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Macrovascular Thrombotic Events in a Mayo Clinic Enterprise-Wide Sample of Hospitalized COVID-19–Positive Compared With COVID-19–Negative Patients

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Abstract

Objective: To determine the difference in the rate of thromboembolic complications between hospitalized coronavirus disease 2019 (COVID-19)–positive compared with COVID-19–negative patients.

Patients and Methods: Adult patients hospitalized from January 1, 2020, through May 8, 2020, who had COVID-19 testing by polymerase chain reaction assay were identified through electronic health records across multiple hospitals in the Mayo Clinic enterprise. Thrombotic outcomes (venous and arterial) were identified from the hospital problem list.

Results: We identified 3790 hospitalized patients with COVID-19 testing across 19 hospitals, 102 of whom had positive test results. The median age was lower in the COVID-positive patients (62 vs 67 years; $P=.03$). The median duration of hospitalization was longer in COVID-positive patients (8.5 vs 4 days; $P<.001$) and more required intensive care unit care (56.9% [58 of 102] vs 26.8% [987 of 3688]; $P<.001$). Comorbidities, including atrial fibrillation/flutter, heart failure, chronic kidney disease, and malignancy, were observed less frequently with COVID-positive admissions. Any venous thromboembolism was identified in 2.9% of COVID-positive patients (3 of 102) and 4.6% of COVID-negative patients (168 of 3688). The frequency of venous and arterial events was not different between the groups. The unadjusted odds ratio (OR) for COVID-positive–patients for any venous thromboembolism was 0.63 (95% CI, 0.19 to 2.02). A multivariable logistic regression model evaluated death within 30 days of hospital discharge; neither COVID positivity (adjusted OR, 1.12; 95% CI, 0.54 to 2.34) nor thromboembolism (adjusted OR, 0.90; 95% CI, 0.60 to 1.32) was associated with death.

Conclusion: Early experience in patients with COVID-19 across multiple academic and regional hospitals representing different US regions demonstrates a lower than previously reported incidence of thrombotic events. This incidence was not higher than a contemporary COVID-negative hospitalized comparator.

 ■ Mayo Clin Proc. 2021;96(7):1718-1726

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The coronavirus disease 2019 (COVID-19) pandemic continues to afflict a substantial proportion of the world's population. The rapid addition of literature on the thromboembolic complications associated with COVID-19 has enhanced the understanding of this disease's prothrombotic nature.[1,2] However, the rates of reported thromboembolic complications have varied from 4% to 69% in patients with COVID-19.[3,4] The wide range of complications, especially venous thromboembolism (VTE), has led to a debate about the need for aggressive thromboprophylaxis with moderate and higher intensity anticoagulation for patients hospitalized with

Mayo Clin Proc. ■ July 2021;96(7):1718-1726 ■ https://doi.org/10.1016/j.mayocp.2021.04.022
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COVID-19.[5,6] It should be noted that the study populations reporting high rates of thromboembolic complications have lacked an adequate control population, include heterogeneous settings (intensive care, ward, ambulatory), inconsistent thromboprophylaxis, and inconsistent event detection strategies (clinically driven vs mandatory), and have a heterogeneous group ranging from Asians, White, and Black patients. From recent literature, we know that ethnicity is an important contributor to intrinsic thrombogenicity, which can affect the frequency of thromboembolic outcomes observed within the study population.[7,8] In this study, we sought to determine the rate of thromboembolic complications among COVID-19—positive patients compared with those who were tested for COVID-19 but had negative results.

PATIENTS AND METHODS

Study Population

Adult (age ≥18 years) hospitalized patients with COVID-19 testing by polymerase chain reaction assay were identified through electronic health records across the Mayo Clinic enterprise from its inception on January 1, 2020, through May 8, 2020. The Mayo Clinic enterprise includes hospitals in Minnesota, Wisconsin, Arizona, and Florida, all operating under the same medical record system, policies, and procedures. Patients were included if COVID-19 testing was performed on admission or during hospitalization and the patient had a completed hospital admission (discharged or died). For patients with multiple hospitalizations during the study period, only the first hospital admission was included. Patients transferred between hospitals within the Mayo Clinic enterprise had the entire episode of care evaluated. Patients were excluded if lacking Minnesota research authorization.

Electronic Health Record Outcome Definitions. Patient characteristics were identified from clinically recorded data. The problem list (a list of physician-maintained diagnoses from discharge diagnoses) with a separate designation for hospital problems was used to identify comorbid conditions and thromboembolic outcomes. Venous and arterial macrovascular thrombotic outcomes were evaluated. Venous thromboembolism included diagnoses of pulmonary embolism (PE), upper and lower extremity deep venous thrombosis (DVT), portal and mesenteric vein thrombosis, and cerebral vein thrombosis. Arterial thrombotic events analyzed included myocardial infarction (ST or non-ST elevation), acute stroke or transient ischemic attack, systemic arterial thrombosis, renal infarction, or limb ischemia. Major and clinically relevant nonmajor bleeding was determined by medical record review as defined by the International Society on Thrombosis and Haemostasis.[9] As determined by the hospital problem list, bleeding events were not included based on the severity of bleeding by these definitions. Thromboembolic outcomes and anticoagulant type, dosing, and duration used in the hospital were also evaluated specifically in COVID-19—positive patients by physician medical record review.

Natural Language Processing Outcome Definitions. Additionally, DVT and PE were evaluated using natural language processing (NLP) from radiology reports occurring immediately before or during admission. All radiology reports of computed tomography (CT) scans that included the chest and used intravenous contrast medium and all venous duplex ultrasonograms of the upper or lower extremity were analyzed. Natural language processing algorithms to identify new/acute, or progressive PE and new/acute, or progressive DVT were created, tested, and applied to the text from the radiology report. A separate database of imaging reports (not this cohort) was initially used for algorithm development (PE and DVT). After initial testing, a reiterative approach to algorithm refinement was used, adding additional reports, with subsequent analyses enriched with positive cases as defined by the previous algorithm. This step was done to more equally review reports with positive findings since a large majority of reports were

TABLE 1. Characteristics and Comorbidities in 3790 COVID-19–Positive and COVID-19–Negative Hospitalized Patients[a,b]

Variable	COVID-19– positive (N=102)	COVID-19– negative (N=3688)	*P* value
Age (y)	62 (52-74)	67 (54-78)	.03
BMI (kg/m^2)	28.9 (24.7-35.7)	27.2 (23.4-32.5)	.005
Male	60 (58.8)	1907 (51.7)	.16
Race			<.001
White	71 (69.6)	3278 (88.9)	
Black	9 (8.8)	193 (5.2)	
Asian	7 (6.9)	56 (1.5)	
Other	5 (4.9)	30 (0.8)	
Unknown	10 (9.8)	131 (3.6)	
LOS (d)	8.5 (4.0-14.25)	4 (3-7)	<.001
ICU care	58 (56.9)	987 (26.8)	<.001
Hospital day of COVID test	1 (0-4)	0 (0-1)	<.001
Blood type	41 (40.2)	2184 (59.2)	.21
AB	2 (4.9)	84 (3.8)	
A	16 (39.0)	905 (41.4)	
B	1 (2.4)	267 (12.2)	
O	22 (53.7)	928 (42.5)	
Comorbidities			
History of VTE	3 (2.9)	127 (3.4)	.78
Atrial fibrillation/flutter	13 (12.7)	848 (23.0)	.02
Heart failure	14 (13.7)	968 (26.2)	.004
Atherosclerosis	12 (11.8)	956 (25.9)	.001
Hypertension	48 (47.1)	2188 (59.3)	.01
Diabetes mellitus	28 (27.4)	1080 (29.3)	.68
Malignancy	13 (12.7)	983 (26.6)	.002
Acute kidney injury	8 (7.8)	332 (9.0)	.69
Chronic kidney disease	14 (13.7)	952 (25.8)	.006
End-stage renal disease	3 (2.9)	153 (4.1)	.55
Asthma	9 (8.8)	312 (8.5)	.90
COPD	9 (8.8)	497 (13.5)	.17
Obstructive sleep apnea	10 (9.8)	422 (11.4)	.61
Hypothyroidism	17 (16.7)	639 (17.3)	.86
Cirrhosis	0	161 (4.4)	.03
Imaging studies (at least once during hospitalization)			
Any chest CT with contrast	27 (26.5)	763 (20.7)	.08
Upper extremity duplex US	4 (3.9)	54 (1.5)	.05
Lower extremity duplex US	21 (20.6)	481 (13.0)	.03

[a]BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CT, computed tomography; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; US, ultrasonography; VTE, venous thromboembolism.
[b]Data are presented as median (IQR) or No. (percentage) of patients.

negative. A physician reviewed radiology imaging reports from the testing database to make a determination of positive or negative for the finding as defined previously. For the DVT algorithm, 1752 lower extremity duplex ultrasonography reports were used in addition to 787 upper extremity duplex ultrasonography reports. The final NLP algorithm for DVT in the lower extremity reports had 98.2% sensitivity and 99.6% specificity

Mayo Clin Proc. ■ July 2021;96(7):1718-1726 ■ https://doi.org/10.1016/j.mayocp.2021.04.022
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TABLE 2. Thromboembolic Events, Bleeding, and Death in 3790 COVID-19–Positive and COVID-19–Negative Hospitalized Patients[a,b]

Variable	COVID-19–positive (N=102)	COVID-19–negative (N=3688)	*P* value
Hospital problem list outcomes			
Any VTE event	3 (2.9)	168 (4.6)	.43
PE	1 (1.0)	91 (2.5)	.34
LE-DVT	0 (0.0)	62 (1.7)	.19
UE-DVT	3 (2.9)	22 (0.6)	.004
Cerebral vein	0 (0.0)	6 (0.2)	.68
Atypical DVT	0 (0.0)	19 (0.5)	.47
Any VTE (ICU admissions)	2/58 (3.4)	71/987 (7.2)	.28
Myocardial infarction	2 (2.0)	91 (2.5)	.74
Arterial thrombosis	0 (0.0)	11 (0.3)	.58
Extremity ischemia	0 (0.0)	17 (0.5)	.49
Stroke	1 (1.0)	103 (2.8)	.27
Any thromboembolism	6 (5.9)	375 (10.2)	.16
Any bleeding	3 (2.9)	259 (7.0)	.11
Time from COVID-19 test to death (d)	6 (4.5-19.5)	13 (5.5-26.5)	.33
Death (inpatient)	6 (5.9)	107 (2.9)	.08
Death (30-d)	9 (8.8)	267 (7.2)	.54
Outcomes measured using MRR and NLP			
PE			
NLP—in-hospital PE	0 (0.0)	80 (2.2)	.13
MRR—in-hospital PE	0 (0.0)	NR	…
LE-DVT			
NLP—in-hospital LE-DVT	1 (1.0)	62 (1.7)	.59
MRR—in-hospital LE-DVT	1 (1.0)	NR	…
UE-DVT			
NLP—in-hospital UE-DVT	4 (3.9)	54 (1.5)	.05
MRR—in-hospital UE-DVT	5 (4.9)	NR	…
MRR			
Atypical DVT	1 (1.0)	NR	…
Myocardial infarction	2 (2.0)	NR	…
Stroke	1 (1.0)	NR	…
Any thromboembolism	10 (9.8)	NR	…
Major bleeding	5 (4.9)	NR	…
Any bleeding	7 (6.9)	NR	…

[a]COVID-19, coronavirus disease 2019; DVT, deep venous thrombosis; ellipses, data not available because medical record review and natural language processing algorithm were not performed in COVID-19–negative patients; ICU, intensive care unit; LE, lower extremity; MRR, medical record review (outcome); NLP, natural language processing algorithm (designated radiology text reports); NR, not reviewed; PE, pulmonary embolism; UE, upper extremity; VTE, venous thromboembolism.

[b]Data are presented as No. (percentage) of patients or median (interquartile range).

and for the upper extremity had 97.8% sensitivity and 99.2% specificity. The final NLP algorithm for PE correctly identified 325 of 327 reports with PE (as defined previously; sensitivity of 99.4%) and 672 of 673 reports without PE (specificity of 99.9%).

Statistical Analyses

Baseline demographic characteristics and clinical features were compared among patient groups: COVID-19–positive vs COVID-19–negative. Continuous variables were reported as median and interquartile ranges and were compared between groups using the Wilcoxon rank sum test. Categorical variables were reported as numbers and percentages and compared between groups using the χ^2 test for independence. The odds ratio (OR) of any VTE and any thromboembolic event (composite of arterial and venous thrombosis) was examined by logistic regression based on results from

COVID-19 testing. A multivariable logistic regression model with age, sex, body mass index, intensive care unit (ICU) admission, malignancy, diabetes mellitus, atrial fibrillation/flutter, cirrhosis, chronic kidney disease, atherosclerotic disease, hypertension, congestive heart failure, and cirrhosis was then used to examine the OR for any VTE and thromboembolism based on results from COVID-19 testing. Study data were collected and managed using REDCap (Research Electronic Data Capture), and data analysis was performed using SAS statistical software (SAS Institute). The Mayo Clinic Institutional Review Board approved the study.

RESULTS

A total of 3790 patients with hospital admission and COVID-19 testing were identified across 19 different hospitals, and 102 patients had positive test results. COVID-19–positive patients were initially identified in early March, with patients being identified in all states with Mayo Clinic sites (Arizona, Florida, Minnesota, and Wisconsin) by the end of March. The median age was lower in the COVID-positive patients (62 vs 67 years; P=.03; Table 1), and most patients were White. Comorbidities such as atrial fibrillation/flutter, heart failure, chronic kidney disease, and malignancy were all observed less frequently with COVID-positive admissions (Table 1). A history of VTE was present in 2.9% of COVID-19–positive (3 of 102) vs 3.4% of COVID-19–negative (127 of 3688) patients (P=.78). Among patients with a previously known and recorded ABO blood type, there was no significant difference between COVID-19–positive and COVID-19–negative patients (P=.21). The median length of hospitalization was longer in COVID-positive patients (8.5 vs 4 days; P<.001), and more required ICU care (56.9% [58 of 102] vs 26.8% [987 of 3688]; P<.001). COVID-19–positive patients were more likely to have upper extremity duplex ultrasonography (3.9% [4 of 102] vs 1.5% [54 of 3688]; P=.05) and lower extremity duplex ultrasonography (20.6% [21 of 102] vs 13.0% [481 of 3688]; P=.03), with a trend toward more CT scans of the chest (26.5% [27 of 102] vs 20.7% [763 of 3688]; P=.08).

Evaluation of Clinical Outcomes Using the Hospital Problem List

Using the hospital problem list to identify outcomes, there were no significant differences between COVID-19–positive and COVID-19–negative patients in the frequency of venous thrombosis, including any VTE event (2.9% [3 of 102] vs 4.6% [168 of 3688]), PE (1.0% [1 of 102] vs 2.5% [91 of 3688]), lower extremity DVT (0% [0 of 102] vs 1.7% [62 of 3688]), cerebral vein (0% [0 of 102] vs 0.2% [6 of 3688]), and atypical DVT (0% [0 of 102] vs 0.5% [19 of 3688]) (P>.05 for all; Table 2). Similarly, there were no significant differences in arterial thrombotic events, including myocardial infarction (2.0% [2 of 102] vs 2.5% [91 of 3688]) , arterial thrombosis (0% [0 of 102] vs 0.3% [11 of 3688]), extremity ischemia (0% [0 of 102] vs 0.5% [17 of 3688]), and stroke (1.0% [1 of 102] vs 2.8% [103 of 3688]) (P>.05 for all; Table 2). Additionally, there were no significant differences in any thromboembolism (5.9% [6 of 102] vs 10.2% [375 of 3688]) and any bleeding (2.9% [3 of 102] vs 7.0% [259 of 3688]) (P>.05 for all; Table 2) between the 2 groups. The unadjusted OR for COVID-positive patients for any VTE was 0.63 (95% CI, 0.19 to 2.02). In a multivariable logistic regression model adjusted for age, sex, body mass index, ICU admission, malignancy, diabetes mellitus, atrial fibrillation/flutter, cirrhosis, chronic kidney disease, atherosclerotic disease, hypertension, congestive heart failure, and cirrhosis, the adjusted OR (aOR) for any VTE for COVID-19–positive patients remained similar (aOR, 0.50; 95% CI, 0.16 to 1.63) and not statistically different (P > .05). Also, when COVID-19–positive patients were compared with COVID-19–negative patients, they did not have a higher OR for any thromboembolism (arterial or venous) (aOR, 0.46; 95% CI, 0.19 to 1.07). In a multivariable analysis evaluating death

Mayo Clin Proc. ■ July 2021;96(7):1718-1726 ■ https://doi.org/10.1016/j.mayocp.2021.04.022
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within 30 days of hospital discharge, neither COVID positivity (aOR, 1.12; 95% CI, 0.54 to 2.34) nor any thromboembolism (aOR, 0.82; 95% CI, 0.54 to 1.23) was associated with death.

Among the 102 COVID-positive patients, standard-dosing anticoagulant prophylaxis was initiated on admission in 82 (80.4%), 17 (16.7%) were taking therapeutic anticoagulants for a preexisting indication, and 3 (2.9%) did not receive anticoagulant prophylaxis.

Evaluation of Clinical Outcomes Using Manual Medical Record Review and NLP

When medical records were reviewed manually for the COVID-19—positive patients, there were minor discrepancies for thromboembolic and bleeding outcomes compared with the hospital problem list. No differences were noted between the medical record review and hospital problem list regarding acute stroke and myocardial infarction outcomes. Despite some minor differences, there were no changes in the aforementioned results (Table 2). Five major bleeding events occurred. All major bleeding occurred in patients receiving therapeutic anticoagulation. Of the 5 major bleeding events, 3 occurred in patients receiving therapeutic anticoagulation for diagnosis of upper extremity catheter-associated DVT. One bleeding event was associated with therapeutic anticoagulation for an incidentally identified right atrial thrombus. The other major bleeding event was related to anticoagulation in a patient receiving extracorporeal membrane oxygenation. Major bleeding occurred in the respiratory tract in 2 patients, in the gastrointestinal tract in 1, as a retroperitoneal hemorrhage in 1, and at other sites in 1. Nonmajor bleeding occurred in 2 patients, 1 who was receiving therapeutic anticoagulation and 1 who was not receiving anticoagulation.

When using NLP to measure outcomes from radiology reports, no significant differences were observed between the COVID-19—positive and COVID-19—negative groups (Table 2). Minor discrepancies were noted between the NLP algorithm interpretation of imaging studies and the medical record review outcomes. The discrepancies included one PE noted on the problem list that occurred at an outside hospital before the patient was transferred to our facility and therefore was not captured as an "in-hospital" event by the NLP imaging definition. Additionally, one upper extremity DVT was described as a chronic DVT on ultrasonography, yet due to the presence of an associated central catheter, the treatment team had decided to initiate anticoagulation and it was therefore considered to be an "acute DVT" on medical record review.

DISCUSSION

In this enterprise-wide sample of regional and tertiary care hospitals early in the COVID-19 pandemic, the clinically important findings in 3790 hospitalized patients included (1) no major difference in the rates of thromboembolic complications (both arterial and venous) among COVID-19—positive vs COVID-19—negative patients, (2) COVID-19 positivity or thromboembolic events were not found to be associated with death within 30 days of hospitalization on multivariable analysis, and (3) COVID-19—positive patients had longer median length of hospitalization and more often needed ICU care than COVID-19—negative patients.

The findings of longer median length of hospitalization and need for ICU care among COVID-19—positive patients are in concordance with those of other studies that report an increased length of hospital stay and the probability of ICU admission in COVID-19—positive patients.[10,11] The length of stay depends on multiple factors, including varying levels of severity of COVID-19 presentation, associated comorbidity burden, and mortality. These findings are important because the longer duration of hospital stays and ICU utilization among COVID-19—positive patients should be accounted for while predicting and managing hospital surge as the number of hospitalizations for COVID-19 continues to rise.

There have been multiple reports documenting high rates of thromboembolic

complications in COVID-19—positive patients.[4,12,13] The variability in the rate of thromboembolic events noted in multiple studies has led to considerable debate regarding the aggressiveness of the thromboprophylactic regimens among hospitalized COVID-19—positive patients.[5,6] However, most studies that report a high rate of thromboembolic complications are in hospitalized patients in the intensive care setting. In our study, the rate of thromboembolic complications in COVID-19—positive patients was 2.9%, which was not substantially different from that of the COVID-19—negative hospitalized patients. The rate of VTE in the overall population is consistent with the preliminary results from an ongoing prospective registry (CORE-19), in which thromboembolic complications were noted to be 3.51%.[14]

It should be noted that the high-risk factors such as age, body mass index, and comorbidity burden among the COVID-19—positive group in the current study was lower (including atrial fibrillation/flutter, heart failure, atherosclerosis, hypertension, chronic kidney disease, cirrhosis, and malignancy), compared to the population included in other studies on VTE among COVID-19 positive patients. Additionally, although there were notable differences in the racial distribution of patients between the COVID-19—positive and COVID-19—negative populations, overall the majority of patients were White (88.4% [3349 of 3790 patients]). There have been reports about racial differences in thromboembolic complications and clinical outcomes in COVID-19—positive patients. White patients have been reported to be at lower risk of poor outcomes than Black or Hispanic patients.[7,8] It is possible that the lower rate of thromboembolic complications in our study was due to the inclusion of a predominantly White population. Our findings reinforce the need for individualized thromboprophylactic regimens for patients admitted to hospitals with COVID-19. Compared with the traditionally used risk assessment models (eg, the Padua Prediction Score), which do not address the increased risk of thromboembolism in the setting of COVID-19, 2 possible approaches of personalizing thromboprophylactic regimens could include (1) assessment of intrinsic thrombogenicity using viscoelastic methods of clot formation[15] and (2) using factor Xa levels to guide the intensity of thromboprophylactic regimens.[16]

Our study has both strengths and limitations. The combined methodologies to identify outcomes within the COVID-19—positive and COVID-19—negative groups makes it extremely unlikely that thromboembolic outcome definitions were substantially underrepresented or overrepresented. Furthermore, the electronic definitions, even with a finite error rate, help eliminate assessment bias. Increased imaging within the COVID-19—positive cohort would be anticipated, with a larger number requiring ICU care. If anything, this finding would bias the results toward a higher thromboembolic rate due to the potential to identify incidental thrombotic events. Including all CT scans of the chest that used contrast medium in the NLP algorithm to identify PE also helps account for the potential incidental PEs identified. Another strength of this analysis is the study design and inclusion of only patients undergoing COVID-19 testing during associated hospital admission. This factor helps to create similar cohorts for comparison because patients testing positive for COVID-19 as an outpatient who are struggling with the illness for days or weeks preceding the hospitalization may be likely to have a higher baseline thrombotic risk than patients presenting more acutely due to the preceding inflammatory state and immobility. Also, selecting a control population that also had testing and was known to have negative results helps reduce unmeasured confounding between the groups and provides the most accurate control population. Some patients with COVID-19 might have been unrecognized early in the pandemic. Another possible source of bias in other studies from large academic medical centers is referral bias.

Mayo Clin Proc. ■ July 2021;96(7):1718-1726 ■ https://doi.org/10.1016/j.mayocp.2021.04.022
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Although this cohort did include patients from tertiary referral centers, it also included numerous smaller regional hospitals that likely better reflect the population as a whole.

Despite attempts to create more similar patient cohorts for comparison, we did see substantial differences in underlying comorbidities between the groups. As expected, patients who required hospitalization in the absence of COVID-19—positive testing had a higher degree of comorbid disease, which could not be fully adjusted for in multivariable analyses due to the sample size and low event rate. However, when considering whether anticoagulation should be used at higher than prophylactic doses, assessing these event rates in an unadjusted comparison can be helpful. Another important consideration in the data presented is that no formal or enterprise-wide algorithm was in place during the study period for either anticoagulation management or serial assessment for thromboembolic events. This factor helps reduce bias that may have occurred in other observational studies from increased testing and screening of COVID-19—positive patients. Additionally, the readmission group was excluded by the design of the current study, and therefore, we may have missed quite a few VTEs in COVID-19—positive patients that occurred at a later stage of the disease; future studies should investigate VTE events more broadly.

CONCLUSION

Early experience with COVID-19—positive patients across multiple academic and regional hospitals representing different regions of the United States demonstrated a lower than previously reported incidence of thrombotic events in a high-risk cohort, which was not considerably higher than that of COVID-19—negative hospitalized patients. Although some COVID-19—positive patients may be at very high risk for thromboembolism, further risk classification strategies are needed to better identify these patients. Our data do not support a more aggressive anticoagulation regimen for all hospitalized patients with COVID-19. We recommend a more conservative/cautious approach until clinical trials demonstrate the benefit of higher-intensity anticoagulation regimens.

ACKNOWLEDGMENTS

The content of this work is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

All the authors were involved in the conception and design of the study or analysis and interpretation of the data and drafting of the manuscript or revising it critically and have read and approved the final submitted manuscript.

Abbreviations and Acronyms: **aOR** = adjusted odds ratio; **COVID-19** = coronavirus disease 2019; **CT** = computed tomography; **DVT** = deep venous thrombosis; **ICU** = intensive care unit; **NLP** = natural language processing; **OR** = odds ratio; **PE** = pulmonary embolism; **VTE** = venous thromboembolism

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Grant Support: This work was supported by the Mayo Clinic Center for Clinical and Translational Science through grant UL1TR002377 from the National Center for Advancing Translational Sciences.

Potential Competing Interests: Dr Sridharan is a member of an advisory group for Alexion Pharmaceuticals, Inc. The other authors report no conflicts of interest.

Data Previously Presented: These data were presented in part at the 2020 International Society on Thrombosis and Haemostasis Virtual Congress.

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