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## Incidence of venous thromboembolism in coronavirus disease 2019: An experience from a single large academic center

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### ABSTRACT

**Background:** Infection with the novel severe acute respiratory syndrome coronavirus 2 has been associated with a hypercoagulable state. Emerging data from China and Europe have consistently shown an increased incidence of venous thromboembolism (VTE). We aimed to identify the VTE incidence and early predictors of VTE at our high-volume tertiary care center.

**Methods:** We performed a retrospective cohort study of 147 patients who had been admitted to Temple University Hospital with coronavirus disease 2019 (COVID-19) from April 1, 2020 to April 27, 2020. We first identified the VTE (pulmonary embolism [PE] and deep vein thrombosis [DVT]) incidence in our cohort. The VTE and no-VTE groups were compared by univariable analysis for demographics, comorbidities, laboratory data, and treatment outcomes. Subsequently, multivariable logistic regression analysis was performed to identify the early predictors of VTE.

**Results:** The 147 patients (20.9% of all admissions) admitted to a designated COVID-19 unit at Temple University Hospital with a high clinical suspicion of acute VTE had undergone testing for VTE using computed tomography pulmonary angiography and/or extremity venous duplex ultrasonography. The overall incidence of VTE was 17% (25 of 147). Of the 25 patients, 16 had had acute PE, 14 had had acute DVT, and 5 had had both PE and DVT. The need for invasive mechanical ventilation (adjusted odds ratio, 3.19; 95% confidence interval, 1.07-9.55) and the admission D-dimer level  $\geq 1500$  ng/mL (adjusted odds ratio, 3.55; 95% confidence interval, 1.29-9.78) were independent markers associated with VTE. The all-cause mortality in the VTE group was greater than that in the non-VTE group (48% vs 22%;  $P = .007$ ).

**Conclusions:** Our study represents one of the earliest reported from the United States on the incidence rate of VTE in patients with COVID-19. Patients with a high clinical suspicion and the identified risk factors (invasive mechanical ventilation, admission D-dimer level  $\geq 1500$  ng/mL) should be considered for early VTE testing. We did not screen all patients admitted for VTE; therefore, the true incidence of VTE could have been underestimated. Our findings require confirmation in future prospective studies. (*J Vasc Surg Venous Lymphat Disord* 2021;9:585-91.)

**Keywords:** COVID-19 coagulopathy; COVID-19 VTE; Hypercoagulable state in COVID-19

Since first described in Wuhan, Hubei Province, China, in December 2019, the novel severe acute respiratory syndrome coronavirus 2 has spread worldwide and was declared a pandemic by the World Health Organization on March 11, 2020.<sup>1</sup> As of August 14, 2020, >21 million people had been infected worldwide, with >5.2 million cases and 167,000 deaths in the United States alone.<sup>2</sup>

Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2, appears to be associated with a hypercoagulable state that results in an increased incidence of thromboembolic complications.<sup>3</sup> The emerging data from Europe and China have shown a high incidence of venous thromboembolism (VTE) in patients with COVID-19.<sup>4-16</sup>

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\*The list of the Temple University COVID-19 Research Group members is available in the [Appendix](#) (online only).

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However, data that have identified risk factors for the prediction of VTE in COVID-19 are limited. We aimed to identify the VTE incidence and the risk factors for VTE occurrence in a high-volume, tertiary referral center.

## METHODS

We performed a retrospectively cohort study of all patients who had been admitted to the Temple University Hospital COVID-19 unit from April 1, 2020 to April 27, 2020 and had undergone VTE diagnostic testing because of a high index of clinical suspicion. Patients were included in the present analysis if they had tested positive for COVID-19 using nasopharyngeal swab reverse transcription polymerase chain reaction or had had findings (eg, multifocal ground glass opacities, crazy paving pattern, patchy consolidations, radial and curvilinear bands, halo sign, reversed halo sign) on computed tomography of the chest and clinical symptoms indicative of a high likelihood of COVID-19 and had received specific COVID-19 therapies. The institutional review board approved the present study and waived the requirement for patient informed consent in accordance with the local standards (protocol no. 27,012). All the patients had received VTE prophylaxis at admission (enoxaparin 40 mg daily, heparin 5000 U every 8 hours, or sequential compression devices if anticoagulant prophylaxis was contraindicated). Screening was not limited, irrespective of the preadmission anticoagulation status, nor for other reasons such as limited code status or to preserve personal protective equipment. Screening for deep vein thrombosis (DVT) was limited to proximal DVT only to limit exposure to the vascular technicians. Using the results of VTE testing, we divided our cohort into a VTE and no-VTE group. A follow-up analysis was performed to assess the outcomes of those with continued admission at the end of the initial study period.

Data are presented as counts and percentages for categorical variables and the median and range or interquartile range for continuous variables. We performed univariable analysis to compare the demographic parameters, inflammatory biomarkers, laboratory test values, treatments, and clinical outcomes between the VTE and no-VTE groups (Table 1). Group comparisons were performed using the *t* test or nonparametric test (Wilcoxon rank sum test) for continuous variables and the Fisher exact test or  $\chi^2$  test for categorical variables. Odds ratios (ORs) and their 95% confidence intervals were computed from the univariable logistic regression models for VTE occurrence. Multivariable logistic regression analysis was performed to identify risk factors for VTE occurrence in our cohort using a stepwise regression method. The multivariate model was constructed by including only variables with *P* value <.05 on univariate analysis. Adjusted ORs and 95% confidence intervals from the final multivariable logistic regression

## ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, retrospective cohort study
- **Key Findings:** We found venous thromboembolism (VTE) incidence rates of 3.5% in patients admitted to a coronavirus disease 2019 unit and 17% in a population tested because of clinical suspicion. We identified an admission D-dimer level of  $\geq 1500$  ng/mL and the need for invasive mechanical ventilation as independent predictors of VTE occurrence.
- **Take Home Message:** Our study represents one of the earliest reported from the United States on the incidence rate of VTE in patients with coronavirus disease 2019. Patients with a high clinical suspicion and identified risk factors (ie, invasive mechanical ventilation, D-dimer admission level of  $\geq 1500$  ng/mL) should be considered for early VTE testing. Our findings require confirmation in future prospective studies.

model were reported, reflecting the OR of a VTE incident occurring for a specific risk factor after adjustment for other independent predictors. *P* values <.05 were considered statistically significant. SAS, version 9.4 (SAS Institute Inc, Cary, NC), was used for all statistical analyses.

## RESULTS

A total of 703 patients had been admitted to the Temple University Hospital COVID-19 unit from April 1, 2020 to April 27, 2020. Of the 703 patients, 147 (20.9%) had undergone diagnostic tests for acute VTE because of high clinical suspicion using extremity venous duplex ultrasonography or pulmonary computed tomography angiography, or both (Fig). Patients with chronic DVT were excluded from our analysis. Chronic DVT shown on venous duplex ultrasonography was defined as a vein that was incompressible, narrow, and irregular and that showed echogenic thrombus attached to the venous walls with the development of collaterals.

**VTE incidence.** Overall, the acute VTE incidence was 3.5%. The incidence of acute VTE in the patients who had undergone VTE testing was 17% (25 of 147). Of the 25 patients, 16 had acute PE (11 with PE only and 5 with concurrent acute DVT). Fourteen patients had acute DVT (nine with DVT only and five with concurrent PE). Of these 14 patients, 9 had lower extremity DVT, 2 had upper extremity DVT, and 3 had both upper and lower extremity DVT. One case of upper extremity DVT was associated with a peripherally inserted central catheter and one was on the side of a previously ligated arteriovenous fistula. All cases of DVT were located in the proximal upper and lower extremities in our cohort.

**Table I.** Baseline demographic, laboratory, and treatment data

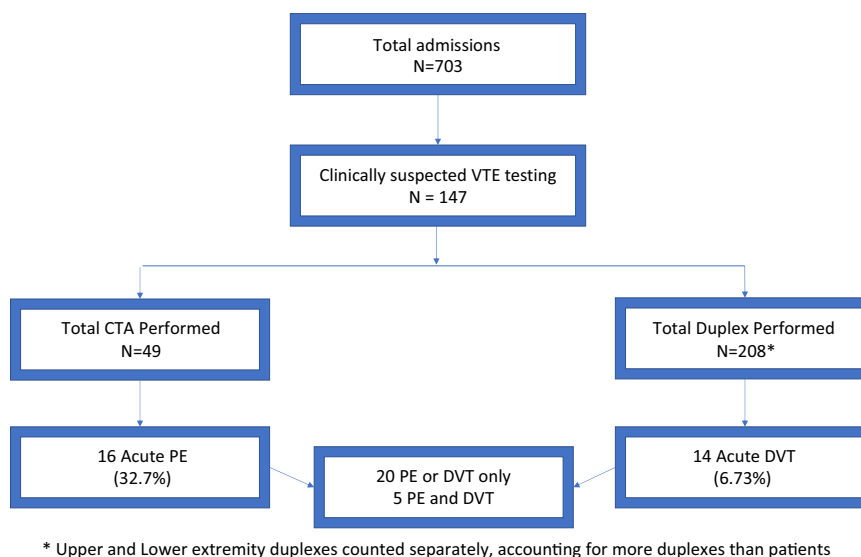
Variable	VTE		P Value	OR (95% CI)
	Yes (n = 25)	No (n = 122)		
<b>Demographic</b>				
Age ≥65 years	14 (56)	47 (38)	.106	2.03 (0.85-4.84)
Male sex	15 (60)	57 (46)	.226	1.71 (0.712-4.10)
BMI ≥30 kg/m <sup>2</sup>	15 (60)	77 (63)	.770	0.87 (0.36-2.11)
Race			.652	0.81 (0.33-1.97)
Black	15 (60)	79 (64)		
Hispanic	5 (20)	24 (20)		
<b>Comorbidities</b>				
History of VTE	2 (8)	9 (7)	.914	1.09 (0.22-5.38)
Cancer	3 (12)	9 (7)	.442	1.71 (0.42-6.83)
CAD	5 (20)	18 (14)	.511	1.44 (0.48-4.34)
CHF	1 (4)	11 (9)	.404	0.42 (0.05-3.41)
Stroke	4 (16)	18 (14)	.874	1.10 (0.33-3.58)
Diabetes	7 (28)	51 (41)	.198	0.54 (0.21-1.39)
COPD	2 (8)	14 (11)	.611	0.67 (0.14-3.15)
CKD	5 (20)	16 (13)	.370	1.65 (0.54-5.03)
<b>Admission laboratory test results</b>				
D-dimer ≥1500 ng/mL (normal, <500 ng/mL)	18 (72)	54 (44)	.011	3.20 (1.26-8.30)
Fibrinogen >385 or <200 U/L (normal, 200-385 U/L)	14 (56)	94 (77)	.073	0.99 (0.99-1.00)
LDH >241 U/L (normal, 87-241 U/L)	20 (80)	87 (71)	.374	1.00 (0.99-1.00)
Ferritin >388 ng/mL (normal, 8-388 ng/mL)	17 (68)	73 (60)	.445	1.00 (0.99-1.00)
Platelet count <150,000 (normal, 150-450 K/mm <sup>3</sup> )	10 (40)	24 (20)	.036	2.72 (1.08-6.80)
<b>Treatment and outcome</b>				
ICU admission	19 (76)	65 (53)	.036	2.77 (1.03-7.43)
Mechanical ventilation	14 (56)	32(26)	.003	2.82 (1.47-8.68)
Cytokine treatment	11 (44)	53 (43)	.959	1.02 (0.45-2.43)
<b>Discharge</b>				
Death	12 (48)	27 (22)	.007	3.24 (1.32-7.93)
Home	8 (32)	64 (52)	.062	2.34 (0.94-5.83)

BMI, Body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; LDH, lactate dehydrogenase; OR, odds ratio; VTE, venous thromboembolism. Data presented as number (%), unless otherwise noted.

**Thromboprophylaxis.** Of the 25 patients, 11 had been diagnosed with VTE within 48 hours of admission. Of the remaining 14 patients with VTE diagnosed >48 hours after admission, 3 patients had received thromboprophylaxis secondary to a recent history of bleeding, 6 patients had received standard thromboprophylaxis before the VTE diagnosis, and 5 patients had required an increase in their thromboprophylaxis dosing because of increasing D-dimer levels and individualized recommendations from the inpatient hematology consultation team. Four of these five patients had received intermediate-dose thromboprophylaxis (enoxaparin 0.5 mg/kg every 12 hours) and the dosage was

increased to full therapeutic anticoagulation with heparin infusion for one patient before the VTE diagnosis secondary to a high clinical suspicion and a D-dimer level >20,000 ng/mL. All the patients had received therapeutic dose anticoagulation after the diagnosis of VTE. No inferior vena cava filters were placed

**VTE risk factors.** We found that an admission D-dimer level of ≥1500 ng/mL, admission platelet count <150,000, intensive care unit (ICU) admission, and the need for mechanical ventilation were significantly different statistically between the VTE and no-VTE groups on univariable analysis (Table I). Subsequently, multivariate logistic regression



**Fig.** Flowchart showing the inclusion and exclusion of the patients. CTA, Computed tomography angiography; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

analysis revealed a D-dimer level of  $\geq 1500$  ng/mL and the need for invasive mechanical ventilation were independent predictors of VTE occurrence (Table II). All other comorbidities, laboratory test results, and cytokine storm treatment were not significantly different between the two groups (Table I). We did not find a statistically significant difference in the D-dimer trends in the patients evaluated for VTE >48 hours after admission who had had positive or negative findings for VTE. An upward trend was noted in most of the patients in both the positive and the negative groups (85.7% vs 69.2%;  $P = .21$ ).

**Outcomes.** Patients with VTE had had a greater incidence of ICU admission (76% vs 51%;  $P = .036$ ), invasive mechanical ventilation (56% vs 26%;  $P = .003$ ), and all-cause mortality (48% vs 22%;  $P = .007$ ) and a lower rate of home discharge (32% vs 52%;  $P = .062$ ) compared with the no-VTE group (Table I).

## DISCUSSION

The VTE incidence rate was 3.5% for the patients admitted to our COVID-19 unit and 17% in a population tested because of clinical suspicion. We did not identify race or obesity as risk factors in our analysis for VTE incidence. A trend was found toward significance for patient

age >65 years ( $P = .106$ ). However, ICU admission and the need for invasive mechanical ventilation were highly significant variables associated with VTE in our COVID-19 population (Table I). The VTE group had had greater all-cause mortality compared with the no-VTE group (48% vs 22%;  $P = .007$ ). Nearly one half of our VTE-positive cohort (11 of 25) had been diagnosed within 48 hours of admission. We did not find any influence of cytokine storm treatment on VTE occurrence in our cohort. We identified an admission D-dimer level of  $\geq 1500$  ng/mL (three times the upper limit of normal) and a need for invasive mechanical ventilation as independent predictors of VTE occurrence.

Our finding of an increased risk of adverse outcomes, including the need for ICU admission and invasive mechanical ventilation and increased all-cause mortality, in the VTE cohort is supported by reported studies from other centers.<sup>4,6</sup> Nearly one half of our VTE cohort (11 of 25) had been diagnosed within 48 hours of admission. We believe that the early VTE presentation in patients with COVID-19 might represent late presentation with severe COVID-19. However, the reported data have remained too limited to generalize the concept of empiric therapeutic anticoagulation for all patients

**Table II.** Multivariate logistical regression model for venous thromboembolism prediction

Variable	OR	SE	Z value	P value	95% CI
ICU admission	1.26	0.77	0.38	.707	0.37-4.23
Admission platelet count <150,000	2.28	1.17	1.61	.108	0.83-6.27
Admission D-dimer $\geq 1500$ ng/mL	3.57	1.84	2.47	.013	1.30-9.83
Admission fibrinogen >385 or <200 U/L	0.43	0.21	-1.68	.093	0.16-1.15
Invasive mechanical ventilation	3.39	1.92	2.16	.031	1.12-10.30

CI, Confidence interval; ICU, intensive care unit; OR, odds ratio; SE, standard error.

**Table III.** Current data on venous thromboembolism in patients with coronavirus disease 2019

Investigator	ICU vs floor	Anticoagulation	VTE (total, PE, DVT)	MV rate	Mortality
<b>United States</b>					
Zier et al, <sup>18</sup> (n = 66)	ICU only	NR	VTE, 22.7%	100%	16.7%
Goyal et al, <sup>19</sup> (n = 393)	ICU and floor (details NR)	NR	VTE total, 3.3%; ICU, 7.7%; non-ICU, 1.1%	30.8%	10.2%
<b>The Netherlands</b>					
Middeldorp et al, <sup>4</sup> (n = 198)	ICU, 37%; floor, 63%	Prophylactic, 84%; therapeutic (started before admission), 9.6%	VTE, 17%; PE ± DVT, 5.6%; proximal LE DVT, 6.6%; distal LE DVT, 4.0%; UE DVT, 0.5%	67%	14%
Klok et al, <sup>5</sup> (initial; n = 184)	ICU only	Prophylactic, 90.8%; therapeutic (started before admission), 9.2%	VTE, 31% (PE, 80.6%; DVT, 9.6%; arterial thrombosis, 9.6%)	NR	13%
Klok et al, <sup>6</sup> (extended analysis; n = 184)	ICU only	Prophylactic, 90.8%; therapeutic (started before admission), 9.2%	VTE, 57% (PE, 86%; DVT, 4%; arterial thrombi, 9.3%)	NR	22%
<b>France</b>					
Leonard-Lorant et al, <sup>7</sup> (n = 106)	ICU, 75%; floor 25%	Prophylactic, 78%; therapeutic, 6%	PE, 30%; DVT, NR	NR	NR
Grillet et al, <sup>8</sup> (n = 100)	ICU, 39%; floor 61%	NR	PE, 23%; DVT, NR	34%; 65% in PE group	NR
Llijtos et al, <sup>9</sup> (n = 26)	ICU only	Prophylactic, 31%; therapeutic (at discretion of treating physician), 69%	DVT in prophylactic group, 100%; DVT in therapeutic group, 56%; PE in prophylactic group, 0%; PE in therapeutic group, 33%	100%	12%
Poissey et al, <sup>10</sup> (n = 107)	ICU only	Prophylactic, 90.9%; therapeutic (started before admission), 9.1%	PE, 20.6%; DVT, 4.7%	77.3%	14%
Helms et al, <sup>11</sup> (n = 150)	ICU only	Prophylactic, 70%; therapeutic (started before admission, NR), 30%	VTE, 42.6%; PE, 16.7%; RRT circuit clot, 18.6%; DVT, NR; hemorrhagic complications, 2.7%	100%	8.7%
<b>Italy</b>					
Lodigiani et al, <sup>12</sup> (n = 388)	ICU, 16%; floor, 84%	ICU: prophylactic, 96.8%; therapeutic (started before admission), 3.2%; floor: prophylactic, 68.3%; therapeutic (started before admission), 6.7%	VTE, 7.7%; PE, 2.8%	NR	26%
Marone et al, <sup>13</sup> (n = 30)	NR	NR	VTE, 53.3%	NR	NR
<b>United Kingdom</b>					
Thomas et al, <sup>14</sup> (n = 63)	ICU only	Prophylactic, 98.4%; therapeutic (started before admission), 1.6%	VTE, 27%; PE, 7.9%	83%	16%
<b>China</b>					
Cui et al, <sup>15</sup> (n = 81)	ICU only	NR	DVT, 25%; PE, NR	NR	10%
Xu et al, <sup>16</sup> (n = 138)	ICU, 10.9%; floor, 90.1%	ICU: prophylactic, 100%; floor: prophylactic, 21.5%	DVT, 2.9%	75% of patients with DVT	25% of patients with DVT

DVT, Deep vein thrombosis; ICU, intensive care unit; LE, lower extremity; MV, mechanical ventilation; NR, not reported; PE, pulmonary embolism; RRT, renal replacement therapy; UE, upper extremity; VTE, venous thromboembolism.

with COVID-19.<sup>4,6,9,17</sup> High-risk patients who cannot be tested for VTE should be considered for empiric therapeutic anticoagulation on a case by case basis.

Our incidence rates for VTE were lower than those previously reported from Europe (France, the Netherlands, Italy, and the UK) and China, with rates of 17% to 100%<sup>4-16</sup> (Table III). However, data from U.S. centers have remained sparse. Two recent studies from the United States that focused primarily on critically ill patients reported thrombotic event rates of 22.7% and 7.7%.<sup>18,19</sup> Several factors could have contributed to our lower VTE rates. All patients admitted to our institution had received VTE prophylaxis. With the recognition of an increased risk of VTE in patients with COVID-19,<sup>3-15</sup> VTE prophylaxis was continuously intensified during the study period, which has also been reported by other centers.<sup>6</sup> Additionally, our overall approach has been to use noninvasive ventilator support (high-flow oxygen therapy and bilevel positive airway pressure) and avoid the immobilization that occurs with invasive mechanical ventilation. Invasive mechanical ventilation has been identified as a risk factor for  $\leq 69\%$  of patients with VTE.<sup>3-15</sup> The rates of invasive mechanical ventilation, high-flow oxygen nasal therapy, and bilevel positive airway pressure usage were  $\sim 8.5\%$ ,  $\sim 24.5\%$ , and  $\sim 3.3\%$  at the end of our study period. Our rates of invasive mechanical ventilation were lower than that in other VTE studies but broadly in line with larger cohorts in China.<sup>20-22</sup> Our lower use of invasive mechanical ventilation might have contributed to our lower reported rates of VTE. We did not screen all admitted patients for VTE; therefore, it is possible that the true incidence of VTE was underestimated.

To the best of our knowledge, no previous studies have evaluated the role of cytokine storm treatment in VTE incidence. Cytokine storm treatment at our institution consisted of high-dose steroids ( $\geq 125$  mg of methylprednisolone) and other advanced therapies such as sarilumab, gimsilumab, tocilizumab, anakinra, intravenous immunoglobulin, and etoposide. However, this advanced treatment was not predictive of VTE incidence in our cohort. Inflammatory markers such as D-dimer values have been investigated as VTE predictors in previous studies.<sup>7,11,12,15</sup> We assessed the D-dimer values at admission, VTE diagnosis, VTE peak, and discharge as potential predictors of VTE. We demonstrated that a D-dimer level of  $\geq 1500$  ng/mL at admission was a predictor of a VTE event. The traditional cutoff of 500 ng/mL or age-adjusted values do not appear to be helpful because most of our cohort had had abnormal D-dimer values at admission.<sup>23</sup> Previous studies have examined cutoff values of 2660 ng/mL and 3000 ng/mL and reported a sensitivity and specificity ranging from 76.9% to 100% and 67% to 94.9%, respectively.<sup>7,15</sup> We focused on the admission D-dimer values, because the substantial fluctuations in D-dimer values during the course of COVID-19 has made the D-dimer levels difficult to use as a predictor of VTE.

**Study limitations.** Our study had several limitations. We performed a single-center, retrospective study; thus, generalizability could be limited. More than one half of the screened population were still hospitalized at the data analysis. Our institutional VTE prophylaxis guidelines were revised during the pandemic, and the use of more aggressive VTE prophylaxis might have affected our reported rate of VTE occurrence. We had not screened all admitted patients for VTE unless clinically indicated; therefore, the true incidence in our population could have been underestimated. The use of multivariate analysis on a small sample size with a relatively lower event rate was another limitation.

## CONCLUSIONS

Our study represents one of the earliest reported from the United States on the incidence rate of VTE in patients with COVID-19. Our overall incidence rate of 3.5% in our patient cohort with COVID-19 and 17% in a selectively screened population were lower than those reported by previous studies, potentially owing to the aggressive treatment of cytokine storm, aggressive VTE prophylaxis, and greater use of noninvasive ventilation. We identified an elevated D-dimer level  $\geq 1500$  ng/mL at admission and the need for invasive mechanical ventilation as potential risk factors for VTE occurrence. These risk factors could allow for risk stratification of high-risk patients and trigger earlier VTE screening. Further prospective study are needed.

## AUTHOR CONTRIBUTIONS

Conception and design: PR, OO, LO, OS, RW, CM, PD, NA, MB, JP, RB, VL, RC, RG, CD, KM, AR, GC, GJC, EC

Analysis and interpretation: PR, OO, LO, DY, OS, RW, CM, PD, NA, MB, AL, XL, EC

Data collection: PR, OO, OS, RW, CM, AS, AL, EC

Writing the article: PR, OO, LO, OS, CM, PD, NA, EC

Critical revision of the article: PR, OO, LO, DY, OS, RW, CM, PD, NA, AS, MB, AL, JP, RB, VL, RC, RG, CD, KM, XL, AR, GC, GJC, EC

Final approval of the article: PR, OO, LO, DY, OS, RW, CM, PD, NA, AS, MB, AL, JP, RB, VL, RC, RG, CD, KM, XL, AR, GC, GJC, EC

Statistical analysis: LO, DY, XL, EC

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PR and EC contributed equally to this article and share co-senior authorship.

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*Additional material for this article may be found online at [www.jvsvenous.org](http://www.jvsvenous.org).*



**APPENDIX (online only).**

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