Venous thromboembolism and major bleeding in patients with COVID-19:

A nationwide population-based cohort study

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Summary: Risks of venous thrombolism and major bleeding were low to moderate in hospitalized and community-managed COVID-19 patients. These risks were comparable with patients suspected of but testing negative for SARS-CoV-2 and with influenza patients.

Abstract

Background: Venous thromboembolism (VTE) is a potentially fatal complication of SARS-CoV-2 infection and thromboprophylaxis should be balanced against risk of bleeding. This study aimed to examine risks of VTE and major bleeding in hospitalized and community-managed SARS-CoV-2 patients compared with control populations.

Methods: Using nationwide population-based registries, 30-day risks of VTE and major bleeding in SARS-CoV-2 positive patients were compared with those of SARS-CoV-2 test-negative patients and with an external cohort of influenza patients. Medical records of all COVID-19 patients at six departments of infectious diseases in Denmark were reviewed in detail.

Results: The overall 30-day risk of VTE was 0.4% (40/9,460) among SARS-CoV-2 patients (16% hospitalized), 0.3% (649/226,510) among SARS-CoV-2 negative subjects (12% hospitalized), and 1.0% (158/16,281) among influenza patients (59% hospitalized). VTE risks were higher and comparable in hospitalized SARS-CoV-2 positive (1.5%), SARS-CoV-2 negative (1.8%), and influenza patients (1.5%). Diagnosis of major bleeding was registered in 0.5% (47/9,460) of all SARS-CoV-2 positive individuals and in 2.3% of those hospitalized. Medical record review of 582 hospitalized SARS-CoV-2 patients observed VTE in 4% (19/450) and major bleeding in 0.4% (2/450) of ward patients, of whom 31% received thromboprophylaxis. Among intensive care patients (100% received thromboprophylaxis), risks were 7% (9/132) for VTE and 11% (15/132) for major bleeding.

Conclusions: Among people with SARS-CoV-2 infection in a population-based setting, VTE risks were low to moderate and were not substantially increased compared with SARS-CoV-2 test-negative and influenza patients. Risk of severe bleeding was low for ward patients, but mirrored VTE risk in the intensive care setting.

Keywords: COVID-19, venous thromboembolism, pulmonary embolism, deep venous thrombosis, hemorrhage, bleeding.

Introduction

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) and the disease it causes, Corona Virus Disease 2019 (COVID-19), has put healthcare systems worldwide under tremendous pressure.

Venous thromboembolism (VTE) is a potentially fatal complication of hospitalization for surgery or medical conditions including infections. COVID-19 may confer an increased risk of VTE by endothelial dysfunction and inflammatory mediated activation of the coagulation cascade, but also indirectly by immobilization, need for central venous catheter, and mechanical ventilation during admission at an intensive care unit (ICU) [1,2]. Yet, the magnitude and duration of this risk in COVID-19 is unclear and recent observational studies have suggested that VTE occurred during hospitalization in 1-7% of non-ICU patients and 7-35% of ICU patients [3–10]. However, these studies consist of small sample sizes of selected patient populations from single or a few hospitals with short and incomplete follow-up and often lack control groups for comparison [3–10]. In addition, although 3/4 of VTE events are thought to occur outside the hospital setting [11], data on risks among community-managed patients with COVID-19 remain scarce.

This study combined nationwide registries with manual chart review to examine absolute risks of VTE and major bleeding in non-hospitalized and hospitalized patients with a positive test for SARS-CoV-2. Moreover, risks of VTE and bleeding were compared with non-hospitalized and hospitalized patients with a negative test for SARS-CoV-2 and with influenza patients.

Methods

Setting

The study was conducted in Denmark where all ~5.800.000 inhabitants are provided with universal, tax-supported health-care, free of charge at the point of delivery. All residents are assigned a unique 10-digit civil registration system (CRS) number, which is used for all health-care contacts, including hospitalizations and prescription medicine, and facilitates individual-level linkage between

nationwide Danish registries [12]. The study period was January 27 to June 1, 2020. As of April 21, 2020, the SARS-CoV-2 test strategy in Denmark changed from examining only symptomatic persons to testing all patients admitted to hospital >24 hours and asymptomatic individuals potentially exposed for SARS-CoV-2 (Supplementary material) [13]. All clinical tests for SARS-CoV-2 during the study period were analyzed at departments of clinical microbiology using reverse-transcriptase polymerase-chain-reaction (PCR). On April 17, 2020, the Danish Society of Thrombosis and Hemostasis introduced a guideline on thromboprophylaxis of COVID-19 patients suggesting intermediate doses of low-molecular weight heparin (LMWH) to ICU patients and low dose LMWH to all ward patients.

Data sources

Data sources for this study included nationwide, population-based administrative health registries combined with electronic medical record (EMR) review in a subgroup of patients (Figure 1).

Established in 1967, the CRS database was used for information on date of birth, sex, and migration and vital status for all study subjects with <0.3% lost to follow-up [12]. The Microbiological Database (MiBa) was used to identify all patients with SARS-CoV-2 confirmed by PCR assays performed on upper or lower respiratory tract specimens [14]. It has received real-time reports from all departments of clinical microbiology in Denmark since 2010. MiBa was also accessed to identify patients with a negative test for SARS-CoV-2. The National Patient Registry was used for information on all hospital admissions, comorbidity, VTE, and bleeding events (Supplementary Table 1) [15]. It keeps record of complete WHO International Classification of Diseases (ICD) diagnosis codes on all inpatient hospitalizations since 1977 and outpatient hospital contacts in Denmark since 1995. For each hospitalization, a treating physician assigns one primary discharge diagnosis code for the condition that prompt hospitalization, and mainly affects treatment course, and up to 20 secondary

codes. The National Prescription Registry holds data on reimbursed prescriptions at community pharmacies by Anatomical Therapeutic Chemical (ATC) codes since 1995 [16]. It was accessed to obtain data on medication use before hospital admission and after discharge (Supplementary Table 1).

In addition, EMRs of all COVID-19 patients treated at departments of infectious disease at Aarhus, Odense, Hvidovre, Rigshospitalet (Copenhagen), Hillerød, and Aalborg university hospitals were reviewed. Clinical data was extracted including data on comorbidities, medication use before and during admission, tobacco and alcohol habits, signs and symptoms at admission, laboratory tests, radiological examinations, and occurrence of VTE or major bleeding events. These data were managed using Research Electronic Data Capture browser-based software (REDCap, Vanderbilt, TN, USA).

Study cohorts

First, using health-care registries, a cohort comprising all cases of SARS-CoV-2 infection Denmark, diagnosed until May 1st, 2020 was assembled. Second, because VTE risk may be related to acute illness in general rather than pathophysiological effects of SARS-CoV-2 *per se*, a comparison cohort comprising all non-hospitalized and hospitalized patients who tested negative for SARS-CoV-2 (and remained test-negative) until May 1st, 2020 was identified. Third, as an additional point of comparison, an external cohort of adults born before 1978 with laboratory-confirmed influenza from 2010 through 2018 was used to examine if SARS-CoV-2 confers a greater VTE risk than another serious viral respiratory infection [17].

For increased clarity on diagnostic exams and in-hospital management of COVID-19 patients, EMRs of all patients hospitalized with laboratory-verified SARS-CoV-2 at six departments of infectious diseases in Denmark from February 27th (day of first Danish patient diagnosed with COVID-19) through May 4th, 2020, were reviewed.

Outcome events

In the registry-based cohort analyses, VTE and major bleeding events were defined as any discharge diagnosis code made either during index-hospitalization (for patients already hospitalized on date of microbiological testing) or during new hospitalization within 30 days after microbiological testing. In an additional analysis including prescription data, VTE was defined by either a diagnosis code for VTE or a post-discharge reimbursed prescription for new anticoagulant therapy likely due to VTE, as indicated by an algorithm based on relevant ATC codes (Supplementary Table 2).

In the EMR cohort analysis, VTE was defined as a deep vein thrombosis (DVT) diagnosed by compression ultrasound or pulmonary embolism (PE) diagnosed by CT pulmonary angiography or lung scintigraphy according to the radiologist's description. Date of VTE was categorized as the day of diagnostic imaging. Major bleeding events were defined as 1) any diagnosis of central nervous system, retroperitoneal or intraocular bleeding, 2) clinical bleeding requiring transfusion of >1 unit of blood, or significant medical or surgical intervention, 3) bleeding significantly contributing to death as judged by the treating physician.

Statistics

Categorical variables were presented as numbers and percentages with 95% confidence intervals (CI) and continuous variables as medians with interquartile ranges (IQR). Covariate balances were examined using standardized mean differences. No patients had missing data on exposure or primary outcome and the primary analyses included all study participants.

The date of microbiological testing was defined as cohort entry (index) date. Individuals were excluded if they had either VTE during the year prior to microbiological testing, less than one year of enrollment in the database prior to test date or emigrated out of the country less than 30 days after sample date. All study subjects in registry-based cohorts were followed from the index date until completion of 30 days of follow-up, death or June 1st, 2020, whichever came first.

For each study cohort, 30-day absolute risks of VTE, major bleeding events, and mortality were computed. Subgroup analyses were performed by age group (0-64, 65+ years of age), sex, presence of risk-factors for VTE (yes/no), and Charlson Comorbidity Index (CCI of 0 and CCI ≥1) [18]. A limited number of primary outcomes among SARS-CoV-2 positive patients precluded planned adjusted analyses of relative risk.

Subjects in the EMR cohort were followed from date of SARS-CoV-2 test until date of VTE, major bleeding, death, emigration out of Denmark, or date of last medical record review (May 4th), whichever came first. Next, 30-day risks of VTE, bleeding, and mortality were computed and stratified by ICU admission (yes/no). In non-ICU patients, risk estimates were further examined by

receipt of anticoagulant therapy (all ICU patients received at least standard dose thromboprophylaxis).

Stata 16.1 (Stata Corp., College Station, TX) was used for all analyses.

Ethics

The study was approved by the Danish Board of Health (ID: 31-1522-84) and registered at the University of Southern Denmark (ID: 10.960) and the legal authorities in North Denmark Region (ID: 2020-045). Thus, patient consent or approval from an ethical committee was not required for this study in Denmark.

Results

Registry-based cohorts

Data retrieval from Danish registries yielded 9,460 SARS-CoV-2 positive patients between February 27th and May 4th, 2020 (1,540 hospitalized; 16%), and 226,510 SARS-CoV-2 negative patients in the same period (26,131 hospitalized; 12%). Between 2010 and 2018, we identified 16,281 patients tested positive with influenza (9,599 hospitalized; 59%). Among hospitalized patients, median age and proportion of males were 72 years (IQR 58-81) and 57% (872/1,540) for SARS-CoV-2 positive patients, 68 years (48-78) and 50% (13,100/26,131) for SARS-CoV-2 negative individuals, and 70 years (59-80) and 51% (4,688/9,599) for influenza patients (Table 1). Presence of comorbidity (CCI >0) at admission was found in 36% (558/1,540) of hospitalized SARS-CoV-2 positive patients, 38% (10,035/26,131) of hospitalized SARS-CoV-2 negative individuals, and 49% (4,717/9,599) of hospitalized influenza patients.

Overall 30-day risk for VTE was 0.4% (40/9,460) among SARS-CoV-2 positive patients compared with 0.3% (649/226,510) for SARS-CoV-2 negative patients and 1.0% (158/16,281) among influenza patients. Among hospitalized patients, risks for VTE were 1.5% (23/1,540) in SARS-CoV-2 positive patients compared with 1.8% (483/26,131) in SARS-CoV-2 negative patients and 1.5% (147/9,599) in hospitalized influenza patients (Tables 2 and 3). In additional analyses using both discharge diagnoses and prescription data to confirm VTE, risk of VTE increased to 2.3% (36/1,540) in hospitalized SARS-CoV-2 positive patients and 2.2% (576/26,131) in hospitalized SARS-CoV-2 negative patients. For all cohorts, risk for PE was approximately three-fold greater than the risk for DVT.

Major bleeding events among hospitalized study participants occurred in 2.3% (36/1,540) of SARS-CoV-2 positive patients, 4.5% (1,170/26,131) of SARS-CoV-2 negative individuals, and 2.4% (234/9,599) of influenza patients.

Thirty-day mortality was 5.5% (523/9,460) among all individuals with a positive test for SARS-CoV-2, 1.3% (2,946/226,510) in SARS-CoV-2 negative patients, and 5.7% (932/16,281) in influenza patients.

EMR cohort

During the study period, 582 patients were treated for SARS-CoV-2 at six departments of infectious disease in Denmark (Table 4). The median age was 69 years (54-78) and 58% were male (335/582). At least one pre-existing risk factor for VTE was observed in 22% of patients (130/582) with body mass index >35 kg/m^2 as the most frequent (8%; 49/582). Median duration of COVID-19 symptoms before admission was 7 days (IQR 4-10) and common symptoms included history of fever in 82%

(445/542), cough in 77% (417/543), and dyspnea in 70% (373/535) of patients. Blood tests at admission showed a median c-reactive protein level of 57 mg/L (IQR 29-120) and D-dimer of 0.87 mg/L (IQR 0.49-1.50). Radiological examinations included chest x-ray in 94% (545/582) of patients, computed tomography of the chest in 13% (76/582), and compression ultrasound of lower extremities in 3% (16/582). In total, 23% (132/582) of patients were admitted to ICU and 19% (109/582) were mechanically ventilated.

Anticoagulant therapy was used in 31% (140/450) of ward patients and 100% (132/132) of ICU patients during admission, primarily as prophylactic dose low-molecular weight heparin (Table 5). Overall, VTE occurred in 5% (28/582) of hospitalized patients after exclusion of five patients with a presumptive diagnosis of PE but without radiological confirmation. Major bleeding was observed in 3% (17/582) and 20% (124/582) had a fatal outcome. Risk of VTE was 4% (19/450) among ward patients and 7% (9/132) among patients admitted at the ICU.

For ward patients receiving thromboprophylactic therapy, VTE occurred in 3% (4/140) and major bleeding was observed in 1% (2/140) patients. For ward patients not treated with thromboprophylaxis, VTE was found in 5% (15/310) and major bleeding in 0% (0/310) patients. All patients admitted at the ICU received anticoagulant therapy and major bleeding was observed in 11% (15/132).

Discussion

In this Danish nationwide, population-based cohort study, 30-day risk of VTE was 0.2% among non-hospitalized and 1.5% in hospitalized SARS-CoV-2 patients (2.3% when adding prescription data). In comparison, major bleeding events occurred in 0.1% of non-hospitalized and 2.3% of hospitalized SARS-CoV-2 positive patients. Risks of VTE and major bleeding were slightly higher by medical record review and were comparable with those of SARS-CoV-2 negative individuals and influenza patients.

Studies addressing VTE risk in SARS-CoV-2 are mostly limited by small or moderate sample sizes from single- or a few centers with selected patient populations and incomplete follow-up [3–10]. In addition, some studies used VTE screening and included asymptomatic VTEs and subsegmental PE, both of which are of uncertain clinical relevance [19]. Consistent with the current study, several other studies have found VTE risks of 3-7% among ward patients and 7-8% in ICU patients [10,20–23].In contrast, VTE was observed in 3% of non-ICU patients and in 23-35% of ICU patients in two Dutch studies where VTE screening and thromboprophylaxis was standard [4,8]. Another two ICU studies observed risks of VTE of 17-21% in SARS-CoV-2 patients compared with 8% in influenza patients and 1% (odds ratio 15.2) in a heterogenous group of ARDS patients [6,9]. In comparison, relatively few cases of VTE were diagnosed in the current study despite more restricted use of thromboprophylaxis. Reasons for the large discrepancy in VTE risk between studies are unclear. Among hospitalized patients in the current study, VTEs may have gone undetected either through lack of clinical suspicion or due to barriers in performing diagnostic exams such as chest CT's in mechanically ventilated ICU patients. Still, mortality rates among hospitalized COVID-19 patients in our study were comparable with or lower than other studies suggesting that missed fatal VTEs were limited [10,21–23]. Moreover, difficulty with diagnostic imaging is unlikely to explain the observed low risk estimates in non-hospitalized patients and non-ICU patients, and compression ultrasound is relatively easy to perform and DVT was rarely diagnosed.

Since most previous studies of VTE in SARS-CoV-2 infection lack comparison cohorts, it remains unclear if risk exceeds that of other infections or medical conditions [24–26]. Danish registry-based studies on bacteremia observed absolute VTE risks comparable to estimates in the present study [27,28], whereas others have found a VTE incidence of 37% in 113 ICU patients with severe sepsis

despite universal use of guideline-recommended thromboprophylaxis [29]. However, most sepsis patients in that study had DVT and PE was only found in 4%.

SARS-CoV-2 may induce thrombosis by immobilization and hospitalization [11]. More directly, the virus may also cause endothelial dysfunction by cell invasion and has been found to invoke hyperinflammation, anti-phospholipid antibody production, and coagulopathy [2]. Some authors suggest that formation of local pulmonary microangiopathic immune-thrombosis may account for a substantial proportion of observed VTEs in SARS-CoV-2 patients rather than embolization from the lower extremities [30,31]. Although many of these attributes of SARS-CoV-2 have received considerable attention, the very same characteristics have also previously been recognized among a number of other pathogens including viruses [24–26].

Thus far, autopsy studies of deceased SARS-CoV-2 patients have yielded varying results ranging from no VTEs [30,32] to findings of DVT in 58% (7/12) and PE in 33% (4/12) of patients [33]. This is consistent with older autopsy studies on more than 5,000 patients where PE were frequent and found in up to 70% of patients who died from infection, primarily pneumonia and sepsis [34,35].

Several guidelines and position papers recommend thromboprophylaxis for all hospitalized COVID-19 patients and some even suggest increased dose thromboprophylaxis and extended anticoagulation for up to 45 days post-discharge in selected COVID-19 patients [36–38]. Still, intermediate or therapeutic dose anticoagulation has had little impact on risk of VTE or mortality in previous studies of COVID-19 and was associated with major bleeding events in the current study [4–6,8,9,39–41]. Thus, the present evidence base for aggressive thromboprophylaxis in COVID-19 patients is uncertain and risk-benefit of high dose heparin therapy should be considered while data from ongoing clinical trials are awaited [42,43].

This study has limitations. Surveillance bias of VTE may be present as diagnostic imaging can be difficult to perform in isolated and mechanically ventilated ICU patients, or patients may have died with undiagnosed VTE. This would result in an underestimation of absolute VTE risk in both severely ill SARS-CoV-2 and influenza patients, but it is unlikely to substantially affect the relative comparison of incidence in these patient groups. On the other hand, since VTE occurrence in SARS-CoV-2 patients received massive attention towards the end of the study period, this may have prompted an increased diagnosis of PEs compared with SARS-CoV-2 negative and influenza patients. Although we were able to include all 9,460 SARS-CoV-2 test positive patients in Denmark until May 1, 2020, the national test strategy in this phase was directed at those who were most sick and in need of medical care. A serological survey indicated that 1.1% (n~63,400) of Danish residents had been infected by May 2020 (municipality screening available at www.ssi.dk). Thus, our results are most generalizable to persons with clinically confirmed SARS-CoV-2 infection. Furthermore, missed infections occurring before or after a negative PCR test in test-negative individuals may have diluted any risk differences between test-positive and test-negative individuals. Changes in test strategy during the study period may have resulted in inclusion of less ill and comorbid SARS-CoV-2 positive and negative patients, whereby proportions experiencing the primary outcome would likely decrease. Still, absolute risks of VTE were consistently low among hospitalized SARS-CoV-2 positive individuals. Although the positive predictive value (PPV) of VTE codes in the National Patient Registry are 86-90% for first-time events [44], the sensitivity for VTE in hospitalized SARS-CoV-2 positive patients and hospitalized comparison cohorts may be more moderate as suggested by the higher rates observed by EMR review. Another limitation was lack of information on thromboprophylaxis and in-hospital therapy in registry-based analyses. However, EMR review suggested that use of thromboprophylaxis was very frequent in ICU patients (100%), but rather limited in non-ICU patients in Denmark (31%) compared with other settings.

In this Danish population-based cohort, SARS-CoV-2 was associated with low risk for VTE among non-hospitalized patients and a moderate risk among hospitalized patients. Importantly, VTE risk was not substantially increased compared with hospitalized SARS-CoV-2 test-negative and influenza patients. Diagnosis of major bleeding in non-hospitalized and hospitalized SARS-CoV-2 patients mirrored that of VTE.

NOTES

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Author contributions:

MDP and JB conceived study. MDP, JB, RWT, AP, NBJ, MH, LCL, and HN designed the study. LCL did the registry-based analyses. Medical record review was conducted by JB, RW, TM, OS, SLN, LFL, SBI, LHO and was analyzed by JB. MDP wrote the first draft, which has been critically revised and approved by all authors.

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Table 1: Registry-based analyses of baseline characteristics for SARS-CoV-2 positive, SARS-CoV-2 negative, and influenza patients (n/N, % or median with interquartile ranges [IQR]).

	Non-hospitalized					Hospitalized				
	SARS-CoV-2 positive	**SARS-CoV-2 negative**	**SMD (SARS + v. SARS-)**	**Influenza patients**	**SMD (influenzav. SARS+)**	**SARS-CoV-2 positive**	**SARS-CoV-2 negative**	**SMD (SARS + v. SARS-)**	**Influenza patients**	**SMD (Influenza v. SARS+)**
N (% of N)	**7,920 (83.7)**	**200,379 (88.5)**		**6,682 (41.0)**		**1,540 (16.3)**	**26,131 (11.5)**		**9,599 (59.0)**	
Age, median (IQR)	46 (32-58)	45 (31-58)	0.10	55 (46-67)	0.68	72 (58-81)	68 (48-78)	0.36	70 (59-80)	0.01
Sex (Female)	4,825 (60.9)	130,171 (65.0)	0.08	3,696 (55.3)	0.11	668 (43.4)	13,100 (50.1)	0.14	4,688 (48.8)	0.11
Charlson score										
0	7,141 (90.2)	179,086 (89.4)	0.03	5,368 (80.3)	0.28	982 (63.8)	16,096 (61.6)	0.04	4,882 (50.9)	0.26
1-2	668 (8.4)	18,416 (9.2)	0.03	1,047 (15.7)	0.22	403 (26.2)	6,999 (26.8)	0.01	3,443 (35.9)	0.21
≥3	111 (1.4)	2,877 (1.4)	0.00	267 (4.0)	0.16	155 (10.1)	3,036 (11.6)	0.05	1,274 (13.3)	0.10
VTE risk factors	1,403 (17.7)	41,321 (20.6)	0.07	1,567 (23.5)	0.14	658 (42.7)	12,790 (48.9)	0.13	4,039 (42.1)	0.01
Previous VTE	194 (2.4)	4,361 (2.2)	0.02	222 (3.3)	0.05	120 (7.8)	1,697 (6.5)	0.05	628 (6.5)	0.05

Surgery[a]	92 (1.2)	3,321 (1.7)	0.04	187 (2.8)	0.12	149 (9.7)	3,719 (14.2)	0.14	1,119 (11.7)	0.06
Hospitalized[a]	129 (1.6)	2,089 (1.0)	0.05	257 (3.8)	0.14	231 (15.0)	3,560 (13.6)	0.04	1,393 (14.5)	0.01
Trauma[a]	66 (0.8)	1,744 (0.9)	0.00	50 (0.7)	0.01	71 (4.6)	1,284 (4.9)	0.01	238 (2.5)	0.12
Active cancer	126 (1.6)	4,378 (2.2)	0.04	265 (4.0)	0.14	125 (8.1)	3,410 (13.0)	0.16	1,125 (11.7)	0.12
Obesity	623 (7.9)	19,409 (9.7)	0.06	496 (7.4)	0.02	189 (12.3)	2,930 (11.2)	0.03	829 (8.6)	0.12
Pregnancy	129 (1.6)	4,322 (2.2)	0.04	72 (1.1)	0.05	10 (0.6)	1,409 (5.4)	0.28	24 (0.3)	0.06
Dialysis	7 (0.1)	229 (0.1)	0.01	60 (0.9)	0.12	22 (1.4)	281 (1.1)	0.03	102 (1.1)	0.03
Thrombophilia	24 (0.3)	778 (0.4)	0.01	19 (0.3)	0.00	5 (0.3)	102 (0.4)	0.01	31 (0.3)	0.00
HRT	259 (3.3)	8,337 (4.2)	0.05	374 (5.6)	0.11	76 (4.9)	1,065 (4.1)	0.04	478 (5.0)	0.00
Other comorbidity										
Atrial fibrillation	270 (3.4)	6,561 (3.3)	0.01	404 (6.0)	0.12	264 (17.1)	4,268 (16.3)	0.02	1,855 (19.3)	0.06
Hypertension	745 (9.4)	20,569 (10.3)	0.03	1,210 (18.1)	0.25	586 (38.1)	8,960 (34.3)	0.08	3,653 (38.1)	0.00
Heart failure	114 (1.4)	2,872 (1.4)	0.00	231 (3.5)	0.13	163 (10.6)	2,661 (10.2)	0.01	1,268 (13.2)	0.08
MI	131 (1.7)	3,517 (1.8)	0.01	255 (3.8)	0.13	117 (7.6)	2,147 (8.2)	0.02	985 (10.3)	0.09
Diabetes mellitus	379 (4.8)	10,237 (5.1)	0.01	505 (7.6)	0.12	287 (18.6)	4,036 (15.4)	0.08	1,708 (17.8)	0.02

COPD	178 (2.2)	6,959 (3.5)	0.07	434 (6.5)	0.21	199 (12.9)	4,241 (16.2)	0.09	2,286 (23.8)	0.28
Renal failure	88 (1.1)	2,175 (1.1)	0.00	310 (4.6)	0.21	132 (8.6)	2,138 (8.2)	0.01	960 (10.0)	0.05
Liver disease	94 (1.2)	2,625 (1.3)	0.01	117 (1.8)	0.05	44 (2.9)	1,121 (4.3)	0.08	377 (3.9)	0.06
Alcohol rel. disease	167 (2.1)	7,753 (3.9)	0.10	176 (2.6)	0.03	79 (5.1)	2,855 (10.9)	0.21	739 (7.7)	0.10
Pre-existing antithrombotic use										
VKA	47 (0.6)	1,514 (0.8)	0.02	181 (2.7)	0.17	64 (4.2)	1,127 (4.3)	0.01	842 (8.8)	0.19
DOACs	204 (2.6)	4,631 (2.3)	0.02	167 (2.5)	0.00	196 (12.7)	3,393 (13.0)	0.01	749 (7.8)	0.16
Aspirin	321 (4.1)	9,376 (4.7)	0.03	762 (11.4)	0.28	261 (16.9)	4,208 (16.1)	0.02	2,275 (23.7)	0.17
Clopidogrel	175 (2.2)	5,068 (2.5)	0.02	235 (3.5)	0.08	171 (11.1)	2,602 (10.0)	0.04	904 (9.4)	0.06
Others	12 (0.2)	546 (0.3)	0.03	70 (1.0)	0.12	20 (1.3)	284 (1.1)	0.02	265 (2.8)	0.10
Radiological examinations										
Chest CT	-	-	-	-	-	166 (11)[b]	4,126 (16)	0.15	1,099 (11)	0.02
Ultrasound of legs	-	-	-	-	-	26 (2)[b]	610 (2)	0.02	107 (1)	0.05

Abbreviations: COPD, chronic obstructive pulmonary diseases; CT, computerized tomography; DOAC, direct oral anticoagulants; HRT, hormone replacement therapy; MI, myocardial infarction; SARS, severe acute respiratory syndrome corona virus 2; SMD, standardized mean differences; VKA, Vitamin K antagonist; VTE, venous thromboembolism.

[a] Surgery, hospitalization, trauma within 30 days. [b] Comparing the first half (February 27 through March 31) with the second half (April 1 through April 30, 2020) of the inclusion period in SARS-CoV-2 positive patients, chest CT was performed in 98/991 (10%) vs. 68/549 (12%) and ultrasound of the legs in 15/991 (2%) vs. 11/549 (2%).

Table 2: Registry-based data of 30-day risks of VTE (n/N, %) in SARS-CoV-2 test positive or negative patients.

	Non-hospitalized			Hospitalized[a]		
	SARS-CoV-2			SARS-CoV-2		
Outcome	**Positive**	**Negative**	**Risk difference (95% CI)**	**Positive**	**Negative**	**Risk difference (95% CI)**
VTE (diagnoses only)	17/7,920 (0.2)	166/200,379 (0.1)	0.1 (0.0 to 0.2)	23/1,540 (1.5)[b]	483/26,131 (1.8)	-0.4 (-1.0 to 0.3)
Deep vein thrombosis	5/7,920 (0.1)	79/200,379 (0.0)	0.0 (0.0 to 0.1)	7/1,540 (0.5)	117/26,131 (0.4)	0.0 (-0.3 to 0.4)
Pulmonary embolism	12/7,920 (0.2)	87/200,379 (0.0)	0.1 (0.0 to 0.2)	16/1,540 (1.0)	366/26,131 (1.4)	-0.4 (-0.9 to 0.2)
VTE (incl. prescriptions)	24/7,920 (0.3)	206/200,379 (0.1)	0.2 (0.1 to 0.3)	36/1,540 (2.3)	576/26,131 (2.2)	0.1 (-0.6 to 0.9)
Major bleeding	11/7,920 (0.1)	474/200,379 (0.2)	-0.1 (-0.2 to 0.0)	36/1,540 (2.3)	1,170/26,131 (4.5)	-2.1 (-2.9 to -1.3)
VTE in subgroups						
VTE risk factors						
No	NA	90/159,058 (0.1)	-	NA	186/13,341 (1.4)	-
Yes	NA	76/41,321 (0.2)	-	NA	297/12,790 (2.3)	-
Sex						
Female	NA	86/130,171 (0.1)	-	NA	221/13,100 (1.7)	-
Male	NA	80/70,208 (0.1)	-	NA	262/13,031 (2.0)	-
Age						
0-64	10/6,758 (0.1)	91/172,156 (0.1)	0.1 (0.0 to 0.2)	11/523 (2.1)	153/11,608 (1.3)	0.8 (-0.5 to 2.0)
65+	7/1,162 (0.6)	75/28,223 (0.3)	0.3 (-0.1 to 0.8)	12/1,017 (1.2)	330/14,523 (2.3)	-1.1 (-1.8 to -0.4)

Charlson score						
0	NA	133/179,086 (0.1)	-	NA	309/16,096 (1.9)	-
≥1	NA	33/21,293 (0.2)	-	NA	174/10,035 (1.7)	-

Abbreviations: NA, not applicable as Danish regulations do not allow reporting of less than 5 individuals in each cell; SARS-CoV-2, severe acute respiratory syndrome corona virus 2; VTE, venous thromboembolism. [a] Numbers refers to start of follow-up. A large number of patients were hospitalized at end of follow-up, 201 SARS-CoV-2 positive patients and 2,712 SARS-CoV-2 negative patients. [b]Among hospitalized SARS-CoV-2 patients, VTE was diagnosed in 16/991 (1.6%) from February 27 through March 31 and in 7/549 (1.3%) from April 1 through April 30, 2020.

Table 3: Registry-based data of 30-day risks of VTE (n/N, %) in SARS-CoV-2 test positive and influenza patients.

Outcome	Non-hospitalized			Hospitalized[a]		
	SARS-CoV-2 positive	Influenza positive	Risk difference (95% CI)	SARS-CoV-2 positive	Influenza positive	Risk difference (95% CI)
VTE (diagnoses only)	17/7,920 (0.2)	11/6,682 (0.2)	0.0 (-0.1 to 0.2)	23/1,540 (1.5)[b]	147/9,599 (1.5)	-0.0 (-0.7 to 0.6)
Deep vein thrombosis	5/7,920 (0.1)	NA	-	7/1,540 (0.5)	NA	-
Pulmonary embolism	12/7,920 (0.2)	NA	-	16/1,540 (1.0)	NA	-
VTE (incl. prescriptions)	24/7,920 (0.3)	-	-	36/1,540 (2.3)	-	-
Major bleeding	11/7,920 (0.1)	32/6,682 (0.5)	-0.3 (-0.5 to -0.2)	36/1,540 (2.3)	234/9,599 (2.4)	-0.1 (-0.9 to 0.7)
VTE in subgroups						
VTE risk factors						
No	NA	NA	-	NA	NA	-
Yes	NA	NA	-	NA	NA	-
Sex						
Female	NA	6/3,696 (0.2)	-	NA	64/4,688 (1.4)	-
Male	NA	5/2,986 (0.2)	-	NA	83/4,911 (1.7)	-
Age						
0-64	10/6,758 (0.1)	5/4,723 (0.1)	0.0 (-0.1 to 0.2)	11/523 (2.1)	49/3,441 (1.4)	0.7 (-0.6 to 1.9)
65+	7/1,162 (0.6)	6/1,959 (0.3)	0.3 (-0.2 to 0.8)	12/1,017 (1.2)	98/6,158 (1.6)	-0.4 (-1.1 to 0.3)
Charlson score						

0	NA	NA	-	NA	NA	-
≥1	NA	NA	-	NA	NA	-

Abbreviations: NA, not applicable as Danish regulations do not allow reporting of less than 5 individuals in each cell; SARS-CoV-2, severe acute respiratory syndrome corona virus 2; VTE, venous thromboembolism. [a] Numbers refers to start of follow-up. A large number of patients were hospitalized at end of follow-up, 201 SARS-CoV-2 positive patients and 2,037 influenza patients. [b] Among hospitalized SARS-CoV-2 patients, VTE was diagnosed in 16/991 from February 27 through March 31 and in 7/549 from April 1 through April 31, 2020.

Table 4: Baseline characteristics of 582 patients hospitalized with SARS-CoV-2 at six departments of infectious diseases in Denmark, 2020.

	SARS-CoV-2	
	Observations, N	**n (%) or median (IQR)**
Age, years	582	69 (54-78)
Female sex	582	247 (42)
Pre-existing VTE risk factors	582	130 (22)
Previous VTE	582	28 (5)
Surgery within 30 days	582	15 (3)
Active/palliative cancer treatment <6 months	582	25 (4)
Body mass index >35 kg/m^2	582	49 (8)
Pregnancy	582	1 (0.2)
Dialysis	582	2 (0.3)
Genetic thrombotic coagulopathy	582	3 (0.5)
Airplane travel <30 days	582	3 (0.5)
Other comorbidity	582	412 (71)
Arterial hypertension	582	218 (37)
Congestive heart failure	582	33 (6)
Ischemic heart disease	582	51 (9)
Diabetes mellitus	582	111 (19)
COPD/asthma	582	101 (17)
Chronic kidney disease	582	37 (6)
Liver disease	582	8 (1)
Alcohol abuse	582	16 (3)
Immuno-suppressive treatment	582	27 (5)
Cancer	582	62 (11)
Pre-existing anticoagulant or antiplatelet therapy	582	141 (24)

Vitamin K antagonist	582	11 (2)
DOACs	582	54 (9)
Low molecular weight heparin	582	10 (2)
Acetylsalicylic acid or other platelet inhibitors	582	67 (12)
Duration of symptoms, days	510	7 (4-10)
Symptoms at admission		
Headache	460	160 (35)
History of fever	542	445 (82)
Cough	543	417 (77)
Sputum	495	154 (31)
Dyspnea	535	373 (70)
Clinical findings at admission		
Breaths per minute	567	20 (18-24)
Oxygen saturation without supplemental oxygen	447	96 (93-97)
Oxygen supplementation at admission	509	213 (42)
Temperature, ℃	566	38.0 (37.3-38.7)
Laboratory findings at admission		
C-reactive protein, mg/L	576	57 (29-120)
Blood leukocytes, 10^9/L	576	6.2 (4.7-8.4)
Lymphocytes, 10^9/L	555	0.9 (0.6-1.3)
Creatinine, µg/L	561	85 (68-106)
D-dimer, mg/L	187	0.87 (0.49-1.50)
International Normalized Ratio	346	1.0 (1.0-1.1)
Activated partial thromboplastin time, sec	115	26 (24-32)
Radiological examinations		
Chest x-ray	582	545 (94)
Pulmonary infiltrates or ARDS	545	482 (85)

Computed tomography of the chest	582	76 (13)
Pneumonic infiltrates or ARDS	76	70 (92)
Time from admission until first CT scan, days	76	7 (2-14)
Ventilation/perfusion scintigraphy	582	6 (1)
Ultrasound of deep veins of the leg during admission	582	16 (3)
Time from admission until ultrasound, days	16	11 (8-25)
Anticoagulant therapy during admission[a]	582	273 (47)
LMWH prophylactic doses	582	225 (37)
LMWH intermediate or high dose	582	52 (8)
DOAC	582	62 (10)
Vitamin K antagonist	582	7 (1)
Time from admission until start of anticoagulant therapy, days	243	2 (1-5)
Intensive care unit admission	582	132 (23)
Assisted respiration during admission	582	328 (56)
Ventilator	582	109 (19)
Duration of admission, days	551	7 (3-13)
Duration of follow-up among non-fatal cases, days	458	38 (27-44)
Time from admission until death, days	124	7 (5-16)
Time from admission until venous thromboembolism, days	30	8 (4-12)
Discharged from hospital or dead at end of follow-up	582	551 (95)

Abbreviations: VTE, venous thromboembolism; COPD, chronic obstructive pulmonary diseases; DOAC, direct oral anticoagulant; ARDS, adult respiratory distress syndrome; LMWH, low-molecular weight heparin. [a] Some patients changed anticoagulant therapy during admission, and some received simultaneous therapy with two anticoagulants.

Table 5: Risk of venous thromboembolism, major bleeding, and death by medical record review of patients hospitalized with SARS-CoV-2 at six departments of infectious diseases in Denmark, 2020.

		Non-ICU		ICU
	Total	**Anticoagulant therapy**	**No anticoagulant therapy**	**Anticoagulant therapy[a]**
Observations	**N=582**	**N=140**	**N=310**	**N=132**
VTE during admission or follow-up, n (% of N)	28 (5)	4 (3)	15 (5)	9[b] (7)
Pulmonary embolism	24 (4)	4 (3)	11[c] (4)	9[b] (7)
Deep vein thrombosis	6[d] (1)	0	4 (1)	2 (1)
Major bleeding during admission, n (% of N)	17 (3)	2[e] (1)	0	15[e] (11)
CNS, retroperitoneal or intraocular hemorrhage	3 (1)	0	0	3 (2)
Transfusion >1 unit of blood or significant intervention required	13 (2)	2 (1)	0	11 (8)
Hemorrhage as a contributing factor to death	3 (1)	0	0	3 (2)
In-hospital mortality, n (% of N)	124 (20)	31 (22)	42 (13)	48 (36)

Patients with VTE before death	4 (1)	1	0	3
Patient with major bleeding during admission before death	7 (1)	0	0	7

Abbreviations: VTE, venous thromboembolism; SARS-CoV-2, severe acute respiratory syndrome corona virus 2; CNS, central nervous system; ICU, intensive care unit. [a] Anticoagulant therapy consisted of standard dose LMWH in 90 patients, intermediate/high dose LMWH in 27 patients, DOACs in 14 patients, and vitamin K antagonist in one patient. [b] Three patients not receiving anticoagulant treatment were diagnosed with pulmonary embolism before they were transferred to the intensive care unit and anticoagulant treatment started. [c] Pre-existing risk factors before diagnosis of VTE were present in four patients (*i.e.* airplane travel within 30 days, active cancer treatment within six months combined with recent surgery within 30 days, hip surgery within 30 days, and previous deep vein thrombosis in one each). [d] Two patients were diagnosed with both deep vein thrombosis and pulmonary embolism. [e] For the two non-ICU patients with major bleeding, anticoagulant therapy consisted of standard dose LMWH in both patients. For the 15 ICU patients with major bleeding, anticoagulant therapy consisted of standard dose LMWH in eight patients, intermediate/high-dose LMWH in five patients, and DOACs in two patients.

Figure 1. Characteristics of study populations, covariate time windows, and follow-up time.

Figure 1