JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 76, NO. 18, 2020
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Registry of Arterial and Venous Thromboembolic Complications in Patients With COVID-19

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ABSTRACT

BACKGROUND Cardiovascular complications, including myocardial infarction, ischemic stroke, and pulmonary embolism, represent an important source of adverse outcomes in coronavirus disease-2019 (COVID-19).

OBJECTIVES To assess the frequency of arterial and venous thromboembolic disease, risk factors, prevention and management patterns, and outcomes in patients with COVID-19, the authors designed a multicenter, observational cohort study.

METHODS We analyzed a retrospective cohort of 1,114 patients with COVID-19 diagnosed through our Mass General Brigham integrated health network. The total cohort was analyzed by site of care: intensive care (n = 170); hospitalized nonintensive care (n = 229); and outpatient (n = 715). The primary study outcome was a composite of adjudicated major arterial or venous thromboembolism.

RESULTS Patients with COVID-19 were 22.3% Hispanic/Latinx and 44.2% non-White. Cardiovascular risk factors of hypertension (35.8%), hyperlipidemia (28.6%), and diabetes (18.0%) were common. Prophylactic anticoagulation was prescribed in 89.4% of patients with COVID-19 in the intensive care cohort and 84.7% of those in the hospitalized nonintensive care setting. Frequencies of major arterial or venous thromboembolism, major cardiovascular adverse events, and symptomatic venous thromboembolism were highest in the intensive care cohort (35.3%, 45.9%, and 27.0 %, respectively) followed by the hospitalized nonintensive care cohort (2.6%, 6.1%, and 2.2%, respectively) and the outpatient cohort (0% for all).

CONCLUSIONS Major arterial or venous thromboembolism, major adverse cardiovascular events, and symptomatic venous thromboembolism occurred with high frequency in patients with COVID-19, especially in the intensive care setting, despite a high utilization rate of thromboprophylaxis. (J Am Coll Cardiol 2020;76:2060–72) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

Manuscript received June 3, 2020; revised manuscript received August 26, 2020, accepted August 29, 2020.

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2020.08.070

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2, has emerged as a devastating global public health crisis. Whereas the morbidity and mortality associated with COVID-19 are usually attributed to acute respiratory distress syndrome (ARDS) and end-organ failure, cardiovascular complications, including myocardial infarction (MI), ischemic stroke, and pulmonary embolism (PE), also cause disability and death in these patients (1–3). An increased frequency of arterial and venous thrombosis was observed early in the COVID-19 pandemic and has been attributed to systemic inflammation, immobility, and a prothrombotic milieu (4,5). Venous thromboembolism (VTE) is now recognized as among the predominant cardiovascular hazards in patients with COVID-19 (4,6–10). The frequency of VTE is highest in the intensive care unit (ICU) setting and has ranged from 25%, when symptomatic disease is considered, to 69%, when surveillance venous ultrasonography is performed (4,6–8). A high prevalence of in situ microthrombosis suspected to be due to endothelial injury from direct viral infection has also been described (11–13). Quantifying the risk of cardiovascular complications in the heterogeneous population of patients with COVID-19 has been hampered by reports of limited sample size, restriction of assessments to the ICU setting, variable outcome definitions, and differing thromboprophylaxis patterns. Antithrombotic therapy has been recommended for hospitalized patients with COVID-19 to prevent thromboembolic cardiovascular events (1,14–16); however, a subset of patients appears to experience arterial and venous events despite standard thromboprophylaxis.

To assess frequency of arterial and venous thromboembolic disease, risk factors, prevention and management patterns, and outcomes in patients with COVID-19, we undertook an investigator-initiated, electronic health record (EHR)-guided multicenter observational cohort study (CORONA-VTE [COVID-19 Registry to Assess Frequency, Risk Factors, Management, and Outcomes of Arterial and Venous Thromboembolic Complications]).

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METHODS

STUDY DESIGN. The study was a retrospective observational cohort analysis using data abstracted through the EHR within the Mass General Brigham integrated health network. Mass General Brigham includes the Massachusetts General Hospital, Brigham and Women's Hospital, 10 regional hospitals, and several outpatient centers. A silent computerized decision support program was embedded as a Best Practice Advisory within the EHR (EPIC, version 2015; Epic Systems Corporation, Verona, Wisconsin) to identify eligible patients. The computerized decision support identified patients with a laboratory-confirmed diagnosis of COVID-19. The program was "silent" because it provided no notification to the clinician regarding its presence or findings. The Mass General Brigham Medical Informatics team designed the program. We confirmed 100% accuracy of the program by reviewing the records of every patient in the registry. No action was required by the provider of record. The study was approved by the Institutional Review Board of Mass General Brigham. The Institutional Review Board waived the requirement of informed consent.

ABBREVIATIONS AND ACRONYMS

ARDS = acute respiratory distress syndrome
CI = confidence interval
COVID-19 = coronavirus disease-2019
DVT = deep vein thrombosis
EHR = electronic health record
ICU = intensive care unit
MI = myocardial infarction
OR = odds ratio
PCR = polymerase chain reaction
PE = pulmonary embolism
TIA = transient ischemic attack
VTE = venous thromboembolism

STUDY POPULATION. From March 13, 2020, to April 3, 2020, our computerized decision support program identified 1,114 consecutive patients 18 years or older and who tested positive for severe acute respiratory syndrome-coronavirus-2 infection based on polymerase chain reaction (PCR) testing (sensitivity 73.3%, specificity 98.6%, false positive rate from 1% to 1.5%) (17). All hospitalized patients were admitted for COVID-19-related respiratory symptoms, including COVID-19 pneumonia or ARDS. Patients admitted to the critical care setting required mechanical ventilation, hemodynamic support, or increased monitoring.

DATA COLLECTION. Data were gathered electronically through the EPIC Best Practice Advisory and manually entered by trained, experienced research assistants (J.E.S., S.R., M.B.P.), a research nurse (R.B.M.), and a physician (O.L.) and managed using the Research Electronic Data Capture, or REDCap tool hosted at Brigham and Women's Hospital (18). Patient demographics and baseline clinical characteristics were recorded, including age, sex, race, ethnicity, and comorbid conditions. Data were collected regarding underlying cardiovascular disease and risk factors, COVID-19 presentation and diagnosis, laboratory testing, disease-specific management, concomitant medications, thromboprophylaxis, and 30-day outcomes. Whereas no COVID-19-specific guidelines for thromboembolism prevention were in place within our system at the time of this study, guidance for thromboprophylaxis in hospitalized patients was available through a VTE guidebook accessible through the network intranet.

TABLE 1 Baseline Characteristics and Comorbid Conditions in Patients With COVID-19 by Care Setting

	Intensive Care (n = 170)	Admitted, Nonintensive Care (n = 229)	Outpatient (n = 715)	Total (N = 1,114)
Age, yrs	61.7 ± 15.8	60.6 ± 18.0	44.8 ± 16.2	50.6 ± 18.3
Female	64 (37.7)	106 (46.3)	433 (60.6)	603 (54.1)
Hispanic/Latinx	52 (30.6)	63 (27.5)	133 (18.6)	248 (22.3)
Race				
White	86 (50.6)	128 (55.9)	407 (56.9)	621 (55.8)
Black	17 (10.0)	27 (11.8)	113 (15.8)	157 (14.1)
Asian	6 (3.5)	9 (3.9)	23 (3.2)	38 (3.4)
Other	61 (35.9)	65 (28.3)	172 (24.1)	298 (26.8)
BMI, kg/m^2	30.3 ± 5.7	30.1 ± 6.9	29.6 ± 11.8	29.8 ± 10.1
Active cancer	11 (6.5)	15 (6.6)	14 (2.0)	40 (3.6)
Serum creatinine >2.5 mg/dl	10 (5.9)	7 (3.1)	4 (0.6)	21 (1.9)
Hemodialysis	7 (70.0)	6 (85.7)	1 (25.0)	14 (66.7)
Smoking				
Current	9 (5.3)	12 (5.2)	29 (4.1)	50 (4.5)
Former	59 (34.7)	82 (35.8)	104 (14.6)	245 (22.0)
Never	93 (54.7)	131 (57.2)	511 (71.5)	735 (66.0)
Chronic lung disease	35 (20.6)	61 (26.6)	111 (15.6)	207 (18.6)
Baseline medications				
Statin	127 (74.7)	146 (63.8)	91 (12.7)	364 (32.7)
Aspirin	67 (39.4)	56 (24.5)	38 (5.3)	161 (14.5)
81 mg	61 (91.0)	53 (95.0)	34 (89.5)	148 (91.9)
325 mg	5 (7.5)	2 (3.6)	3 (7.9)	10 (6.2)
Immunosuppressive	21 (12.4)	26 (11.4)	44 (6.2)	91 (8.2)
$P2Y_{12}$ inhibitor	6 (3.5)	8 (3.5)	5 (0.7)	19 (1.7)
Dual antiplatelet	6 (3.5)	6 (2.6)	4 (0.6)	16 (1.4)
Therapeutic anticoagulation	43 (25.3)	21 (9.2)	16 (2.3)	80 (7.2)
Unfractionated heparin	21 (48.8)	1 (4.8)	1 (6.3)	23 (28.8)
Enoxaparin	7 (16.3)	2 (9.5)	0 (0.0)	9 (11.3)
Warfarin	6 (14.0)	7 (33.3)	8 (50.0)	21 (26.3)
Apixaban	7 (16.3)	7 33.3)	3 (18.8)	17 (21.3)
Rivaroxaban	2 (4.7)	3 (14.3)	4 (25.0)	9 (11.3)
Thromboprophylaxis	152 (89.4)	194 (84.7)	1 (0.1)	347 (31.2)
LMWH	109 (71.7)	159 (69.4)	1 (100.0)	269 (77.5)
Unfractionated heparin	46 (30.3)	34 (14.9)	0 (0.0)	80 (23.1)
Rivaroxaban	2 (1.3)	0 (0.0)	0 (0.0)	2 (0.6)

Values are mean ± SD or n (%).
BMI = body mass index; COVID-19 = coronavirus disease-2019; LMWH = low-molecular weight heparin.

The study population was analyzed as a total cohort (n = 1,114). Additionally, stratified analysis was performed based on site of care: ICU (n = 170); non-ICU hospitalized (n = 229); and nonhospitalized patients (n = 715). ICU patients were defined as those who were admitted to a critical care setting at any point following diagnosis of COVID-19. Therefore, the 3 cohorts were mutually exclusive.

Thirty-day clinical outcomes of symptomatic VTE, catheter- or device-related arterial thrombosis, MI, non-MI-related coronary revascularization, ischemic stroke, transient ischemic attack (TIA), or systemic embolism; major adverse limb events; heart failure hospitalization; new atrial fibrillation; and myocarditis, including diagnosis and treatments, were extracted from the EHR. Additional outcomes of interest included 30-day all-cause mortality, major and clinically relevant nonmajor bleeding, disseminated intravascular coagulation, and thrombocytopenia. Only the first occurrence of a particular 30-day outcome was counted.

Standardized outcome definitions were adopted and used for outcome adjudication (Supplemental Appendix). Exhaustive EHR review was conducted for each subject, including review of discharge summaries, office notes, diagnostic testing reports, medical treatment summaries, and procedure reports, regardless of the facility or office location. Follow-up data for 30-day outcomes were obtained for 96% of the study cohort. Follow-up was unavailable in 40 outpatients and 5 hospitalized non-ICU patients and 1 ICU patient who all survived to hospital discharge.

Symptomatic VTE was defined as symptomatic deep vein thrombosis (DVT) (including symptomatic catheter- or device-related DVT) or PE, confirmed by imaging, within 30 days of enrollment. No systematic screening protocol for VTE in patients with COVID-19 was in place during the study. Acute ischemic stroke was defined as a new, focal neurologic deficit of sudden onset, lasting ≥24 h, not due to a readily identifiable nonvascular cause (e.g., brain tumor, trauma), as confirmed by a neurologist, imaging, or autopsy. TIA was defined as a transient episode of neurologic dysfunction lasting <24 h and caused by suspected focal cerebral, spinal cord, or retinal ischemia without evidence of acute infarction and confirmed by a neurologist. Systemic embolism was defined as sudden loss of perfusion of a limb or extracranial organ. Acute MI was defined as the detection of a rise and/or fall of cardiac biomarkers (cardiac troponin T), with at least 1 value >99th percentile upper reference limit and with at least 1 of the following: 1) symptoms of myocardial ischemia; 2) new (or presumably new) significant ST-segment/T-wave changes or left bundle branch block; 3) development of pathological Q waves; 4) new loss of viable myocardium or regional wall motion abnormality by imaging; or 5) identification of intracoronary thrombus by angiography or autopsy (19). Heart failure hospitalization was defined as symptoms and signs of heart failure with institution or adjustment of treatment and associated hospitalization or extension of length of stay. Heart failure with preserved ejection fraction and heart failure with reduced ejection fraction were included. Major adverse limb events included acute limb ischemia or critical limb threatening ischemia. Catheter- or device-related arterial thrombosis, in situ arterial thrombosis, and systemic

arterial embolism were considered separately. Catheter- or device-related arterial thrombosis was not classified as a major adverse limb event.

Bleeding events were classified by the International Society of Thrombosis and Haemostasis criteria for major and clinically relevant nonmajor bleeding (20). All-cause mortality was determined by review of the EHR. Causes of death were categorized as due to PE, MI, stroke, sudden cardiac death or arrhythmia, other cardiovascular disease, infection, cancer, or other condition.

All study outcomes were adjudicated by a dedicated, independent Clinical Endpoint Committee (U.C., Z.A., and V.N.) composed of 3 cardiovascular medicine specialists (Supplemental Appendix).

STATISTICAL ANALYSIS. The primary statistical analysis was the frequency of adjudicated, objectively confirmed major arterial and venous thromboembolic events at 30 days in patients with COVID-19. Major arterial and venous thromboembolic events comprised a composite of symptomatic VTE, catheter- or device-related arterial thrombosis, MI, non-MI-related coronary revascularization, stroke, TIA, or systemic embolism, and major adverse limb events at 30 days. The composite outcome of major adverse cardiovascular events included symptomatic VTE, catheter- or device-related arterial thrombosis, MI, non-MI-related coronary revascularization, stroke, TIA, or systemic embolism; major adverse limb events; heart failure hospitalization; new diagnosis of atrial fibrillation; and myocarditis. Secondary analyses included frequencies of adjudicated all-cause death, major and clinically relevant nonmajor bleeding, disseminated intravascular coagulation, thrombocytopenia, individual thromboembolic outcomes, and other cardiovascular events at 30 days. Means, medians, and frequency distributions were calculated for continuous variables. Number and percentages were reported for binary and categorical variables. Kaplan-Meier plots were presented for the time from COVID-19 PCR diagnosis to each of the 3 major composite outcomes for the inpatient groups. Cumulative incidence estimates and 95% confidence intervals (CIs) accounted for death as a competing risk for symptomatic VTE, major arterial and venous thromboembolism and noncardiovascular death for the major cardiovascular events outcome (21).

We utilized multivariable logistic regression modeling to identify groups of factors that may identify ICU patients with COVID-19 at greatest risk for major adverse outcomes. Variables included in the regression model were selected based on the univariable results and on a priori knowledge. They included age, sex, history of coronary artery disease, prescription of prophylactic anticoagulation, ARDS, and baseline D-dimer level by decile. A bias correction for rare events was used in regressions involving ARDS and symptomatic VTE (22). All analyses were performed using STATA version 15 (STATA Corporation, College Station, Texas) and SAS version 9 (SAS Institute Inc., Cary, North Carolina).

TABLE 2 Baseline Cardiovascular Disease and Risk Factors in Patients With COVID-19 by Care Setting

	Intensive Care (n = 170)	Admitted, Nonintensive Care (n = 229)	Outpatient (n = 715)	Total (N = 1,114)
Coronary artery disease	29 (17.1)	39 (17.0)	22 (3.1)	90 (8.1)
MI	9 (5.3)	18 (17.9)	8 (1.1)	35 (38.9)
Prior PCI	7 (4.1)	16 (7.0)	7 (1.0)	30 (33.3)
Stable angina	4 (2.4)	5 (2.2)	5 (0.7)	14 (15.5)
Prior CABG	4 (2.4)	6 (2.6)	1 (0.1)	11 (12.2)
Unstable angina	0 (0.0)	1 (0.4)	1 (0.1)	2 (2.2)
Cardiomyopathy	5 (2.9)	10 (4.4)	6 (0.8)	21 (1.9)
LVEF, %	40.2 ± 15.6	49.1 ± 16.2	38.5 ± 12.5	44.0 ± 15.2
HFrEF	4 (2.4)	12 (5.2)	3 (0.4)	19 (1.7)
HFpEF	8 (4.7)	15 (6.6)	6 (0.8)	29 (2.6)
Prior atrial fibrillation	16 (9.4)	21 (9.2)	15 (2.1)	52 (4.7)
Prior stroke/TIA	11 (6.5)	16 (7.0)	14 (2.0)	41 (3.7)
Hypertension	95 (55.9)	129 (56.3)	175 (24.5)	399 (35.8)
Hyperlipidemia	73 (42.9)	97 (42.4)	149 (20.8)	319 (28.6)
Diabetes	66 (38.8)	68 (29.7)	67 (9.4)	201 (18.0)
Prior VTE	9 (5.3)	10 (4.4)	19 (2.7)	38 (3.4)

Values are n (%) or mean ± SD.

CABG = coronary artery bypass grafting; COVID-19 = coronavirus disease-2019; HFpEF = heart failure preserved ejection fraction; HFrEF = heart failure reduced ejection fraction; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; VTE = venous thromboembolism.

RESULTS

OVERALL COVID-19 COHORT. The overall study cohort of 1,114 patients diagnosed with COVID-19 had a mean age of 50.6 years and mean body mass index of 29.8 kg/m^2 (Table 1). Women accounted for 54% of the overall study cohort. Patients with COVID-19 were 22.3% Hispanic/Latinx and 44.2% non-White. Cardiovascular risk factors of hypertension (35.8%), hyperlipidemia (28.6%), and diabetes (18.0%) were common (Table 2). The most common symptoms of COVID-19 were cough (74.0%), fever (70.7%), and myalgias (51.1%) (Table 3). COVID-19-associated pneumonia was the most common complication (37.8%).

At 30 days from diagnosis, major arterial or VTE events, major adverse cardiovascular events, and symptomatic VTE occurred in 5.9%, 8.3%, and 4.6%, respectively (Table 4, Figure 1). All-cause 30-day mortality was 5.7% in the overall cohort of patients with COVID-19. The most frequent cause of death was

TABLE 3 Characteristics of COVID-19 and Treatment by Care Setting

	Intensive Care (n = 170)	Admitted, Nonintensive Care (n = 229)	Outpatient (n = 715)	Total (N = 1,114)
Symptoms				
Cough	124 (72.9)	184 (80.4)	516 (72.2)	824 (74.0)
Fever/chills	138 (81.2)	189 (82.5)	460 (64.3)	781 (70.7)
Myalgias	71 (41.8)	107 (46.7)	391 (54.7)	569 (51.1)
Shortness of breath	133 (78.2)	137 (59.8)	228 (31.9)	498 (44.7)
Sore throat	33 (19.4)	46 (20.1)	261 (36.5)	340 (30.5)
Malaise/fatigue	81 (47.7)	104 (45.4)	145 (20.3)	330 (29.6)
Gastrointestinal	62 (36.5)	90 (39.3)	137 (19.2)	289 (25.9)
Coryza	19 (11.2)	34 (14.9)	232 (32.5)	285 (25.6)
Headache	28 (16.5)	44 (19.2)	126 (17.6)	198 (17.8)
Loss of smell/taste	12 (7.1)	21 (9.2)	163 (22.8)	196 (17.6)
Chest pain	16 (9.4)	42 (18.3)	48 (6.7)	106 (9.5)
Length of hospital stay, days	16 (8-24)	5 (3-8)	–	–
Still hospitalized by 30 days	49 (28.8)	4 (1.8)	–	–
COVID-19 pneumonia	164 (96.5)	189 (82.5)	68 (9.5)	421 (37.8)
ARDS	134 (78.8)	13 (5.7)	1 (0.1)*	148 (13.3)
Mechanical ventilation	128 (75.3)	1 (0.4)†	–	129 (11.6)
Multisystem organ failure	56 (32.9)	9 (3.9)	0 (0.0)	65 (5.8)
Sepsis/septic shock	97 (57.1)	8 (3.5)	0 (0.0)	105 (9.4)
Systemic arterial hypotension	133 (78.2)	37 (16.2)	1 (0.1)‡	171 (15.3)
Laboratory assessment§	170 (100.0)	228 (99.6)	108 (15.1)	506 (45.4)
LDH, U/l	404.2 ± 226.4	315.7 ± 183.2	234.7 ± 97.1	343.4 ± 202.9
Lactate, mmol/l	1.7 ± 1.1	1.4 ± 0.7	1.3 ± 0.6	1.6 ± 0.9
NT-proBNP, pg/ml	2,124.1 ± 7,937.8	1,613.4 ± 7,492.1	343.4 ± 983.2	1,788 ± 7,473.9
High-sensitivity troponin T, ng/l	69.0 ± 305.4	24.3 ± 71.1	10.4 ± 15.3	40.5 ± 199.6
D-dimer, ng/ml	2,515.6 ± 7,913.3	1,156.5 ± 1,410.2	757.4 ± 994.7	1,692.3 ± 5,254.5
High-sensitivity CRP, mg/l	120.3 ± 83.6	72.7 ± 56.7	–	97.0 ± 75.8
High-sensitivity IL-6, pg/ml	327.4 ± 648.8	29.2 ± 24.3	–	208.1 ± 507.7
COVID-19 specific therapies				
Azithromycin	149 (87.7)	151 (65.9)	51 (7.1)	351 (31.5)
Hydroxychloroquine	148 (87.1)	131 (57.2)	7 (1.0)	286 (25.7)
Remdesivir	27 (15.9)	24 (10.5)	0 (0.0)	51 (4.6)
IL-6 receptor antagonist	22 (12.9)	4 (1.8)	0 (0.0)	26 (2.3)
Lopinavir/ritonavir	13 (7.7)	5 (2.2)	0 (0.0)	18 (1.6)

Values are n (%), median (interquartile range), or mean ± SD. Dashes indicate data were not available. *Patient was a resident at an assisted living facility and was diagnosed with COVID-19 as an outpatient. When she developed ARDS, she was transitioned to palliative care without hospitalization. †Patient experienced acute respiratory failure while hospitalized in the non-intensive care setting, was initiated on mechanical ventilation, but was ultimately transitioned to comfort measures. ‡Patient presented to the emergency department with hypotension that resolved with intravenous fluid. §Laboratory reference values: LDH = 110 to 210 U/l; lactate = 0.5 to 2.0 mmol/l; NT-proBNP = 0 to 1,800 pg/ml; high-sensitivity cardiac troponin T = 0 to 9 ng/l; D-dimer < 500 ng/ml; high-sensitivity CRP = 0 to 3 mg/l; high-sensitivity IL-6 < 5.00 pg/ml.

ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease-2019; CRP = C-reactive protein; IL = interleukin; LDH = lactate dehydrogenase; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

sepsis (89.5%) followed by cardiovascular disease (7%).

ICU PATIENTS WITH COVID-19. The cohort of 170 patients with COVID-19 admitted at any point to an ICU had a mean age of 61.7 years, was predominantly male (62.3%), and was obese (mean body mass index 30.3 kg/m^2) (Table 1). Fifty percent of ICU patients with COVID-19 were non-White and 30.6% were Hispanic/Latinx. A history of coronary artery disease (17.1%) and cardiovascular risk factors of hypertension (55.9%), hyperlipidemia (42.9%), and diabetes (38.8%) were particularly common in the ICU cohort (Table 2). Statins, aspirin, and antithrombotic therapy were prescribed at baseline in 74.7%, 32.9%, and 25.3% of patients with COVID-19 in the ICU cohort, respectively. Prophylactic anticoagulation was prescribed in 89.4% of patients with COVID-19 in the ICU cohort. No patients who survived to hospital discharge were prescribed post-discharge thromboprophylaxis for primary prevention.

Fever (81.2%), cough (72.9%), and shortness of breath (78.2%) were the most frequent symptoms of COVID-19 in patients in the ICU cohort (Table 3). Patients with COVID-19 in the ICU cohort had a median length of hospital stay of 16 days and were still

TABLE 4 30-Day Cardiovascular Outcomes of COVID-19 by Care Setting

	Intensive Care (n = 170)	Admitted, Nonintensive Care (n = 229)	Outpatient (n = 715)	Total (N = 1,114)
Major arterial or venous thromboembolic event	60 (35.3)	6 (2.6)	0 (0.0)	66 (5.9)
Major cardiovascular events	78 (45.9)	14 (6.1)	0 (0.0)	92 (8.3)
Symptomatic VTE	46 (27.0)	5 (2.2)	0 (0.0)	51 (4.6)
Symptomatic DVT*	39 (22.9)	0 (0.0)	0 (0.0)	39 (3.5)
Upper extremity	6 (12.5)	–	–	6 (12.5)
Proximal lower extremity	4 (8.3)	–	–	4 (8.3)
Isolated calf	3 (6.3)	–	–	3 (6.3)
Catheter-/device-related	30 (76.9)	–	–	30 (76.9)
Symptomatic PE	3 (1.8)	5 (2.2)	0 (0.0)	8 (0.7)
High-risk	2 (66.7)	1 (20.0)	–	3 (37.5)
Intermediate-high-risk	0 (0.0)	1 (20.0)	–	1 (12.5)
Intermediate-low-risk	0 (0.0)	1 (20.0)	–	1 (12.5)
Low-risk	1 (33.3)	2 (40.0)	–	3 (37.5)
Catheter-/device-related arterial thrombosis	11 (6.5)	0 (0.0)	0 (0.0)	11 (1.0)
Disseminated intravascular coagulation	10 (5.9)	4 (1.7)	0 (0.0)	14 (1.3)
Death	40 (23.5)	15 (6.7)	2 (0.3)	57 (5.1)
In-hospital	39 (97.5)	15 (100.0)	–	54 (94.7)
Outpatient	1 (2.5)	0 (0.0)	2 (100.0)	3 (5.3)
Thrombocytopenia	79 (46.5)	67 (30.6)	15 (2.1)	161 (14.5)
Platelet nadir, /μl	105.3 ± 36.7	112.9 ± 26.3	122.6 ± 23.8	110.0 ± 32.0
Myocardial infarction	13 (7.7)	1 (0.5)	0 (0.0)	14 (1.3)
ST-segment elevation	0 (0.0)	1 (100.0)	–	1 (7.1)
Non-ST-segment elevation	13 (100.0)	0 (0.0)	–	13 (92.9)
Fatal	1 (7.7)	0 (0.0)	–	1 (7.1)
Percutaneous intervention	0 (0.0)	1 (100.0)	–	1 (7.1)
Medical therapy only	13 (100.0)	0 (0.0)	–	13 (92.9)
Stroke	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.1)
Fatal	1 (100.0)			1 (100.0)
Heart failure hospitalization	5 (2.9)	1 (0.5)	0 (0.0)	6 (0.6)
New atrial fibrillation	21 (12.4)	6 (2.7)	0 (0.0)	27 (2.6)
Myocarditis	7 (4.1)	0 (0.0)	0 (0.0)	7 (0.7)

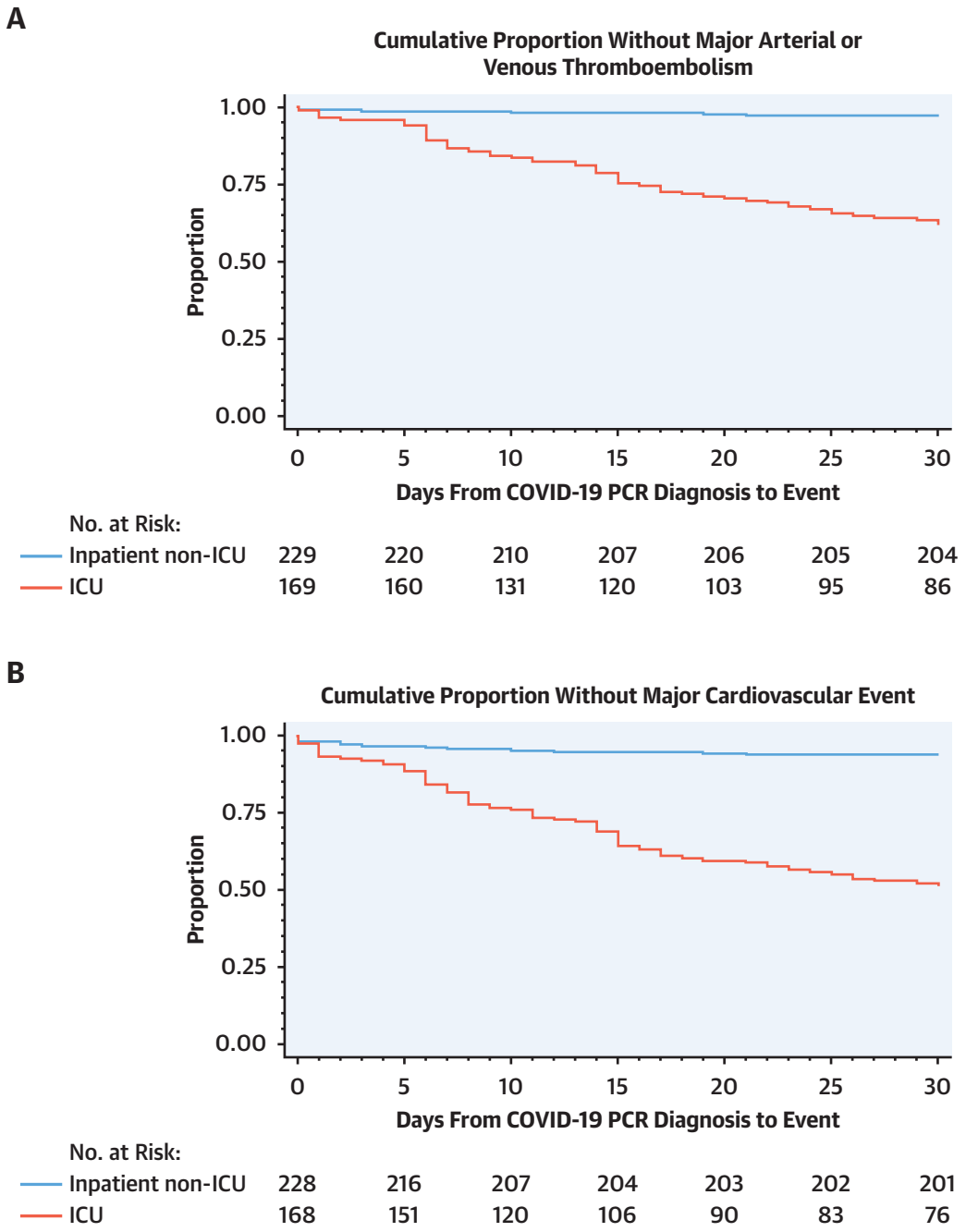
Values are n (%) or mean ± SD. *Patients may have had deep vein thrombosis in multiple locations.
DVT = deep vein thrombosis; PE = pulmonary embolism; other abbreviations as in Tables 1 and 2.

hospitalized at 30 days 28.8% of the time. Admission to the ICU was associated with a high frequency of COVID-19-related complications of pneumonia (96.5%), ARDS (78.8%), sepsis (57.1%), and hypotension (78.2%).

At 30 days from diagnosis, major arterial or venous thromboembolic events, major adverse cardiovascular events, and symptomatic VTE occurred in 35.3%, 45.9%, and 27.0% of patients with COVID-19 in the ICU cohort, respectively (**Table 4, Figure 1, Central Illustration**). Nearly all occurred during hospitalization (98.3%, 97.4%, and 97.6%, respectively). The estimated cumulative incidences at 30 days for major arterial and venous thromboembolism, major cardiovascular events, and symptomatic VTE in the ICU cohort were 0.34 (95% CI: 0.28 to 0.42), 0.44 (95% CI: 0.38 to 0.52), and 0.24 (95% CI: 0.19 to 0.31), respectively.

Symptomatic DVT was largely composed of catheter- or device-related thrombosis (76.9%). Symptomatic PE occurred in only 3 ICU patients with COVID-19, but 2 of these were hemodynamically unstable (high-risk) PE. Catheter- or device-related arterial thrombosis occurred in 6.5% of ICU patients. MI occurred in 7.7% of ICU patients and was exclusively non-ST-segment elevation. Among patients with COVID-19 in the ICU cohort, 23.5% were deceased at 30 days, with 97.5% dying while in the hospital and 92.5% of those due to sepsis. Patients with COVID-19 in the ICU cohort who were receiving prophylactic anticoagulation were more likely to have major arterial or VTE events (15.9% vs. 0.7%; $p < 0.0001$), major adverse cardiovascular events (20.2% vs. 1.1%; $p < 0.0001$), and symptomatic VTE (11.5% vs. 0.1%; $p < 0.0001$) than those not receiving thromboprophylaxis.

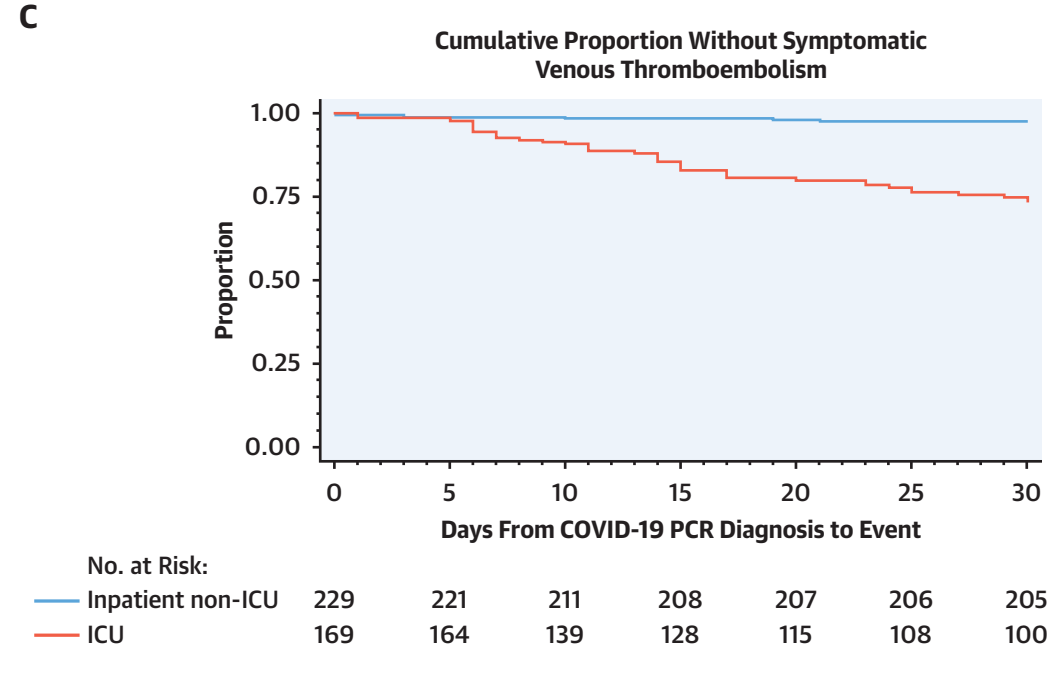
FIGURE 1 Time From COVID-19 PCR Diagnosis to Major Composite Outcomes



Kaplan-Meier plots demonstrating time from coronavirus disease-2019 (COVID-19) polymerase chain reaction (PCR) diagnosis to each of the 3 major composite outcomes. Major arterial and venous thromboembolism **(A)**, major cardiovascular events **(B)**, and symptomatic venous thromboembolism (VTE) **(C)** were more frequent in intensive care unit (ICU) patients than in hospitalized non-ICU patients. Adjusting for competing risk of death, estimated cumulative incidences at 30 days for major arterial and venous thromboembolism, major cardiovascular events, and symptomatic VTE in the ICU cohort were 0.34 (95% confidence interval [CI]: 0.28 to 0.42), 0.44 (95% CI: 0.38 to 0.52), and 0.24 (95% CI: 0.19 to 0.31), respectively. The estimated cumulative incidences at 30 days for major arterial and venous thromboembolism, major cardiovascular events, and symptomatic VTE in the hospitalized non-ICU cohort were 0.03 (95% CI: 0.01 to 0.06), 0.06 (95% CI: 0.03 to 0.1), and 0.02 (95% CI: 0.01 to 0.05), respectively. Three patients had outcomes prior to PCR diagnosis and were excluded from the plots.

Continued on the next page

FIGURE 1 Continued



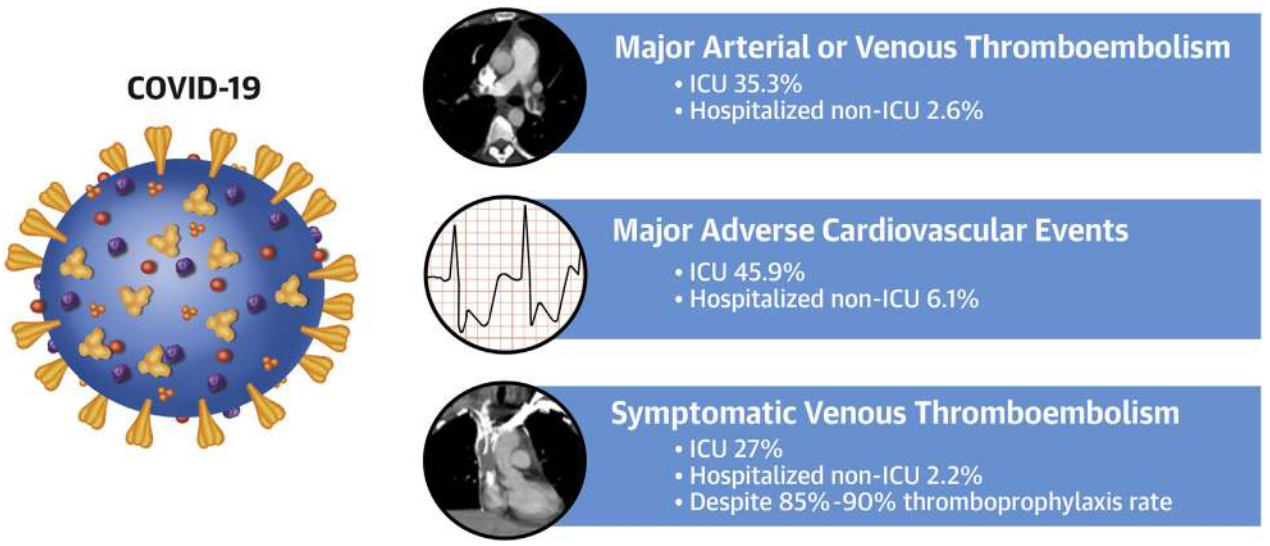
In patients with COVID-19 in the ICU cohort, ARDS was associated with a 7-fold increased odds of major arterial or VTE events (adjusted odds ratio [OR]: 6.69; 95% CI: 1.85 to 24.14), 6-fold increased odds of major adverse cardiovascular events (adjusted OR: 5.79; 95% CI: 2.01 to 16.69), and 24-fold increased odds of symptomatic VTE (adjusted OR: 24.39; 95% CI: 1.50 to 398.00) (Table 5).

NON-ICU HOSPITALIZED PATIENTS WITH COVID-19. There were 229 hospitalized patients with COVID-19 who were never admitted to the ICU; this cohort had a mean age of 60.6 years, was obese (mean body mass index: 30.1 kg/m^2), and was more likely to be male (53.7%) (Table 1). Forty-four percent were non-White and 27.5% were Hispanic/Latinx. Histories of coronary artery disease (17.0%) and cardiovascular risk factors of hypertension (56.3%), hyperlipidemia (42.4%), and diabetes (29.7%) were common in non-ICU hospitalized patients with COVID-19 (Table 2). Statins, aspirin, and antithrombotic therapy were prescribed at baseline in 63.8%, 24.5%, and 9.2% of patients with COVID-19 in the hospitalized, non-ICU cohort, respectively. Prophylactic anticoagulation was prescribed in 84.7% of these patients. No patients were prescribed post-discharge anticoagulation for primary prevention of thromboembolic complications.

Fever (82.5%), cough (80.4%), and shortness of breath (59.8%) were the most frequent symptoms in patients with COVID-19 in the hospitalized non-ICU setting (Table 3). Patients with COVID-19 in the hospitalized non-ICU cohort had a median length of hospital stay of 5 days. COVID-19-associated pneumonia was the most common complication (96.5%).

At 30 days from COVID-19 diagnosis, major arterial or VTE events, major adverse cardiovascular events, and symptomatic VTE occurred in 2.6%, 6.1%, and 2.2%, respectively of patients in the hospitalized non-ICU cohort (Table 4, Figure 1). The estimated cumulative incidences at 30 days for major arterial and venous thromboembolism, major cardiovascular events, and symptomatic VTE in the hospitalized non-ICU cohort were 0.03 (95% CI: 0.01 to 0.06), 0.06 (95% CI: 0.03 to 0.1), and 0.02 (95% CI: 0.01 to 0.05), respectively. Major arterial or venous thromboembolic events, major adverse cardiovascular events, and symptomatic VTE occurred during hospitalization in 50%, 78.6%, and 40% of this cohort, respectively. Those receiving prophylactic anticoagulation were more likely to have major arterial or VTE events (1.4% vs. 0.1%; $p = 0.01$), major adverse cardiovascular events (3.8% vs. 0.1%; $p < 0.0001$), and symptomatic VTE (1.4% vs. 0.0%; $p<0.0001$) than those not receiving thromboprophylaxis.

CENTRAL ILLUSTRATION **Cardiovascular Complications in Patients With Coronavirus Disease-2019 at 30 Days From Diagnosis**



Piazza, G. et al. J Am Coll Cardiol. 2020;76(18):2060–72.

Cardiovascular complications, including major arterial or venous thromboembolism, in 1,114 patients with coronavirus disease-2019 (COVID-19) at 30 days from diagnosis. Adjudicated major arterial (including myocardial infarction, stroke/transient ischemic attack, systemic embolism, and major adverse limb events) or venous thromboembolism, major adverse cardiovascular events, and symptomatic venous thromboembolism (VTE) (including catheter- and device-related deep vein thrombosis [DVT]) were frequent in patients with COVID-19 admitted to the intensive care unit (ICU) setting (n = 170). Among those admitted to the non-ICU setting (n = 229), the frequency of major arterial or venous thromboembolism, major adverse cardiovascular events, and symptomatic VTE was also elevated but lower than for those with critical illness. The increased frequency of thromboembolic complications occurred in the context of a relative high rate of thromboprophylaxis prescription. Outpatients (n = 715) were considered to be low risk for major arterial or venous thromboembolism, major adverse cardiovascular events, and symptomatic VTE.

Among patients with COVID-19 in the hospitalized non-ICU cohort, the frequency of death at 30 days was 6.7%. All deaths occurred during the hospitalization, and 80% were due to sepsis.

OUTPATIENTS WITH COVID-19. The mean age was 44.8 years in 715 patients with COVID-19 who were not hospitalized (Table 1). Patients with COVID-19 in the outpatient cohort were more likely to be female (60.6%), and were 18.6% Hispanic/Latinx and 43.1% non-White. Cardiovascular risk factors of hypertension (24.5%), hyperlipidemia (20.8%), and diabetes (9.4%) were common (Table 2). The most common symptoms of COVID-19 were cough (72.2%), fever (64.3%), and myalgias (54.7%) (Table 3). COVID-19-associated pneumonia was the most common complication (37.8%). Prophylactic anticoagulation was rare in the outpatient cohort. The outpatient cohort had a low risk of major arterial or VTE events, major adverse cardiovascular events, and symptomatic VTE (Table 4). Two outpatients died by 30 days due to sepsis without hospitalization, after being designated as hospice care.

DISCUSSION

Major arterial or VTE events, major adverse cardiovascular events, and symptomatic VTE occurred with high frequency over 30 days in patients with COVID-19 in the ICU cohort, despite a nearly 90% prescription of thromboprophylaxis. ARDS complicating COVID-19 was strongly associated with an increased odds of major arterial or venous thromboembolism, major adverse cardiovascular events, and symptomatic VTE. The 30-day mortality rate in the ICU cohort was 23.5% or 1 in 4 patients. Despite a nearly 85% thromboprophylaxis rate, hospitalized non-ICU patients with COVID-19 were also susceptible to these cardiovascular complications, although not to the extent of those in the critical care setting. The outpatient cohort had a low risk of adverse events.

The global experience of the COVID-19 pandemic has identified an increased risk of arterial and venous thromboembolism and other major adverse cardiovascular events, especially among ICU patients

(4,7,8,23-25). Thromboembolic events, in particular DVT and PE, complicating COVID-19 have been estimated to occur in 20% to 40% of patients requiring admission to the ICU and have been associated with increased mortality (4,6-8,26). Similarly, myocardial injury, whether due to ischemic insult or inflammation, has also been linked to adverse outcomes, including increased in-hospital mortality, in patients with COVID-19 (23,25). With respect to cardiovascular complications, we observed that non-ST-segment elevation MI predominated in our ICU cohort. This was likely due to a high prevalence of underlying heart disease, cardiovascular risk factors, and clinical courses complicated by systemic arterial hypotension and hypoxemia.

In the current study, we found comparable 30-day frequencies of thromboembolism (35.3%) and major adverse cardiovascular events (45.9%) in the ICU cohort. All events underwent rigorous adjudication and included only symptomatic VTE. VTE occurred despite a high rate of prophylactic anticoagulation. Counterintuitively, we observed a higher frequency of adverse events in patients with COVID-19 in the ICU and hospitalized non-ICU cohorts who were receiving thromboprophylaxis compared with those who were not. Possible explanations for this observation include confounding by indication and failure of standard thromboprophylactic dosing (26).

A prothrombotic state due to immobility, a high frequency of thromboembolic risk factors, severe systemic inflammation, virus-mediated hypercoagulability, bacterial coinfection, and indwelling catheters and devices may explain the increased frequency of arterial and venous thromboembolism despite thromboprophylaxis (5,16,27). Catheter- and device-associated DVT accounted for 76.9% of the DVTs observed in our study. Our finding of high frequency of catheter-associated DVT supports the judicious use of central venous catheters that have been widely implemented especially in the ICU to minimize recurrent health care team exposure and facilitate monitoring.

ARDS may play a critical role in the prothrombotic state of COVID-19 (28). Patients with COVID-19 and ARDS have elevated D-dimer, fibrinogen, and interleukin-6 levels (28). The prothrombotic state associated with elevated D-dimer and fibrin degradation product levels has correlated with increased mortality in COVID-19 (5). In our analysis of 170 patients with COVID-19 in the ICU cohort, we observed similar increases in D-dimer and inflammatory biomarkers of high-sensitivity C-reactive protein and high-sensitivity interleukin-6. However, we found that presence of ARDS had the strongest association with adverse outcomes, including major arterial or venous thromboembolism, major adverse cardiovascular events, symptomatic VTE, and death. The severe inflammatory state associated with ARDS and other complications of COVID-19 and its resultant hypercoagulability may explain, at least in part, the high frequency of thromboembolic events. Improved risk stratification, utilizing biochemical markers of inflammation and activated coagulation as well as clinical indicators, such as ARDS, may play an important role in the early identification of patients with an increased likelihood of developing symptomatic VTE or arterial thrombosis. They may benefit from full- or intermediate-intensity antithrombotic therapy rather than prophylactic anticoagulation. An enhanced understanding of the interplay between infection, inflammation, and thrombosis may yield opportunities for therapeutic intervention to reduce mortality.

Whereas the highest burden of thromboembolism and major adverse cardiovascular events rests on those in the ICU, patients with COVID-19 admitted to

TABLE 5 Univariate and Multivariate Analysis of Factors Associated With Increased Odds of Adverse Events at 30 Days in Patients With COVID-19 in the Critical Care Setting

	Univariate		Multivariate	
	OR	95% CI	Adjusted OR	95% CI
Major arterial or venous thromboembolic event				
Age	0.98	0.96-1.00	0.97	0.95-0.99
Male	1.33	0.69-2.58	1.31	0.64-2.71
VTE prophylaxis	1.47	0.5-4.35	0.76	0.22-2.57
ARDS	8.14	2.38-27.87	6.69	1.85-24.14
D-dimer (decile)	1.13	1.0-1.29	1.17	1.03-1.33
Major cardiovascular event				
Age	1.01	0.99-1.03	1.00	0.98-1.03
Male	1.92	1.02-3.64	2.07	1.03-4.16
VTE prophylaxis	1.07	0.4-2.85	0.58	0.18-1.90
ARDS	7.42	2.72-20.25	5.79	2.01-16.69
D-dimer (decile)	1.13	1.01-1.27	1.12	0.99-1.27
History of CAD	0.68	0.3-1.53	0.71	0.27-1.85
Symptomatic VTE				
Age	0.98	0.96-1.01	0.97	0.95-1.0
Male	1.63	0.76-3.49	1.54	0.69-3.44
VTE prophylaxis	6.07	0.78-47.1	2.51	0.41-15.44
ARDS	32.4	1.87-562.29	24.39	1.50-398.00
D-dimer (decile)	1.10	0.97-1.25	1.11	0.97-1.27
Death				
Age	1.08	1.04-1.11	1.08	1.05-1.12
Male	1.82	0.83-3.95	1.91	0.78-4.64
VTE prophylaxis	0.44	0.16-1.21	0.63	0.18-2.22
ARDS	2.94	0.97-8.89	3.23	0.87-12.06
D-dimer (decile)	1.04	0.91-1.18	0.93	0.80-1.09
History of CAD	1.95	0.82-4.63	1.09	0.38-3.16

CAD = coronary artery disease; CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 to 3.

the non-ICU setting still bear an important risk of these complications, especially VTE (8,29). The frequency of VTE in patients with COVID-19 admitted to the non-ICU setting has varied from 5% to 15% depending on whether systematic screening for asymptomatic DVT was performed (8,29). We observed a lower 30-day frequency of thromboembolism (2.6%) in the hospitalized non-ICU cohort, likely due to high baseline rate of utilization of thromboprophylaxis (85%), decision support for thromboembolism prevention (30,31), and rigorous event adjudication.

The health and economic implications of these frequent cardiovascular complications, including arterial and venous thromboembolism, myocardial injury, and heart failure, are unlikely to be fully realized until the pandemic abates, social distancing measures are relaxed, medical centers reopen for routine care, and large population datasets are analyzed. In the current study, cardiovascular complications accounted for 7% of deaths at 30 days in patients with COVID-19 compared with sepsis in nearly 90%. The consequences associated with the high frequency of cardiovascular events are likely to be substantial, given the high prevalence of cardiovascular disease and risk factors in the COVID-19 population. As documented in other studies, we observed an ethnically and racially diverse population infected with COVID-19 (32). The impact of cardiovascular complications of COVID-19 on preexisting health care disparities could be devastating in underserved communities.

Our study provides a cross-sectional view of the cardiovascular complications of COVID-19 in a large health care network, consisting of 2 academic medical centers serving the Greater Boston area, several community hospitals, and numerous outpatient care sites. The study incorporates a wide scope of clinically meaningful cardiovascular endpoints and utilizes a rigorous process of event adjudication. Although data on patients with COVID-19 in the ICU have been the subject of most reports, our study provides insights into the broad spectrum of all hospitalized and outpatient populations.

STUDY LIMITATIONS. The current study must also be interpreted within the limitations of its retrospective design. Although the clinical significance of asymptomatic VTE remains a matter of debate, we did not perform surveillance screening, and, therefore, we probably underestimated the frequency of VTE. Catheter- and device-related DVT composed a large proportion of VTE in the ICU cohort and may have inflated the estimate. Because we designated the study cohorts as mutually exclusive, we may have underestimated the frequency of events in the hospitalized, non-ICU setting. For example, a hospitalized patient in the noncritical care setting with a DVT who subsequently is admitted to the ICU would be counted as an event in the ICU cohort. Because we did not study a comparator group without COVID-19 but with other medical illness of similar severity, we were unable to determine the extent to which COVID-19 itself increases the risk of thromboembolic events. A U.K.-based study of 1,877 hospital discharges related to COVID-19 and 18,159 related to non-COVID-19 medical illness did not show a difference in the rate of hospitalization-associated VTE (OR: 1.6; 95% CI: 0.77 to 3.1) (33).

Although we obtained 30-day follow-up data on 96% of subjects in the total study population, we were unable to obtain follow-up for 40 outpatients, and, therefore, we are likely to have underestimated 30-day outcomes in this cohort. We were also unable to assess microvascular thrombosis, particularly in the pulmonary circulation, which has emerged as an important concern in COVID-19. We were not able to obtain data regarding medication adherence to antiplatelet, antithrombotic, statin, and insulin therapy prior to the diagnosis of COVID-19. We were also unable to determine the rationale for omission of thromboprophylaxis. Finally, a limited sample size precluded more extensive statistical assessment of less frequent cardiovascular complications and development of larger multivariable models. We anticipate a greater ability to discern important associations with subsequent analyses of this rapidly growing registry.

CONCLUSIONS

Arterial or venous thromboembolism and major adverse cardiovascular events were common over 30 days in ICU patients with COVID-19. ARDS was strongly associated with cardiovascular complications. Patients with COVID-19 in the hospitalized non-ICU cohort were also susceptible to cardiovascular complications, although not to the extent of those in the critical care setting. The high frequency of arterial or venous thromboembolism in hospitalized patients despite routine thromboprophylaxis suggests the need for improved risk stratification and enhanced preventive efforts.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Arterial and venous thromboembolism and other major adverse cardiovascular events represent critical hazards to patients with COVID-19 despite routine thromboprophylaxis, especially among those in hospital intensive care units.

TRANSLATIONAL OUTLOOK: The high frequency of arterial and venous thromboembolism in hospitalized patients with COVID-19 warrants further investigation to refine risk stratification and establish safe and effective antithrombotic management.

REFERENCES

1. Bikdeli B, Madhavan MV, Jimenez D, et al., for the Global COVID-19 Thrombosis Collaborative Group. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75:2950–73.

2. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. JAMA Cardiol 2020;5:751–3.

3. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. J Am Coll Cardiol 2020;75:2352–71.

4. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145–7.

5. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844–7.

6. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020;18:1421–4.

7. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 2020;18:1743–6.

8. Lodigiani C, Iapichino G, Carenzo L, et al., for the Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9–14.

9. Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). Blood Transfus 2020;18:167–9.

10. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020;18:1995–2002.

11. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383:120–8.

12. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417–8.

13. Wichmann D, Sperhake JP, Lutgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. Ann Intern Med 2020;173:268–77.

14. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis and treatment of VTE in patients with coronavirus disease 2019: CHEST guideline and expert panel report. Chest 2020;158:1143–63.

15. Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and Standardization Committee communication: clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020;18:1859–65.

16. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094–9.

17. Boger B, Fachi MM, Vilhena RO, Cobre AF, Tonin FS, Pontarolo R. Systematic review with meta-analysis of the accuracy of diagnostic tests for COVID-19. Am J Infect Control 2020 Jul 10 [E-pub ahead of print].

18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.

19. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35.

20. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692–4.

21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

22. Firth D. Bias reduction of maximum likelihood estimates. Biometrika 1993;80:27–38.

23. Li X, Guan B, Su T, et al. Impact of cardiovascular disease and cardiac injury on in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis. Heart 2020;106:1142–7.

24. Poyiadji N, Cormier P, Patel PY, et al. Acute pulmonary embolism and COVID-19. Radiology 2020 May 14 [E-pub ahead of print].

25. Shi S, Qin M, Cai Y, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. Eur Heart J 2020;41:2070–9.

26. Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 2020;191:148–50.

27. Bikdeli B, Madhavan MV, Gupta A, et al. Pharmacological agents targeting thromboinflammation in COVID-19: review and implications for future research. Thromb Haemost 2020;120:1004–24.

28. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost 2020;18:1747–51.

29. Demelo-Rodriguez P, Cervilla-Munoz E, Ordieres-Ortega L, et al. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. Thromb Res 2020;192:23–6.

30. Kucher N, Koo S, Quiroz R, et al. Electronic alerts to prevent venous thromboembolism among hospitalized patients. N Engl J Med 2005; 352:969-77.

31. Piazza G, Hurwitz S, Galvin CE, et al. Alert-based computerized decision support for high-risk hospitalized patients with atrial fibrillation not prescribed anticoagulation: a randomized, controlled trial (AF-ALERT). Eur Heart J 2020;41: 1086-96.

32. Khatana SAM, Groeneveld PW. Health disparities and the coronavirus disease 2019 (COVID-19) pandemic in the USA. J Gen Intern Med 2020;35: 2431-2.

33. Roberts LN, Whyte MB, Georgiou L, et al. Post-discharge venous thromboembolism following hospital admission with COVID-19. Blood 2020 Aug 3 [E-pub ahead of print].

KEY WORDS anticoagulation, cardiovascular disease, coronavirus, COVID-19, deep venous thrombosis, myocardial infarction, pulmonary embolism, stroke, thromboembolism

APPENDIX For supplemental material about the CORONA-VTE, please see the online version of this paper.