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Original Contributions

SARS-CoV-2 Positivity in Ambulatory Symptomatic Patients Is Not Associated With Increased Venous or Arterial Thrombotic Events in the Subsequent 30 Days

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□ **Abstract—Background: COVID-19 has been associated with increased risk of thromboembolism in critically ill patients. Objective: We sought to examine the association of SARS-CoV-2 test positivity and subsequent acute vascular thrombosis, including venous thromboembolism (VTE) or arterial thrombosis (AT), in a large nationwide registry of emergency department (ED) patients tested with a nucleic acid test for suspected SARS-CoV-2. Methods: The RECOVER (Registry of Potential COVID-19 in Emergency Care) registry includes 155 EDs across the United States. We performed a retrospective cohort study to produce odds ratios (ORs) for COVID-19–positive vs. COVID-19–negative status as a predictor of 30-day VTE or AT, adjusting for age, sex, active cancer, intubation, hospital length of stay, and intensive care unit (ICU) care. Results: Comparing 14,056 COVID-19–positive patients with 12,995 COVID-19–negative patients, the overall 30-day prevalence of VTE events was 1.4% vs. 1.3%, respectively ($p = 0.44$, χ^2). Multivariable analysis identified that testing positive for SARS-CoV-2 status was negatively associated with both VTE (OR 0.76; 95% confidence interval [CI] 0.61–0.94) and AT (OR 0.51; 95% CI 0.32–0.80), whereas intubation, ICU care, and age 50 years or older were positively associated with both VTE and AT. Conclusions: In contrast to other reports, results from this large, hetereogenous national sample of ED patients tested for SARS-CoV-2, showed no association between vascular thrombosis and COVID-19 test positivity. © 2022 Elsevier Inc. All rights reserved.**

□ **Keywords—COVID-19; critical care; SARS-CoV-2; thrombosis; venous; thromboembolism**

Introduction

COVID-19 triggers inflammation and the development of thromboembolic events (1). The reported incidence of thromboembolism in patients with COVID-19 varies widely among studies. Klok et al. reported a 31% incidence of thrombotic complications in patients with COVID-19 admitted to the intensive care unit (ICU) (2). Similarly, a meta-analysis of 102 studies reported a venous thromboembolism (VTE) frequency of approximately 14.7% and arterial thrombotic (AT) frequency of 3.9% in COVID-19–positive patients. Early in the pandemic, most reports of the frequency of VTE were from hospitalized and ICU-level patients or from autopsies (2–6).

In contrast to the above studies, a retrospective study performed across a multihospital health system in New York found the incidence of VTE in hospitalized patients to be 1.09% (7). Similarly, Cohen et al. found a VTE rate in admitted patients of 2.9% and 4.9% in the ICU (8). A retrospective cohort study of more than 220,000 patients from Northern California tested for SARS-CoV-2 over a

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similar time as our study reported an incidence of VTE of 0.8% in patients who tested positive for COVID-19. The authors also found the incidence of VTE increased with hospitalization compared with those patients treated as outpatients (4.8% vs. 1.8%) (9). Freund et al. examined the incidence of pulmonary embolism (PE) in all patients undergoing computed tomographic pulmonary angiography during an 8-week period of the pandemic (March–April 2020) and found no increased probability of PE diagnosis in COVID-19–positive patients (10). These more recent studies are similar in that they included patients with varying levels of illness (1,2,5,7–13).

Fewer studies have reported on AT in acute COVID-19 illness. Malas et al. identified 8 studies reporting increased risk of AT (4). The overall AT rate in COVID-19–positive patients in the ICU was 2% and 5% in their report, which pooled myocardial infarction, cerebrovascular accidents, and acute limb ischemia as AT events (4). Early signals from small studies in New York and Wuhan, China have reported acute ischemic stroke in the context of hospitalized COVID-19–positive patients (14,15). Reports from other groups are similar, with a reported occurrence of stroke between 2.7% and 3.8% of patients (4,11).

The published literature to date has focused on the incidence of thromboembolism in hospitalized or critically ill patients; however, globally, most people with acute COVID-19 infection are outpatients. Analysis of thromboembolic risk has focused mainly on specific cohorts of hospitalized patients with COVID-19 and has not taken into account ambulatory patients with mild COVID-19, which may have overestimated overall thromboembolic risk (16). Therefore, we sought to examine the risk of vascular thrombosis (VTE and AT) in a large nationwide sample of U.S. ED patients tested for COVID-19.

Methods

The RECOVER (Registry of Potential COVID-19 in Emergency Care) study is a large observational clinical study of patients from 155 U.S. emergency departments (EDs) across 27 states (17). Eligible participants included ED patients with a SARS-COV-2 test during, or 14 days prior to, the index visit, from March to September 2020. The index visit from which data were abstracted came from the first ED visit that occurred within 14 days of SARS-COV-2 testing unless meeting specific exclusions (17). Exclusions included the following predefined circumstances when there was a lack of reasonable probability of being related to COVID-19 infection: trauma, alcohol or drug intoxication, poisoning, suicidality, suspected rape or other domestic violence, involuntary commitment, other isolated symptoms clearly not related to COVID-19 (e.g., suture removal), and testing done purely for policy (e.g., any admitted patient) rather than testing based on clinical suspicion. Patients were enrolled from March to September 2020 with intent to enroll eligible patients consecutively. COVID-19–positive disease status required a positive molecular reverse transcription polymerase chain reaction (RT-PCR) test performed on a nasopharyngeal swab or positive serum antibody titer for SARS-CoV-2 within 30 days; all others were considered COVID-19–negative (17). Presenting symptoms and risk factors for all tested patients can be found in Table 1 of the protocol methodology published previously (17). The protocol for the registry was reviewed by the Institutional Review Boards at all participating sites, which approved the protocol under waiver of authorization for participation in research as well as informed consent.

The registry was built using REDCap (www.project-redcap.org) and recorded 360 possible answers to a total of 204 questions. Outcomes were recorded up to 30 days after index visit. All follow-up was done by means of interrogating the electronic medical record at each site. Outcomes examined for this planned substudy included development of VTE, arterial thromboembolism, admission status, hospital length of stay, advanced oxygen delivery (i.e., requirement of oxygen support above nasal canula), need for critical care, and mortality. The criterion standard required image-proven VTE interpreted by a board-certified radiologist. Deep vein thrombosis (DVT) was diagnosed when the medical records indicated a noncompressible deep vein (above the calf in the lower extremity and proximal to the axillary or jugular veins in the upper extremity) observed on compression ultrasonography and interpreted as positive for thrombosis. PE required a filling defect on computed tomographic pulmonary angiography, or a segmental or larger unmatched perfusion defect on scintillation ventilation-perfusion lung scanning interpreted as positive or high probability for PE, respectively. Arterial thromboembolism required a new diagnosis of myocardial infarction, stroke, mesenteric ischemia, or arterial obstruction of an extremity demonstrated on either planar or computed tomography angiography of the extremity. World Health Organization (WHO) COVID-19 severity scores were calculated based on recommendations by the WHO Working Group on Clinical Characterization and Management of COVID-19 Infection. Severity scores were defined as follows: *ambulatory disease* was defined as test positivity not requiring hospital admission; *moderate disease* was defined as test positivity requiring hospital admission with or without oxygen via nasal canula; *severe disease* was defined as test positivity requiring advanced oxygen support, including noninvasive ventilation, mechanical ventilation, requirement of vasopressor support, dialysis, or extracorporeal membrane oxygenation; and *death* was defined as mortality within 30 days of test positivity (18).

Table 1. Study Characteristics of Patients Enrolled in the RECOVER Registry

Characteristic	SARS-CoV-2–Positive	SARS-CoV-2–Negative
Total n	14,056	12,995
Age, y, mean ± SD	56.4 ± 19.5	48.6 ± 20.9
Sex, n (%)		
Male	7423 (53)	6002 (46)
Female	6633 (47)	6993 (54)
Intubated, n (%)	1821 (13)	563 (4)
ICU admission, n (%)	2187 (15)	1169 (9)
Hospital LOS, d, mean ± SD	5.93 ± 9.8	2.68 ± 5.9
Active cancer, n (%)	966 (7)	1899 (15)
Venous thromboembolism, n (%)	194 (1.4)	167 (1.3)
χ^2, *p* value	0.44	
DVT and PE, n (%)	47 (0.33)	48 (0.36)
Arterial thromboembolism, n (%)	40 (0.3)	46 (0.4)
χ^2, *p* value	0.31	

DVT = deep vein thrombosis; ICU = intensive care unit; LOS = length of stay; PE = pulmonary embolism; RECOVER = Registry of Potential COVID-19 in Emergency Care; SD = standard deviation.

Data abstractors and their site investigators all attended a 1-h training session to introduce the manual of operations that described patient eligibility and the goals of the registry with specific instructions on data abstraction and the data dictionary. Trained abstractors used the written manual of operations as they transferred data from the local electronic medical record and directly entered data into REDcap. Sites were encouraged to contact the overall principal investigator for any questions about patient eligibility or data entry. The final RECOVER database is devoid of any protected health information. Funding was derived from unrestricted departmental internal monies under the direction of the senior principal investigator. For more information on the development and methodology of the registry, please refer to Kline et al. (17). This study examined outcomes of new or recurrent VTE and AT within 30 days of index visit using case–control methodology when cases are COVID-19–positive and controls are COVID-19–negative.

Initial unadjusted analysis of risk for VTE and AT outcomes based on COVID-19 test status was tested with χ^2 analysis and univariate odds ratios (ORs) with 95% confidence intervals (CIs). Subsequently, two multivariable logistic regression models were constructed (one for VTE and one for AT) investigating COVID-19 test status with adjustment for age, sex, active cancer diagnosis at time of index visit, intubation, hospital length of stay (if admitted to hospital), and ICU stay within 30 days of index visit. Calculation of frequencies, χ^2 values, unadjusted ORs, and multivariable logistic regression ORs was performed using SPSS software (IBM Corp.). Although this was a registry for which there was no a priori sample size calculation for this subanalysis, we did a rough post-hoc estimate of power prior to the data analysis of this report. A sample size of 20,000 and a 50% positive rate for COVID-19 and 10% prevalence of VTE allowed for adequate power to detect a minimum 0.8% difference in 30-day frequency of VTE and AT rates based on COVID-19 status and 95% CI testing. A 5% prevalence of VTE with similar sample size would allow for adequate power to detect a minimum 0.6% difference.

Results

As of December 2020, the registry contained 27,051 patient records, including 14,056 patients who were COVID-19–positive and 12,995 patients who were COVID-19–negative. The mean age was slightly older in the COVID-19–positive group (56.4 ± 19.5 years vs. 48.6 ± 20.9 years). Fifty-three percent (n = 7423) of COVID-19–positive patients and 46% (n = 6002) of COVID-19–negative patients were male. Thirty-eight percent of COVID-19–positive patients were never admitted and 49% of COVID-19–negative patients were never admitted to the hospital within 30 days. Thirteen percent (n = 1821) of COVID-19–positive patients were intubated within the 30-day follow-up period and 4% (n = 563) of COVID-19–negative patients were intubated. Similarly, 16% (n = 2187) of COVID-19–positive patients and 9% (n = 1169) of COVID-19–negative patients were admitted to an ICU. Average length of stay was longer in COVID-19–positive patients (6 vs. 3 days).

Table 2. Multivariate Logistic Regression with Outcome of Venous Thromboembolism

Variable	Odds Ratio	95% CI	*p* Value
Cancer	1.55	1.21–2.05	0.002
Age older than 50 y	1.45	1.13–1.84	0.003
Sex	0.99	0.81–1.22	0.92
Hospital LOS	1.03	1.02–1.03	< 0.0005
Intubation	1.94	1.38 –2.72	< 0.0005
ICU	2.12	1.55–2.89	0.006
SARS-CoV-2–positive	0.76	0.61–0.94	0.013

CI = confidence interval; ICU = intensive care unit; LOS = length of stay.

The overall 30-day incidence of VTE was 361 (1.4%), with 205 (0.8%) positive for DVT, 179 (0.7%) positive for PE, and 95 (0.4%) positive for both PE and DVT. There was no statistically significant difference in incidence of VTE in COVID-19–positive (1.4%; n = 194) vs. COVID-19–negative (1.3%; n = 167; $p = 0.44$, χ^2) patients. Incidence of AT was also not significantly different; 0.3% in COVID-19–positive (n = 40) vs. 0.4% in COVID-19–negative (n = 46; $p = 0.31$, χ^2) patients (Table 1). Unadjusted OR showed no association between COVID-19–positive test status and either VTE (OR 1.04; 95% CI 0.95–1.14). Multivariable logistic regression analysis found COVID-19–positive test status to be significantly negatively associated with VTE (adjusted OR 0.76; 95% CI 0.61–0.94). However, the following variables were significantly independently associated with VTE: intubation (OR 1.94; 95% CI 1.38–2.72), ICU admission (OR 2.12; 95% CI 1.55–2.89), days of hospital stay (OR 1.03; 95% CI 1.02–1.03), age 50 years or older (OR 1.44; 95% CI 1.13–1.84), and active cancer (OR 1.55; 95% CI 1.21–2.05) (Table 2). Biological sex (OR 0.99; 95% CI 0.80–1.22) was not independently associated with VTE.

Similarly, COVID-19–positive test status was not associated with increased subsequent AT (unadjusted OR 0.90; 95% CI 0.71–1.12). Multivariable logistic regression analysis found COVID-19–positive status to be statistically significantly negatively associated with AT (adjusted OR 0.51; 95% CI 0.32–0.81). Intubation (OR 2.54; 95% CI 1.29–5.02), ICU admission (OR 2.43; 95% CI 1.30–4.55), and age 50 years or older (OR 1.87; 95% CI 1.11–3.160) were significantly associated with AT (Table 3). Biological sex (OR 1.13; 95% CI 0.74–1.73), hospital length of stay (OR 1.01; 95% CI, 1.00–1.03), and active cancer (OR 0.80; 95% CI 0.41–1.58) were not found to be associated with AT.

These results suggest an association between thrombosis and critical illness. In order to further characterize these associations, we calculated WHO Severity Index scores based on criteria defined by the WHO Clinical Working Group on COVID-19 (18). The WHO Severity Index described the following four severity states; ambulatory, moderate disease, severe disease, and death. Multivariable logistic regression analysis of all tested patients with adjustment for WHO disease severity states again demonstrated SARS-CoV-2–positive status was negatively associated with development of VTE (OR 0.700; 95% CI 0.56–0.87) or AT (OR 0.426; 95% CI 0.27–0.68) (Table 4). We then plotted incidence of VTE and AT against the WHO Severity Index in all tested patients. Incidence plots of VTE illustrate a trend of higher incidence of VTE in the severe disease category regardless of COVID-19 status (Figure 1A). Incidence of plots of AT revealed a lower incidence of AT in SARS-CoV-2–positive patients compared with SARS-CoV-2–negative patients in all disease indices (Figure 1B). To further characterize VTE frequency, we performed a subgroup analysis in SARS-CoV-2–positive patients only and stratified the presence of VTE based on disease status and age deciles. As expected, frequency of VTE increased with age and disease severity similar to our multivariable analyses (Figure 1C).

Discussion

The results of this study did not find an increased risk of vascular thrombosis among COVID-19–positive patients in this large, heterogeneous nationwide sample of patients undergoing testing in the U.S. acute care setting. After adjusting for variables commonly associated with VTE risk, COVID-19–positive status was found to be negatively associated with the outcome of VTE. This was true despite the COVID-19–positive cohort being 8 years older on average than the COVID-19–negative group. The findings of this study may impact care on several levels. First, the data emphasize the lack of evidence for empiric anticoagulation among noncritically ill patients with COVID-19. Second, the data do not support efforts to perform routine diagnostic testing for vascular throm-

Table 3. Multivariate Logistic Regression with Outcome of Arterial Thrombosis

Variable	Odds Ratio	95% CI	*p* Value
Cancer	0.80	0.41–1.58	0.522
Age older than 50 y	1.87	1.11–3.16	0.018
Sex	1.13	0.74–1.73	0.573
Hospital LOS	1.01	0.99–1.03	0.131
Intubation	2.55	1.29–5.02	0.007
ICU	2.43	1.30–4.55	0.006
SARS-CoV-2–positive	0.51	0.32–0.81	0.004

CI = confidence interval; ICU = intensive care unit; LOS = length of stay.

Table 4. Multivariate Logistic Regression with WHO COVID-19 Severity Score and Outcomes of Venous Thromboembolism and Arterial Thrombosis

Variable	Venous Thromboembolism			Arterial Thrombosis		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Moderate disease (n = 10,180)	12.81	6.87–23.90	0.000	5.22	1.58–17.26	0.007
Severe disease (n = 2197)	28.69	15.04–54.71	0.000	13.59	3.92–47.15	0.000
Death (n = 2744)	16.07	8.34–30.96	0.000	20.34	6.11–67.67	0.000
SARS-CoV-2–positive	0.700	0.56–0.87	0.002	0.426	0.27–0.68	0.000

Other co-factors included in this regression analysis were hospital length of stay, age, sex, and cancer status; reference variable for severity score is ambulatory designation (n = 11,930).
CI = confidence interval; OR = odds ratio; WHO = World Health Organization.

bosis shortly after COVID-19 diagnosis. Third, this work provides justification for language that reassures noncritically ill COVID-19–positive patients that they have a low risk of clotting. This study is unique in that it examined a large sample of ED patients with varying degrees of illness during a period of 7 months in both COVID-19–positive and COVID-19–negative samples, allowing internal risk ratio estimations. Although several authors have reported a similar low risk of VTE after COVID-19 diagnosis, these findings are in contrast to most prior reports of increased VTE risk (2–6,8–10,13). Prior reports were retrospective studies of highly selected, small cohorts (2–6,13). The studies were early in the pandemic, possibly biased toward representing the severe spectrum of disease, and had short duration of follow-up, different geographic locations, and lack of reference to negative disease status.

The findings from the adjusted model suggest a multifactorial, canonical explanation for the development of clinically evident vascular thrombosis in COVID-19–positive patients. As could be expected from prior knowledge, the multivariable model in Table 2 showed that advanced age, cancer, and immobility (associated with intubation, need for intensive care, or longer hospital length of stay) increased risk of VTE, whereas COVID-19–positive status reduced risk (16,19,20). With the exception of cancer and length of stay, Table 3 shows the same pattern for AT, including COVID-19–positive status associated with significant risk reduction. These data provide a more comprehensive, quantitative assessment of vascular thrombosis risk in ambulatory COVID-19–positive patients (21). In our sample, only 15% of patients with COVID-19 required intensive care, compared with higher rates in prior reports (22). In a systematic review of four prospective studies, objectively confirmed DVT rates varied from 13% to 31% in the ICU (23). In one study, the rate of AT in all ICU patients approached 2% (24). The obvious confounding effect is that severe COVID-19 infection is associated with intensive care, which carries its own inherent risk of VTE from prolonged immobilization, indwelling central venous catheters, and hypoxemia (16,19,20,25). These studies, taken together with the present findings, suggest that critical illness alone is a primary determinant of vascular thrombosis in COVID-19–positive patients and, therefore, could inherently bias and inflate the prevalence of VTE and AT in COVID-19–

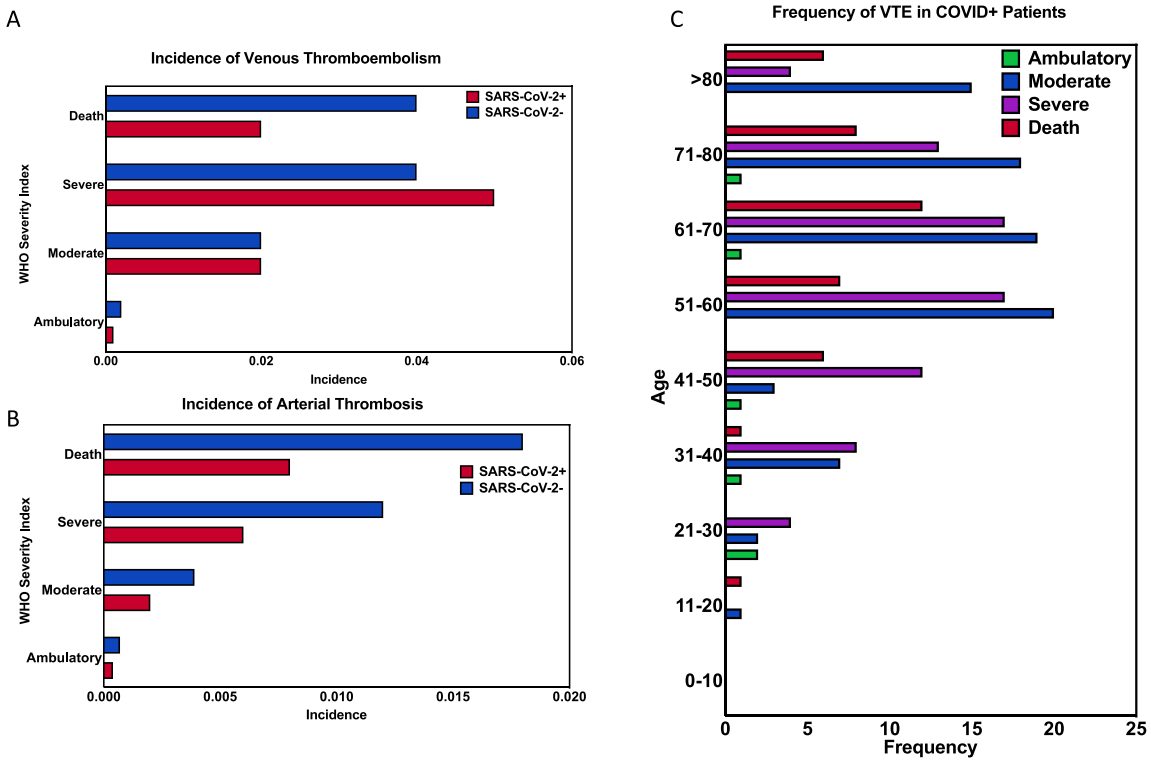

Figure 1. Frequencies and incidence of thrombosis. (A) Incidence of venous thromboembolism (VTE). Incidence of arterial thrombosis. (C) Frequency of VTE in COVID-19–positive patients. WHO = World Health Organization.

positive patients when no COVID-19–negative reference sample is included in analysis.

The finding of a significant negative association between SARS-CoV-2 status and development of vascular thrombosis on multivariable-adjusted analysis was not an expected finding and could reflect an unmeasured potential confounding variable. However, this possibility is low, inasmuch as the E-value analysis for both VTE and AT revealed E-values of 1.98 and 3.33, respectively (26,27). This would suggest that a variable with an association as large as 1.98 for VTE and 3.33 for AT would be required to explain away the negative associations identified in this study. Because most patients were ambulatory, the difference is probably not explained by antithrombotic treatment or surveillance bias. One explanatory hypothesis centers on the development of a specific adaptive host response to SARS-CoV-2. In the normal host response to viral-mediated sepsis, the coagulation cascade is activated to function as a host defense to limit the spread of virus. Many enveloped viruses in turn adapted to promote their own virulence by expressing host proteins that activate the coagulation cascade, such as tissue factor (TF). SARS-CoV-2 and Herpes simplex virus have both been demonstrated to express TF on their viral capsid to increase infectivity (28–30). Therefore, if the host response had previously adapted to prior non–SARS-CoV-2 infection, this partial immunity could limit the activation of coagulation cascades as a means to combat infectivity of SARS-CoV-2. Further study is required to understand the pathophysiology of SARS-CoV-2 infection.

The implication of high VTE incidence in COVID-19 infection in early studies (1,2,5,11) raised the question of whether the benefit of prophylactic anticoagulation outweighed the bleeding risk of anticoagulant therapy in critically ill patients. As a result, there was a call for clinical trials to evaluate the efficacy of prophylactic anticoagulation with patient outcomes in COVID-19 disease (2,4,31). In a retrospective cohort study of hospitalized patients, Cohen et al. found that the use of prophylactic-dose anticoagulation, but not treatment-dose anticoagulation, was associated with reduced VTE and mortality (8). These findings suggest that standard of care prophylaxis in hospitalized patients is enough to reduce incidence of VTE, even in a COVID-19–positive disease state. Ongoing randomized trials, ACTIV-4 and the COVID-19 Outpatient Thrombosis Prevention trial, will only truly be able to determine whether prophylactic anticoagulation is associated with improved patient outcomes.

Limitations

Our study design was limited to the data collected retrospectively by the RECOVER registry. The sample is geographically, racially, and ethnically diverse. The registry was restricted to ED patients who received SARS-CoV-2 diagnostic testing and we found the overall COVID-19 disease prevalence during the 7-month period of data collection to approximate 50%. All patients deemed COVID-19–negative had a negative result of at least one RT-PCR test on a nasopharyngeal swab on the day of ED visit, and no evidence of infection for the subsequent 30 days. Thus, asymptomatic patients with COVID-19 or patients who were given a clinical diagnosis and who appeared well and were therefore not tested and were discharged from the ED were not included. Therefore, our findings cannot be generalized to asymptomatic or untested patients. We did not adjust for hierarchical effect by hospital because proportional numbers of patients were enrolled from each site by protocol. Another limitation is the potentially limited diagnostic sensitivity of molecular testing, making it possible that some small number of patients may have been misclassified with respect to COVID-19 status (32). Furthermore, at least early in the pandemic, there was a selection bias due to limited testing capabilities. Molecular testing, however, is the most used and accurate test for disease status in reports and clinical care (32). The electronic surveillance used in this study only considered those patients who had presented again to the same hospital system or to a hospital system sharing the same electronic medical record (e.g., Epic Systems) of the parent hospital system and therefore may miss those patients who might have presented to another hospital system not encompassed by the parent electronic medical record or a rare outcome, such as death.

Conclusions

Results from a national sample found no evidence of increased risk of vascular thrombosis associated with COVID-19 in a large, heterogeneous sample of patients. Our study raises questions about the need for empirical anticoagulation in patients diagnosed with SARS-CoV-2 that a randomized clinical trial currently underway will be better suited to answer.

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ARTICLE SUMMARY

1. Why is this topic important?

Early pandemic data and literature have implicated an association of COVID-19 infection with increased risk of vascular thrombosis, for example, deep venous thrombosis, pulmonary embolism, stroke, and myocardial infarction. This has implications for possible prophylactic treatment to prevent the development of vascular thrombosis.

2. What does this study attempt to show?

This study attempts to identify whether SARS-CoV-2 test positivity is associated with increased risk of vascular thrombosis.

3. What are the key findings?

In contrast to the large body of literature, we found that COVID-19 illness alone is not associated with increased embolic risk. Consistent with the literature, age and critical illness in patients infected with SARS-CoV-2 are more associated with embolic risk.

4. How is patient care impacted?

This cohort study demonstrates that prophylactic anticoagulation is likely unnecessary for all patients infected with COVID-19, and should be limited to patients with classical risk factors, such as age and critical illness.