


Real-World Analysis of Thromboembolic Events and Mortality of COVID-19 Outpatients in the United States

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W. Frank Peacock, MD, FACEP, FACC, FESC¹ , James M. Crawford, MD, PhD^{2,3}, Yen-Wen (Cindy) Chen, PhD⁴, Veronica Ashton, MPH⁴, Alicia K. Campbell, PharmD⁴, Dejan Milentijevic, PhD, MBA⁴, and Alex C. Spyropoulos, MD, FACP, FCCP, FRCPC^{2,3,5} 

Abstract

Limited data are available on thromboembolic events (TEEs) and mortality in outpatients with coronavirus disease 2019 (COVID-19). This retrospective, observational cohort study identified non-hospitalized COVID-19 outpatients (01/21/2020-01/07/2021) using de-identified Optum[®] COVID-19 Electronic Health Records data. Patient characteristics, occurrence of TEEs, all-cause mortality, and anticoagulant or thrombolytic medication use were evaluated. Of 1,246,067 patients with COVID-19 diagnosis, 141 471 met entry criteria. Mean (standard deviation [SD]) age was 46.1 (17.2) years, 56.8% were female, 72.9% Caucasian, 11.2% African American, and 11.1% Hispanic. Comorbidity burden was low (mean [SD] Quan-Charlson comorbidity index score of 0.43 [1.10]); however, of those with body mass index data, half were obese. During the follow-up period, a TEE occurred in 1.4%, with the proportion of patients with ischemic stroke, myocardial infarction, deep vein thrombosis, and pulmonary embolism being similar (approximately 0.4% each). All-cause mortality was 0.7%. Medications included corticosteroids (13.7%), anticoagulants (4.9%), and antiplatelets (2.9%). Overall, in this large cohort analysis, certain demographic and clinical characteristics of patients who experienced TEEs were identified and may help guide management decisions and future clinical trials for COVID-19 outpatients.

Keywords

COVID-19, thrombosis, thromboembolism, anticoagulation, risk factors

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic has infected more than 380 million people worldwide and led to more than 5 million deaths as of February 2022.¹ Most cases of coronavirus disease 2019 (COVID-19) result in mild symptoms including fever, cough, fatigue, and shortness of breath.² However, COVID-19 is also associated with abnormalities in coagulation as evidenced by thrombocytopenia and elevated levels of fibrinogen and fibrin degradation products, prolonged prothrombin time and activated partial thromboplastin time, and very elevated D-dimer levels.³ Cardiovascular complications, including arterial thromboembolism (ATE), venous thromboembolism (VTE), and myocardial infarction (MI) are reported.^{4,5} Other COVID-19 pathology that may contribute

to thromboembolic events includes hyperinflammation, cytokine release, platelet activation, and endothelial dysfunction.^{6,7}

¹ Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine, Houston, TX, USA

² The Institute of Health Systems Science at the Feinstein Institutes for Medical Research, Manhasset, NY, USA

³ The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

⁴ Janssen Scientific Affairs, LLC, Titusville, NJ, USA

⁵ Northwell Health at Lenox Hill Hospital, New York, NY, USA

Corresponding Author:

W. Frank Peacock, Emergency Medicine, Baylor College of Medicine, Ben Taub General Hospital, 1504 Taub Loop, Houston, TX, 77021, USA.
Email: Frankpeacock@gmail.com



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Limited data exist on the occurrence of thromboembolic events in COVID-19 outpatients, with retrospective studies identifying a rate of <1% in this subgroup.^{8,10} These studies are limited as they may not have captured data for patients who developed thrombosis or other complications of COVID-19 that required subsequent hospitalization.¹¹ Limited randomized clinical trial evidence suggests that COVID-19 outpatients are at low risk of thrombotic events, mortality, and hospitalization, but enrollment numbers have been suboptimal.¹² Small case series have illustrated the risk of VTE associated with COVID-19 in patients with mild to moderate symptoms who are isolating at home.^{13,14}

To better understand the risk of thromboembolic complications in outpatients with COVID-19, additional information is needed from larger populations. The primary objectives of this large real-world healthcare database study were to evaluate COVID-19 outpatients for demographic and clinical characteristics, use of medications relevant to thrombosis, occurrence of thromboembolic events, and all-cause mortality.

Methods

Data Source

The large, longitudinal, and low-latency Optum[®] COVID-19 Electronic Health Records (EHR) dataset was used for this retrospective, observational study of COVID-19 patients in the United States. This Optum[®] COVID-19 EHR dataset identified COVID-19 patients based on diagnosis codes and laboratory tests. The dataset included the following elements: patient demographics, outpatient visits, coded diagnostic procedures,

medications, laboratory results, hospitalizations, clinical notes, and patient outcomes from a network of healthcare provider organizations across the United States. As of January 7, 2021, 3.6 million patients were included in this dataset.

Research Ethics

The study protocols for data acquisition were compliant with U.S. patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996. The use of secondary data analyses of de-identified patient records does not constitute human subjects research and is therefore exempt from Institutional Review Board registration and review requirements under the US Federal Policy for the Protection of Human Subjects (also known as the “Common Rule”).

Study Design and Study Population

The study design is illustrated in Figure 1. Optum[®] EHR data were analyzed to identify adult COVID-19 outpatients between January 21, 2020 and January 7, 2021 (cohort identification period). Patients were defined as COVID-19 outpatients if they received any service other than inpatient hospitalization and had a code for COVID-19 (ICD-10-CM: U07.1, B97.29, B97.21, B34.2, J12.81, J12.89, J20.8, J22, J40, J80, J98.8, A41.89, R05, R06.02, or R50.9) in any diagnosis position on or after January 21, 2020 AND a positive COVID-19 antigen or polymerase chain reaction laboratory test (Supplemental Table 1) within 14 days before or after the date of the

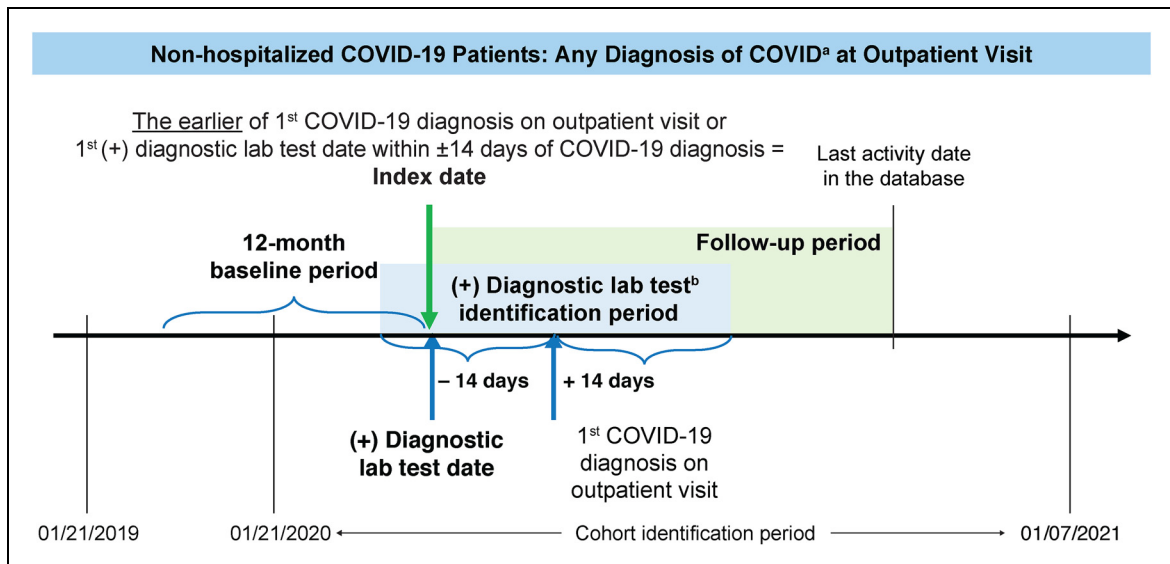


Figure 1. Study design for outpatients with COVID-19.

COVID-19 = coronavirus disease 2019.

A patient's index date could be any time during the cohort identification period, between January 21, 2020 and January 7, 2021, with no minimum follow-up required. The timeline in the figure depicts an index date early in the cohort identification period and is not shown to scale.

^aDefined as ICD-10-CM: U07.1, B97.29, B97.21, B34.2, J12.81, J12.89, J20.8, J22, J40, J80, J98.8, A41.89, R05, R06.02, or R50.9.

^bDiagnostic laboratory test includes polymerase chain reaction–based or antigen testing.

COVID-19 diagnosis code, were included in the study. If a COVID-19 outpatient was hospitalized within 14 days following the first outpatient COVID-19 diagnosis, they were excluded from the outpatient cohort.

The date of the earliest evidence of confirmed COVID-19 on or after January 21, 2020 was defined as the index date (Figure 1). Additional inclusion criteria required patients to be ≥ 18 years of age as of the index date and have activity in the Optum[®] COVID-19 EHR database at least 12 months prior to the index date (baseline period). Patients with missing data on sex or birth year were excluded from the study. The follow-up period was defined as the period from the index date to the last activity date in the database (up to January 7, 2021).

Demographics, Outcomes, and Analyses

Outcomes were measured during the follow-up period. There were 3 primary outcomes: (1) demographic and clinical characteristics of COVID-19 outpatients; (2) medication use and (3) the occurrence of thromboembolic events and all-cause mortality. Demographic characteristics were collected on the index date and included age, sex, race, ethnicity, geographic region, insurance type, and month and year of index date. During the 12-month baseline period preceding the index date, clinical characteristics were recorded, including comorbidities (Supplemental Table 2) and concomitant medication use (Supplemental Table 3). Variables such as body mass index (BMI), obesity class, and Quan-Charlson comorbidity index (QCI) score (Supplemental Table 4) were based on the last measure before the index date.

Patients were followed for a variable time period after the index date, noting that January 7, 2021 was both the end of the cohort identification period and the last possible activity date in the database. During the follow-up period, the use of any of the medications of interest (anticoagulants, antiplatelets, tissue plasminogen activator, aspirin, antithrombin III, remdesivir, corticosteroids, or convalescent plasma [Supplemental Table 5]) was assessed. Patients with use of any of the medications of interest during the follow-up period were defined as treatment users. Prior users were defined as patients with use of any medications of interest during the follow-up period who also had received any of the medications of interest within the 45 days prior to the index date. The number and proportion of treatment users and prior users of any medication in the class (overall and by each medication class) were assessed.

Thromboembolic events of interest were ischemic stroke (IS), deep vein thrombosis (DVT), pulmonary embolism (PE), MI, acute limb ischemia (ALI), and major nontraumatic lower limb amputation (Supplemental Table 6). The number and proportion of patients who developed thromboembolic events, and the time to the first event during the variable follow-up period, were assessed in total and by each event of interest. All-cause mortality was determined as the number and proportion of patients who died during follow-up, with time to death estimated from the date of death, which is

defined in the Optum[®] database as the last day of the calendar month during which the patient died.

Exploratory outcomes. Demographics, clinical characteristics, and baseline medication use were further stratified and reported for COVID-19 outpatients who experienced thromboembolic events during the variable follow-up period.

The number and proportion of patients who received the same medication of interest both during the 45 days prior to the index date and during the variable follow-up period were reported.

The descriptive analyses in this study were conducted using univariate statistics including percentages, means, standard deviations (SD), and medians. Statistical comparative assessments between patient groups or medication classes were not performed in this study. All statistical analysis used SAS Enterprise Guide 7.1 Version X.

Results

Baseline Patient Characteristics

An ICD-10-CM code for COVID-19 in any diagnosis position during the cohort identification period was identified in 1,246,067 patients. Of these, 181,995 had a positive COVID-19 laboratory test within 14 days of COVID-19 diagnosis and were in the Optum[®] database for ≥ 12 months prior to COVID-19 diagnosis, meeting the stated inclusion and exclusion criteria. Of the 181,995 eligible patients, 141,471 (77.7%) were not hospitalized within 14 days after earliest evidence of COVID-19 infection. All further data pertain to this non-hospitalized COVID-19 outpatient cohort.

The mean (SD) age of COVID-19 outpatients was 46.1 (17.2) years, 56.8% were female, 72.9% Caucasian, 11.2% African American, and 11.1% Hispanic (Table 1). Most patients (58.8%) were from the Midwest United States, with 18.2% from the South. Nearly half of the cases had an index month of either November or December 2020 (Figure 2). Among 62.8% of patients with a BMI measure, the mean (SD) BMI was 31.3 (7.9) kg/m² and 50.9% were obese (BMI >30 kg/m²). The comorbidity burden of COVID-19 outpatients was low, with a mean (SD) QCI score of 0.43 (1.10). The most common comorbidities were hypertension, hyperlipidemia, anxiety, diabetes, and depression. Prior thromboembolic events were rare, with proportions of patients with IS, MI, DVT, and PE ranging from 0.3% to 0.6%, with ALI and major non-traumatic lower limb amputation occurring in $<0.10\%$ of patients during the 12-month baseline period. During the baseline period, antibiotics, anti-inflammatory agents, and corticosteroids were the most frequently reported concomitant medications, followed by antihypertensives, antidepressants, and antihyperlipidemics (Table 1). Anticoagulants were used in 5.81% of outpatients during the baseline period. The most common ambulatory settings recorded on the index date were ambulatory patient services (41.4%), emergency (19.9%), and office or clinic (18.6%; Supplemental Table 7).

Table 1. Baseline^a Demographics, Clinical Characteristics, and Medication Use in COVID-19 Outpatients Overall and Among Those With a Thromboembolic Event of Interest During Follow-Up.^b

	All Outpatients	Outpatients with Thromboembolic Event of Interest ^b
Number of patients	141,471	1,931
Age, years		
Mean (SD)	46.13 (17.23)	63.35 (15.54)
Age group, n (%)		
18-24	17,178 (12.14)	22 (1.14)
25-34	25,571 (18.08)	78 (4.04)
35-44	25,150 (17.78)	125 (6.47)
45-54	26,498 (18.73)	308 (15.95)
55-64	25,453 (17.99)	431 (22.32)
≥65	21,621 (15.28)	967 (50.08)
Sex, n (%)		
Male	61,132 (43.21)	1,055 (54.63)
Female	80,339 (56.79)	876 (45.37)
Race, n (%)		
African American	15,840 (11.20)	314 (16.26)
Asian	2,502 (1.77)	23 (1.19)
Caucasian	103,161 (72.92)	1,394 (72.19)
Other/unknown	19,968 (14.11)	200 (10.36)
Ethnicity, n (%)		
Hispanic	15,771 (11.15)	186 (9.63)
Not Hispanic	113,449 (80.19)	1,612 (83.48)
Unknown	12,251 (8.66)	133 (6.89)
Geographic region, n (%)		
Northeast	18,700 (13.22)	366 (18.95)
West	8,707 (6.15)	153 (7.92)
Midwest	83,179 (58.80)	1,028 (53.24)
South	25,763 (18.21)	336 (17.40)
Other/unknown	5,122 (3.62)	48 (2.49)
Insurance type, n (%)		
Commercial	73,220 (51.76)	560 (29.00)
Medicaid	9,079 (6.42)	125 (6.47)
Medicare	9,384 (6.63)	439 (22.73)
Other	24,065 (17.01)	477 (24.70)
Uninsured	1,760 (1.24)	20 (1.04)
Unknown	2,666 (1.88)	21 (1.09)
Missing	21,297 (15.05)	289 (14.97)
BMI, kg/m ²		
Patients with BMI measure, n (%)	88,813 (62.78)	1494 (77.37)
Mean BMI (SD)	31.30 (7.88)	32.12 (8.30)
BMI category, ^c n (%)		
Underweight	712 (0.80)	14 (0.94)
Normal	17,128 (19.29)	237 (15.86)
Overweight	25,749 (28.99)	436 (29.18)
Obese	45,224 (50.92)	807 (54.02)
Obesity class, ^c n (%)		
Class 1 (BMI 30.0-34.9 kg/m ²)	21,465 (24.17)	369 (24.70)
Class 2 (BMI 35.0-39.9 kg/m ²)	12,692 (14.29)	218 (14.59)
Class 3 (BMI ≥40 kg/m ²)	11,067 (12.46)	220 (14.73)
QCI, mean (SD)	0.43 (1.10)	1.82 (2.31)
Individual comorbidity, n (%)		
Hypertension	33,894 (23.96)	1,154 (59.76)
Hyperlipidemia	30,013 (21.21)	981 (50.80)
Anxiety	17,741 (12.54)	324 (16.78)
Diabetes	15,285 (10.80)	638 (33.04)
Depression	13,592 (9.61)	298 (15.43)
Thyroid disease	12,021 (8.50)	303 (15.69)
Osteoarthritis	9,896 (7.00)	349 (18.07)

(continued)

Table 1. (continued)

	All Outpatients	Outpatients with Thromboembolic Event of Interest ^b
Asthma	8,818 (6.23)	180 (9.32)
Anemia	7,876 (5.57)	420 (21.75)
Sleep apnea	7,116 (5.03)	244 (12.64)
Chronic kidney disease	5,052 (3.57)	373 (19.32)
Nonalcoholic fatty liver disease	5,035 (3.56)	327 (16.93)
Cancer ^d	4,449 (3.14)	204 (10.56)
Chronic obstructive pulmonary disease	3,290 (2.33)	239 (12.38)
Congestive heart failure	2,774 (1.96)	308 (15.95)
Prior stroke/transient ischemic attack	2,256 (1.59)	330 (17.09)
Osteoporosis	2,160 (1.53)	87 (4.51)
Peripheral vascular disease	1,849 (1.31)	126 (6.53)
Old MI	1,339 (0.95)	160 (8.29)
Rheumatoid arthritis	1,232 (0.87)	42 (2.18)
Stable angina	590 (0.42)	45 (2.33)
Liver cirrhosis	519 (0.37)	25 (1.29)
Unstable angina	220 (0.16)	21 (1.09)
Uveitis	97 (0.07)	3 (0.16)
Thromboembolic event during baseline period, n (%)		
IS	892 (0.63)	242 (12.53)
MI	795 (0.56)	172 (8.91)
DVT	710 (0.50)	202 (10.46)
PE	437 (0.31)	171 (8.86)
ALI	59 (0.04)	20 (1.04)
Major nontraumatic lower limb amputation	112 (0.08)	29 (1.50)
Baseline medication use, n (%)		
Antibiotics	39,871 (28.18)	854 (44.23)
Anti-inflammatory agents	25,717 (18.18)	399 (20.66)
Corticosteroids	25,176 (17.80)	535 (27.71)
Antihypertensives	22,272 (15.74)	775 (40.13)
Antidepressants	21,743 (15.37)	432 (22.37)
Antihyperlipidemics	20,242 (14.31)	801 (41.48)
Beta-blockers	14,363 (10.15)	672 (34.80)
Antiarrhythmics	13,309 (9.41)	479 (24.81)
Antidiabetics	13,062 (9.23)	539 (27.91)
Antianxiety agents	11,753 (8.31)	334 (17.30)
Diuretics	11,332 (8.01)	519 (26.88)
Calcium channel blockers	9,497 (6.71)	425 (22.01)
Anticoagulants	8,221 (5.81)	774 (40.08)
Antiplatelet agents	6,303 (4.46)	524 (27.14)
Antineoplastic agents	1,839 (1.30)	84 (4.35)

Abbreviations: ALI, acute limb ischemia; BMI, body mass index; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; IS, ischemic stroke; MI, myocardial infarction; PE, pulmonary embolism; QCI, Quan-Charlson comorbidity index; SD, standard deviation.

^aThe baseline period was defined as the 12 months prior to the index date.

^bSubset of all COVID-19 outpatients (n = 141 471) with a thromboembolic event of interest (IS, MI, DVT, PE, ALI, and major nontraumatic lower limb amputation) during the variable follow-up period.

^cPercentage of patients is calculated based on the number of patients with an available BMI measure; thus, mean BMI, BMI category, and obesity class were reported only for those patients with a BMI measure available in the data.

^dA diagnosis for cancer required 2 diagnosis codes for the same type of cancer ≥ 30 days apart.

Thromboembolic Events and Medication Use During Follow-up

Patients were followed for a mean (SD) duration of 59.5 (72.9) days after the index date. Thromboembolic events of interest during the variable follow-up period occurred in 1.4% of COVID-19 outpatients (Table 2). The number and proportion of patients with each thromboembolic event of interest (IS, MI, DVT, and PE) were

similar, with each affecting approximately 0.4% of patients. ALI and major nontraumatic lower limb amputation occurred in 38 (0.03%) and 28 (0.02%), respectively. The mean time to first thromboembolic event ranged from 33 days for PE to 73 days for ALI among outpatients who experienced an endpoint (Table 2).

Fewer than 1% of COVID-19 outpatients died during follow-up. Of the 1,042 fatalities, 131 (12.6%) experienced a thromboembolic event during follow-up.

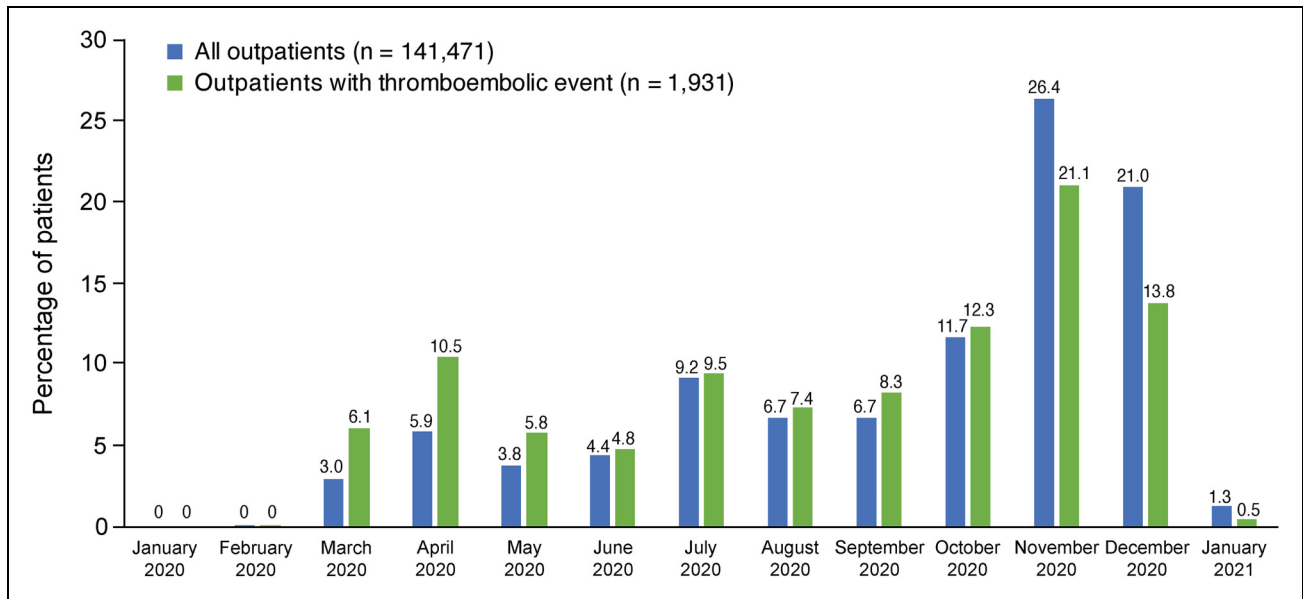


Figure 2. Month of index COVID-19 diagnosis for all outpatients and outpatients with a thromboembolic event of interest.^a

ALI = acute limb ischemia; COVID-19 = coronavirus disease 2019; DVT = deep vein thrombosis; IS = ischemic stroke; MI = myocardial infarction; PE = pulmonary embolism.

^aSubset of all COVID-19 outpatients (n = 141,471) with a thromboembolic event of interest (IS, MI, DVT, PE, ALI, and major nontraumatic lower limb amputation) during the variable follow-up period.

Table 2. Thromboembolic Events and Mortality in All COVID-19 Outpatients During Follow-up.

	All Outpatients
Number of patients	141,471
Occurrence of thromboembolic events, n (%)	
Any of the thromboembolic events of interest ^a	1,931 (1.36)
IS	493 (0.35)
MI	538 (0.38)
DVT	512 (0.36)
PE	529 (0.37)
ALI	38 (0.03)
Major nontraumatic lower limb amputation	28 (0.02)
Time to first event, days, mean (SD) ^b	
Any of the thromboembolic events of interest ^a	38.2 (53.2)
Ischemic stroke	47.8 (61.1)
MI	36.0 (55.8)
DVT	39.2 (48.8)
PE	32.7 (46.2)
ALI	72.7 (72.0)
Major nontraumatic lower limb amputation	51.3 (43.1)
Death ^c	
Patients who died during follow-up, n (%)	1,042 (0.74)
Time to death, days, mean (SD)	47.1 (47.5)

Abbreviations: ALI, acute limb ischemia; DVT, deep vein thrombosis; IS, ischemic stroke; MI, myocardial infarction; PE, pulmonary embolism; SD, standard deviation.

^aThe thromboembolic events of interest included IS, MI, DVT, PE, ALI, and major nontraumatic lower limb amputation.

^bTime to first event was examined among patients with the event.

^cIn the Optum[®] COVID-19 EHR database, the death date was defined as the last day of the calendar month during which the patient died. Therefore, the results reported here are estimates.

Use of medications of interest during follow-up was relatively low among all outpatients (Table 3). The most commonly used medications of interest during the follow-up period were corticosteroids (13.7%), anticoagulants (4.9%), and antiplatelets (2.9%). These were more commonly used in those with a thromboembolic event who died versus survivors: corticosteroids (29.9% vs 13.6%), anticoagulants (32.8% vs 4.7%), and antiplatelets (17.8% vs 2.8%), respectively. The combined prior use of medications of interest and use during follow-up was minimal (2.0%).

Characteristics of Patients with Thromboembolic Events

Outpatients who developed a thromboembolic event during follow-up were found to have the following characteristics: older age (mean age [SD], 63.4 [15.5] years), male sex (54.6%), African American race (16.3%), and obesity (54.0%; Table 1). Outpatients who developed thromboembolic events had a high comorbidity burden, with mean (SD) QCI of 1.82 (2.31). High proportions of patients who developed thrombosis were observed for the comorbidities of congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, anemia, nonalcoholic fatty liver disease, diabetes, and cancer. Prior thromboembolic events among patients who developed thrombosis included IS in 12.5%, prior DVT in 10.5%, prior MI in 8.9%, and prior PE in 8.9%. Baseline medication use for patients who developed thrombosis is shown in Table 1. Anticoagulant use during the baseline period was reported in

Table 3. Use of Medications of Interest in All COVID-19 Outpatients During Follow-up.

	Use During Follow-up ^a	Both Prior Use ^a and Use During Follow-up ^b
Number of patients	141 471	141 471
Medication use, n (%)		
Any of the medications of interest ^c	24 018 (16.98)	2849 (2.01)
Anticoagulants		
Any anticoagulants ^d	6888 (4.87)	1063 (0.75)
Vitamin K antagonists	466 (0.33)	160 (0.11)
Factor Xa inhibitors	1613 (1.14)	240 (0.17)
UFH	2489 (1.76)	401 (0.28)
LMWH	3989 (2.82)	227 (0.16)
DTIs	59 (0.04)	10 (0.01)
Antiplatelets	4135 (2.92)	515 (0.36)
Aspirin ^e	3776 (2.67)	528 (0.37)
tPA	269 (0.19)	39 (0.03)
Remdesivir	987 (0.70)	8 (0.01)
Corticosteroids	19 389 (13.71)	1472 (1.04)
Convalescent plasma	174 (0.12)	0
Antithrombin III	1 (0.00)	0

Abbreviations: DTI, direct thrombin inhibitor; LMWH, low-molecular weight heparin; tPA, tissue plasminogen activator; UFH, unfractionated heparin.

^aPrior use was defined as documentation of the medication(s) of interest during the 45-day period prior to the index date.

^bFollow-up use was defined as documentation of the medication(s) of interest on or after the index date.

^cThe medications of interest included anticoagulants, antiplatelets, aspirin, tPA, remdesivir, corticosteroids, convalescent plasma, and antithrombin III.

^dAnticoagulants included vitamin K antagonists, factor Xa inhibitors, UFH, LMWH, and DTIs.

^eAspirin may be underrepresented if not included in insurance claims.

40.1% of outpatients who developed a thromboembolic event versus 5.8% of all outpatients.

Discussion

Overall, thromboembolic events occurred in 1.4% of patients and death in <1% of patients in this very large cohort of 141,471 COVID-19 outpatients who did not require hospitalization. The characteristics of all outpatients suggested a relatively young, healthy population, albeit most were overweight or obese. Those who developed thromboembolic events had characteristics of older age, male sex, African American race, and obesity. In addition, the comorbidity index of outpatients with thrombosis was suggestive of substantial comorbidity burden and certain conditions associated with more severe COVID-19 disease,¹⁵ including congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, anemia, liver disease, diabetes, and cancer. A substantial proportion of outpatients who developed thromboembolic events during COVID-19 follow-up had a history of prior thromboembolic events and were already receiving anticoagulants during the 12-month baseline period.

Our study results are in line with results of a recent large outpatient study of 10 871 pre-hospitalized adults with COVID-19.¹⁶ That study found a VTE rate of 1.09%, which is very similar to our study results. In addition, that study found that many adults had multiple cardiovascular comorbidities, including hypertension, hyperlipidemia, chronic lung disease, coronary artery disease, prior VTE, and very elevated D-dimer levels.¹⁶ Factors associated with VTE in COVID-19 patients include older age (≥ 65 years), active smoking, prior

stroke, extremes of BMI, and especially elevated D-dimer levels.^{17,21}

COVID-19 induces a pro-coagulant state likely related to systemic inflammation; release of pro-inflammatory cytokines, including interleukins, interferons, and tumor necrosis factor; and endothelial cell dysfunction.^{3,6,7} Hypercoagulability also triggers the formation of pulmonary microthrombi, overactivation of serum complement, and alteration of cardiac biomarkers and platelet function.^{6,7} In a report of 4 patients with COVID-19 who developed VTE at home, immobility and elevated D-dimer levels were documented in all patients prior to diagnosis.¹³ Moreover, an Italian cohort of 388 patients found VTE in 16 COVID-19 patients, half of whom were diagnosed within 24 h of hospital admission and 15 with elevated D-dimer levels.²² These data suggest that the increased risk of thromboembolic events not only occurs in patients who do not require hospitalization but may begin prior to development of more severe symptoms and complications of COVID-19.²³

A prospective cohort study found that COVID-19 outpatients who were receiving anticoagulation at the time of diagnosis had a 43% reduced risk of hospitalization, highlighting a need for studies to determine the optimal type, dose, and duration of anticoagulant therapy.²⁴ A number of trials have been initiated to evaluate direct oral anticoagulants in COVID-19 outpatients at risk of progression, with a few being stopped early due to futility and low event rates.^{12,23,25,26} The recently published ACTIVE 4b trial in COVID-19 outpatients with ≥ 1 cardiovascular risk factor suggested no advantages of the DOAC apixaban or aspirin in preventing key cardiovascular complications or hospitalization versus placebo, but was underpowered to detect differences as the trial was terminated early

due to futility.¹² The ongoing PREVENT-HD trial is a large outpatient placebo-controlled investigation currently evaluating the efficacy and safety of prophylactically dosed rivaroxaban in outpatients who have symptomatic COVID-19 and at least 1 additional thromboembolic risk factor.²³ The trial is set to be completed by May 2022.²⁷

Recommendations on the use of thromboprophylaxis in outpatients with thromboembolic risk factors have not reached consensus from medical societies and healthcare organizations. The VAS-European Independent Foundation in Angiology/Vascular Medicine recommends a prophylactic dose of lowmolecular weight heparin, rivaroxaban, or betrixaban in COVID-19 outpatients at high risk of VTE.²⁸ Whereas the Global COVID-19 Thrombosis Collaborative Group recommends increased mobility for outpatients with mild COVID-19 and consideration of thromboprophylaxis after risk assessment only on an individual basis.⁶ VTE risk should be assessed by IMPROVE or PADUA scores and weighed against the risk of bleeding. Conversely, the National Institutes of Health recommends that anticoagulants and antiplatelet therapy not be initiated for prevention of VTE or arterial thrombosis in non-hospitalized COVID-19 patients unless there are other indications for therapy or they are participating in a clinical trial.²⁹

Our study has several strengths and limitations. Using a large and geographically diverse database, this observational and descriptive study provides results that are generalizable to adult COVID-19 patients across the United States, representing most racial/ethnic groups but few Asian patients. The database also allows near real-time analysis of real-world data with a lag time of only 1 to 2 months. Identification of COVID-19 patients using diagnostic tests should have limited false positive results. However, there are some limitations to this analysis, including the requirement for healthcare provider organizations to participate in the EHR network in order to be included; therefore, data on the geographic distribution of the cohort may be impacted by geographic differences in participation. Differences in data availability for individual patients related to laboratory tests for specific medical conditions may impact demographics and clinical characteristics, and death data may not be available for all patients. Furthermore, to protect privacy, the date of death is defined in the Optum[®] database as the last day of the calendar month during which the patient died; thus, the time of death in this study is an estimation. EHR data capture written prescriptions, but that does not necessarily indicate that the medication was administered or taken, and use of over-the-counter medications, such as aspirin, may be underestimated. Outpatients with COVID-19 are a heterogeneous group and a limitation of this analysis is the inability to assess patient mobility. Some COVID-19 outpatients may not visit a healthcare provider due to mobility limitations and stay isolated at home in bed with an increased risk of thrombosis that could not be captured in our analysis. The outcomes of this analysis are presented descriptively, such that differences in patient characteristics and treatment objectives are not controlled and therefore may limit interpretability of the results of this study. Finally, due to the observational and descriptive nature of this study, causal inferences between treatments and outcomes were not assessed.

Key Points/Clinical Implications

- In >141,000 adults with COVID-19 who were not hospitalized, the incidence of thromboembolic events was 1.4% and <1% of patients died
- Patients who had a thromboembolic event were typically of older age, male sex, African American race, and obese with a higher burden of comorbidities
- These findings provide valuable information regarding monitoring and treating patients with COVID-19 who do not require hospitalization for potential thromboembolic events
- The study was limited by its observational design, descriptive analysis, and characteristics of EHR data that precluded analysis of patient mobility

Conclusions

In this large real-world analysis of more than 141 000 COVID-19 outpatients in the United States, the occurrence of thromboembolic events was 1.4% and the occurrence of death was <1%. Demographic and clinical characteristics known to be associated with an increased risk of thromboembolic events were also observed in the study cohort. These results may help guide management decisions for potential use of primary thromboprophylaxis, including future clinical trial designs for high-risk outpatients with COVID-19.

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Author Contributions

A.C. Spyropoulos, J.M. Crawford, and W.F. Peacock contributed to the analysis and/or interpretation of data; critical writing or revising the intellectual content; and final approval of the version to be published. Y.-W. Chen, V. Ashton, A.K. Campbell, D. Milentijevic contributed to the concept and design, analysis and/or interpretation of data; critical writing or revising the intellectual content; and final approval of the version to be published.

Data Availability

Data for these analyzes were made available to the authors through third-party license from Optum[®], a commercial data provider. As such, the authors cannot make these data publicly available due to data use agreement. Other researchers can access these data by purchasing a license through Optum[®]. Inclusion criteria specified in the Methods section would allow other researchers to identify the same cohort of patients we used for these analyzes. Interested individuals may see <https://www.optum.com/business/solutions/life-sciences/explore-data.html> for more information on accessing Optum[®] data.



Declaration of Conflicting Interests

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ORCID iDs

W. Frank Peacock  <https://orcid.org/0000-0002-2730-6742>
 Alex C. Spyropoulos  <https://orcid.org/0000-0002-3175-461X>

Supplemental Material

Supplemental material for this article is available online.

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