, Chan A. A Case of COVID-19 Complicated by Venous Thromboembolism Despite Being on Prophylactic Anticoagulation. *J Med Cases.* 2020;11(7):189-191.
11. Salam S, Mallat J, Elkambergy H. Acute high-risk pulmonary embolism requiring thrombolytic therapy in a COVID-19 pneumonia patient despite intermediate dosing deep vein thromboprophylaxis. *Respir Med Case Rep.* 2020;31:101263.
12. Tan BK, Mainbourg S, Friggeri A, et al. Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis. *Thorax.* 2021:thoraxjnl-2020-215383.
13. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. *Crit Care.* 2020;24(1):360.
14. Singh A, Brandow AM, Panepinto JA. COVID-19 in individuals with sickle cell disease/trait compared with other Black individuals. *Blood Advances.* 2021;5(7):1915-1921.
15. Panepinto JA, Brandow A, Mucalo L, et al. Coronavirus Disease among Persons with Sickle Cell Disease, United States, March 20-May 21, 2020. *Emerg Infect Dis.* 2020;26(10):2473-2476.
16. Shet AS, Lizarralde-Iragorri MA, Naik RP. The molecular basis for the prothrombotic state in sickle cell disease. *Haematologica.* 2020;105(10):2368-2379.
17. https://trinetx.com/real-world-data/. Accessed 12.08.2021, 2021.
18. Singh A, Mora J, Panepinto JA. Identification of patients with hemoglobin SS/Sβ0 thalassemia disease and pain crises within electronic health records. *Blood Advances.* 2018;2(11):1172-1179.
19. Michalik DE, Taylor BW, Panepinto JA. Identification and Validation of a Sickle Cell Disease Cohort Within Electronic Health Records. *Acad Pediatr.* 2017;17(3):283-287.
20. Fang MC, Fan D, Sung SH, et al. Validity of Using Inpatient and Outpatient Administrative Codes to Identify Acute Venous Thromboembolism: The CVRN VTE Study. *Med Care.* 2017;55(12):e137-e143.

21. Lawrence K, Joos C, Jones AE, Johnson SA, Witt DM. Assessing the accuracy of ICD-10 codes for identifying acute thromboembolic events among patients receiving anticoagulation therapy. *Journal of Thrombosis and Thrombolysis.* 2019;48(2):181-186.
22. Brunson A, Keegan T, Mahajan A, White R, Wun T. High incidence of venous thromboembolism recurrence in patients with sickle cell disease. *Am J Hematol.* 2019;94(8):862-870.
23. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood.* 2020;135(23):2033-2040.
24. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. . Accessed 01.18.2022.

Table 1. Characteristics of patients with sickle cell disease hospitalized with and without COVID-19

Characteristic	**Total (N=5154)**	**SCD_COVID (N=281)**	**SCD_NO_COVID (N=4873)**	**p-value**
Age, mean (SD)	28.2 (17.6)	31.3 (18.0)	28.0 (17.6)	**0.0021**
<18 years of age, %	32.0%	22.4%	32.5%	**0.004**
Females, %	54.2	51.2	54.3	0.3146
SCD Subtype HbSS/Sβ^0, %	77.2	77.9	77.1	0.3318
3 or more hospitalization in past 3 years , %	59.1	62.8	58.8	0.2511
Prior history of comorbidities, %				
Asthma	26.5	26.3	26.5	0.9594
Hypertension	26.2	35.2	25.7	**0.0004**
Heart_failure	10.9	14.2	10.7	0.0620
Ischemic heart disease	5.6	7.8	5.5	0.0959
Diabetes mellitus	8.7	9.6	8.7	0.5835
Acute/chronic kidney disease	20.0	29.2	19.5	**<.0001**
Liver disease	10.6	13.5	10.4	0.1008
Obesity	13.5	20.6	13.1	**0.0003**
Chronic Obstructive Pulmonary disease	4.4	6.4	4.2	0.0852
Cerebral Infarction, %	9.1	9.3	9.1	0.9456
Prior DVT and/or pulmonary embolism	15.8	22.8	15.3	**0.0009**
ICU admissions after index event				
Within 30 days of index event, %	4.9	9.6	4.7	**<0.001**
Within 90 days of index event, %	5.7	11.0	5.3	**<0.001**
Within 180 days of index event, %	6.8	12.8	6.5	**<0.001**

Table 2. Model parameters and estimates for outcome of VTE incidence at 1 month, 3 months and 6 months post index event

Table 2a. Outcome – VTE incidence at 1 month

Parameter	Estimate	Standard Error	Pr > |Z|	Adjusted RR (95% CI)
Intercept	-4.7962	0.1626	<.0001	-
Patients with SCD hospitalized with COVID (yes vs no)	-0.0556	0.1964	0.7773	0.95 (0.64 – 1.39)
Age	0.0081	0.0035	**0.0218**	1.01 (1.00 – 1.02)
Prior history of hypertension (yes vs no)	-0.1192	0.1268	0.3473	0.89 (0.69 – 1.14)
Prior history of obesity (yes vs no)	0.2317	0.1221	0.0578	1.26 (0.99 – 1.60)
Prior history of VTE/pulmonary embolism(yes vs no)	3.0830	0.1700	**<.0001**	21.82 (15.64 – 30.45)
Prior history of acute/chronic kidney disease (yes vs no)	0.2592	0.1279	**0.0428**	1.30 (1.01 – 1.67)

Table 2b. Outcome – VTE incidence at 3 months

Parameter	Estimate	Standard Error	Pr > |Z|	Adjusted RR (95% CI)
Intercept	-4.3676	0.1265	<.0001	-
Patients with SCD hospitalized with COVID (yes vs no)	0.0478	0.1655	0.7726	1.05 (0.76 – 1.45)
Age	0.0106	0.0029	**0.0003**	1.01 (1.01 – 1.02)
Prior history of hypertension (yes vs no)	-0.1395	0.1106	0.2071	0.87 (0.70 – 1.08)
Prior history of obesity (yes vs no)	0.2409	0.1036	**0.0200**	1.27 (1.04 – 1.56)
Prior history of VTE/pulmonary embolism(yes vs no)	2.7530	0.1359	**<.0001**	15.69 (12.02 – 20.48)
Prior history of acute/chronic kidney disease (yes vs no)	0.2577	0.1097	**0.0188**	1.29 (1.04 – 1.60)

Table 2c. Outcome – VTE incidence at 6 months

Parameter	Estimate	Standard Error	Pr > |Z|	Adjusted RR (95% CI)
Intercept	-3.9230	0.1029	<.0001	
Patients with SCD hospitalized with COVID (yes vs no)	0.0572	0.1481	0.6995	1.06 (0.79 – 1.41)
Age	0.0093	0.0025	**0.0002**	1.01 (1.00 – 1.01)
Prior history of hypertension (yes vs no)	-0.1334	0.0936	0.1540	0.88 (0.73 – 1.05)
Prior history of obesity (yes vs no)	0.1975	0.0896	**0.0275**	1.22 (1.02 – 1.45)
Prior history of VTE/pulmonary embolism(yes vs no)	2.5353	0.1124	**<.0001**	12.62 (10.12 – 15.73)
Prior history of acute/chronic kidney disease (yes vs no)	0.2858	0.0943	**0.0024**	1.33 (1.11 – 1.60)