Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Thrombosis Research 208 (2021) 4–10

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Risk of symptomatic venous thromboembolism in mild and moderate COVID-19: A comparison of two prospective European cohorts

Delphine Douillet [a,b,c,*], Jérémie Riou [d,e], Andrea Penaloza [c,f], Thomas Moumneh [a,b,c], Caroline Soulie [g], Dominique Savary [a,h], Francois Morin [a], Rafaël Mahieu [i,j], Pierre-Marie Roy [a,b,c]

[a] Emergency Department, Angers University Hospital, Angers, France
[b] UNIV Angers, UMR MitoVasc CNRS 6015 - INSERM 1083, Angers, France
[c] FCRIN, INNOVTE, Saint Etienne, France
[d] UNIV Angers, UMR MINT, INSERM 1066 - CNRS 6021, Angers, France
[e] Methodology and Biostatistics Department, Delegation to Clinical Research and Innovation, Angers University Hospital, Angers, France
[f] Emergency Department, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Bruxelles, Belgium
[g] Emergency Department, Cholet Hospital, Cholet, France
[h] EHESP, Irset, UMR INSERM S1085, CAPTV CDC, University of Rennes, Rennes, France
[i] Department of Infectious Diseases, Angers University Hospital, Angers, France
[j] UNIV Angers, UMR CRCINA, INSERM 1232, SFR ICAT, Angers, France

ARTICLE INFO

Keywords:
Venous thromboembolism
SARS-CoV-2 infection
COVID-19
VTE risk

ABSTRACT

Background: Severely ill patients with SARS-CoV-2 have an increased risk of venous thromboembolism (VTE) i.e., deep vein thrombosis and pulmonary embolism. However, the VTE risk in patients with mild and moderate COVID-19, hospitalized or managed at home, remain uncertain. The aims of this study were to assess the rate and the risk factors symptomatic VTE, in patients with mild and moderate COVID-19 and to compare them to a cohort of similar patients without COVID-19.

Methods: Patients presenting to the emergency department (ED) of participating centers for confirmed or probable mild or moderate COVID-19 and not having acute VTE were included. This COVID-19 cohort was retrospectively compared to a prospective cohort of similar ED patients using propensity score matching. The main outcome was the rate of symptomatic VTE within the 28 days after ED presentation.

Results: A total of 2292 patients were included in the COVID-19 cohort. The 28-day incidence of symptomatic VTE was 1.3% ($n = 29/2292$, 95%CI: 0.9 to 1.8), 2.3% ($n = 20/866$, 95%CI: 1.5 to 3.5) in moderate COVID-19 patients and 0.6% ($n = 9/1426$; 95%CI: 0.3 to 1.2) in mild COVID-19 patients managed as outpatients. An age over 65 years and hospitalization were independent risk factors of VTE. After adjustment, patients in the COVID-19 cohort had an absolute increase in over symptomatic VTE risk of +1.69% (95%CI, 0.88 to 2.51) versus patients in the comparison cohort ($n = 1539$).

Conclusions: Patients with moderate COVID-19 presenting to the ED had a high risk of subsequent VTE.

Trial registration: Ethics committee of the CHU of Angers (N°2020/87).

1. Background

The coronavirus disease 2019 (COVID-19) viral pneumonia leads to hypoxia, a hyper-inflammatory state and immunothrombosis. A complex interaction between coagulopathy, thrombocytopathy and endotheliopathy contributes to COVID-19-associated thrombo-inflammation [1]. The initial reports from hospitals in Wuhan, China, showed that patients with severe COVID-19 had higher levels of D-dimer [2,3]. Subsequently, COVID-19 was reported to be associated with a high risk of venous thromboembolism (VTE), especially in critically ill patients [4–6]. The incidence of VTE was estimated at 9–47% in COVID-19 patients hospitalized in intensive care units [4–10] and at 9–19.8% in patients hospitalized in medical wards [7,11,12]. In contrast, some large retrospective studies did not observe a significant risk of VTE in

* Corresponding author at: Département de Médecine d'Urgence, Centre Hospitalier Universitaire d'Angers, 4 rue Larrey, 49100 Angers, France.
E-mail address: Delphine.Douillet@chu-angers.fr (D. Douillet).

https://doi.org/10.1016/j.thromres.2021.10.001
Received 7 July 2021; Received in revised form 30 September 2021; Accepted 3 October 2021
Available online 8 October 2021

hospitalized patients with COVID-19 [12,13]. Whether patients with mild and moderate COVID-19 have a higher risk of VTE than similar patients with another disease and whether they require specific thromboprophylaxis are still matter of debate. The International Society of Thrombosis and Haemostasis (ISTH) suggests that "in the absence of COVID-19-specific data, it is reasonable to consider extended-duration thromboprophylaxis with Low-Molecular Weight Heparin (LMWH) or a Direct Oral Anticoagulant (DOAC) for at least 2 weeks and up to 6 weeks post-hospital discharge in selected COVID-19 patients who are at low risk for bleeding and with key VTE risk factors." [14,15]. The American College of Chest Physician (ACCP) guidelines on the contrary suggest "inpatient thromboprophylaxis only over inpatient plus extended thromboprophylaxis after hospital discharge" [16]. Finally, to our knowledge, the rate of symptomatic VTE in patients with mild COVID-19 and who do not require hospitalization is unknown.

The aims of this study were to assess the rate and the risk factors of symptomatic VTE in patients with mild and moderate COVID-19 within the 28 days following an emergency department (ED) presentation, and to compare the VTE incidence in this COVID-19 cohort and in a prospective cohort of similar patients without COVID-19.

2. Methods

2.1. Study design

This study was a post-hoc analysis of a prospective multicenter cohort study of consecutive patients presenting to ED with mild and moderate COVID-19 and comparison with propensity score matching to another prospective cohort of similar patients who presented to the ED. The STROBE (Strengthening the reporting of observational studies in epidemiology) checklist was followed (Appendix S1).

2.1.1. COVID-19 cohort

The first cohort of COVID-19 patients came from the HOME-CoV study [17]. The HOME-CoV study was a pragmatic prospective multicenter before/after design trial which aimed to validate the HOME-CoV rule [18] in triaging patients with confirmed or probable mild to moderate COVID-19 for home treatment. The first period was observational and the decision between hospitalization and home treatment was left up to the emergency physicians according to their current practices. During the interventional period, the physicians had to apply the HOME-CoV rule [18]. Patients were selected for home treatment if all criteria were negative, and for hospitalization otherwise. Patients who were managed at home were followed by their general practitioners without "hospital at home" facilities [17]. Patients were included, with their informed consent, if they had symptomatic COVID-19 confirmed by a positive SARS-CoV-2 Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) or had typical symptoms of COVID-19 and COVID-19 was the most likely hypothesis according to the physician-in-charge. Screening by RT-PCR or performing a CT-scan was not systematic during patient management. Due to the low availability of RT-PCR tests at the time the study was performed, RT-PCR testing was not systematic and was mainly reserved for patients requiring hospitalization and/or when there was a diagnostic doubt. A CT-scan was performed in dyspneic patients as an alternative to chest X-ray and/or to exclude alternative diagnosis to COVID-19 pneumonia as acute pulmonary embolism. Patients with mild COVID-19 were defined as patients managed as outpatients. Patients with moderate COVID-19 were defined as hospitalized patients without mechanical ventilation. Patients who required intensive care were excluded. Between April and May 2020, in 34 EDs (31 in France, 2 in Belgium and one in the Principality of Monaco), 3133 patients were included. Patients were followed up by phone at Day 7 and Day 28 and the occurrence of a VTE was recorded. The date of the VTE diagnosis and the examination to authenticate the VTE event was recorded to allow analysis over time. Data on the prescription of preventive anticoagulants were collected.

2.1.2. Comparison cohort

The comparison cohort came from the PERCEPIC study [19]. This trial was designed to prospectively assess the predictive value of a negative PERC to rule out pulmonary embolism (PE). The PERCEPIC study was a multicenter, prospective, observational study. Participants were admitted in a participating ED with suspected PE (including dyspnea, chest pain, and other symptoms like syncope or hemoptysis) and had provided informed consent. Between May 2015 to April 2016, 12 EDs (9 in France and 3 in Belgium) participated and 1757 patients were included. The occurrence of a VTE event was assessed at 90 days from admission to the ED, the day of VTE diagnosis and the examination to authenticate the VTE event were recorded. No data on the prescription of preventive anticoagulant was collected.

2.2. Selection of participants in the present study

In both cohorts, patients were eligible for inclusion in the present study if they were admitted to the ED with acute dyspnea and/or chest pain and if they had undergone diagnostic testing for VTE in the ED: D-dimer test and/or Computed Tomography Pulmonary Angiogram (CTPA). The D-dimer threshold was adjusted for age, a level below agex10 ruling-out VTE in patients aged of fifty or more [20]. Patients for whom the diagnosis of VTE was established during the initial workup in the ED or within the 24 h following ED presentation, and patients lost to follow up at Day 28 were excluded.

2.3. Outcome measure

The outcome was the rate of symptomatic VTE occurring within the 28 days following ED presentation. The diagnostic strategy was leave free to the physicians. A VTE was defined as a symptomatic PE objectively confirmed by CTPA or a ventilation-perfusion scan and/or a symptomatic deep venous thrombosis (DVT) confirmed by leg vein compression ultrasonography (CUS).

2.4. Analysis

The outcome was compared between the COVID-19 cohort and the comparison cohort after adjustment using a weighting-based propensity score. Subgroup analysis were performed, using similar methods, according to the severity of symptoms and patients' management (mild or moderate COVID-19) and according to the level of certainty of the SARS-CoV-2 disease in the COVID-19 cohort (in patients with COVID-19 confirmed by a positive SARS-CoV-2 RT-PCR and in patients with a positive RT-PCR or a chest CT which indicated COVID-19 according to the local interpretation).

The impact of thromboprophylaxis and possible risk factors of subsequent VTE were analyzed in the overall cohort of COVID-19 patients.

2.5. Statistical analysis

For descriptive analysis, quantitative variables were reported as mean ± standard deviation (SD) when their distribution can be considered as Gaussian, and with median and interquartile ranges (IQR) otherwise. Qualitative variables were reported using numbers and proportions. Comparisons were performed using Student or Mann-Whitney tests for quantitative variables and using the Fisher Exact test for qualitative variables.

Hazard ratios (HR) with 95% confidence intervals (CI) were reported. $P < 0.05$ was considered as statistically significant. To analyse the VTE risk factors in COVID-19 patients, a multivariable model was built, including all variables identified in the literature as VTE risk factors with a p value <0.2 in the univariate analysis. We then performed a multiple linear regression with a backward stepwise elimination, while verifying the absence of collinearity between the explanatory variables.

Weighting-based propensity scores (Inverse Probability Weighting) was performed using the average treatment effect among the overlap population (ATO), to balance covariates between the COVID-19 and comparison cohorts (Table S1 and Fig. S1). Balance between groups was performed using the average treatment effect among the overlap population (ATO), which optimizes the efficiency of comparisons [21,22]. Once the patient profiles have been balanced between the two cohorts, a logistic regression including a random effect on the center was performed enabling computation of the confidence interval for the difference in event rates between the two cohorts was performed. The first step was a superiority analysis of the COVID cohort on the primary outcome (i.e., VTE rate during the 28-day follow up). The absolute risk difference between groups and 95%CI was computed. Time-to-event curves were calculated by means of the Kaplan–Meier method. The Scaled-Schoenfeld residuals were computed to check the proportionality assumption. Statistical tests were performed to validate the non-proportionality combined with a plot of these residuals against time. The same methodology was used, and the propensity scores were recalculated in the moderate form of COVID-19 subgroup (i.e., hospitalized patients) and in the mild form of COVID-19 subgroup (i.e., outpatients) and according to the COVID-19 status. Censored data represent the end of follow-up at the time of ceasing the data collection. The hierarchization of objectives allowed us to avoid the problem of multiplicity as much as possible. However, when a problem of multiplicity was encountered, a correction of the *p*-values was carried out using the Holm procedure allowing a strong control of the Family Wise Error Rate (FWER) at 5% risk. Statistical analyses were performed using R software (version 3.5.1, R-Core Team) and the following R package: pec, WeigthIt packages and Survey and plotted by Kaplan–Meier curves.

2.6. Ethical considerations

The present study obtained approval from the ethics committee of the CHU of Angers (N°2020/87).

3. Results

3.1. Population

Among 3133 patients in the HOME-CoV study, 2292 patients were included in the COVID-19 cohort for the present study and 841 patients were excluded. The reasons for exclusion were as follows: 189 patients did not have dyspnea or chest pain at ED admission, 360 did not have a D-dimer assay or a CTPA performed and 221 were lost to follow-up at D28. Finally, 71 (2.3%) patients were excluded because of a confirmed PE during the initial workup. The characteristics of the patients included are summarized in Table 1.

COVID-19 was confirmed by a positive RT-PCR for SARS-CoV-2 in 449/2292 (19.6%) patients. CT scans were indicative of a COVID-19 infection in 1059/2292 (46,2%) patients, 213 patients also had a positive SARS-CoV-2 RT-PCR. A total of 1426/2292 (62.2%) patients were considered to have a mild COVID-19 and were treated at home. Approximately 5% of patients had long-term anticoagulant treatment (123/2292) and 606/2169 (27.9%) patients received prophylactic treatment. Of those under thromboprophylactic treatment, 11.9% received intermediate or curative regimen (n = 72/606) and 88.1% current preventive dosage (n = 534/606) (Table S2). Of the other treatments, 63/2292 (2.7%) patients received hydroxychloroquine, 10/2292 (0.43%) received an antiviral drug (lopinavir or ritonavir), 660/2292 (28.8%) received an antibiotic therapy with mainly amoxicillin, azithromycin, or ceftriaxone, and 138/2292 (6.0%) patients were treated with corticosteroids.

3.2. Risk of venous thromboembolism

In the COVID-19 cohort, the VTE rate within the 28 days following ED presentation was 1.27% (95%CI: 0.88 to 1.81) (n = 29/2292). Among the 29 VTEs, 11 were DVT confirmed by CUS and 18 were non-high-risk PE confirmed by CTPA, 18 (62%) were treated with low molecular weight heparin and 11 (38%) with a direct oral anticoagulant. In moderate COVID-19 patients, the overall VTE rate was 2,3% (20/866, 95%CI: 1.5 to 3.5) versus 0.6% (9/1426; 95%CI: 0.3 to 1.2) in patients with mild COVID-19 managed as outpatient. Among moderate COVID-19 patients hospitalized in a medical unit; 111/866 (12.8%) patients got worse requiring admission in an intensive care unit. Their 28-day VTE-rate was 11.7% (13/111, 95%CI 7.0 to 19.0%) versus 0.9% (7/755, 95%CI 0.5 to 1.9%) in other patients with moderate COVID-19 who did not get worse. More than two-thirds of VTE events (69.0%, n = 20/29) occurred between 48 h and day 7 following ED presentation. Among

Table 1
Baseline and adjusted characteristics of the patients in the COVID-19 cohort and the general population cohort.

Patient characteristics	Baseline score		Weighting-based propensity score	
	COVID-19 cohort n = 2292	Comparison cohort n = 1539	COVID-19 cohort n = 550	Comparison cohort n = 550
Demographic characteristics				
Age – median (IQR) – yr	52 (38–69)	53 (37–69)	53 (38–69)	53 (38–69)
Female sex – no. (%)	1256 (54.8)	896 (58.2)	325 (59.1)	325 (59.1)
Medical history – no. (%)				
COPD	185 (8.1)	108 (7.0)	43 (7.8)	43 (7.8)
Chronic respiratory failure	43 (1.9)	45 (2.9)	15 (2.7)	15 (2.7)
Severe or end-stage renal disease (GFR < 30 ml/min)	154 (6.7)	45 (2.9)	22 (4.0)	22 (4.0)
Chronic cardiac failure NYHA III/IV	169 (7.4)	85 (5.5)	34 (6.2)	43 (7.8)
Hypertension	683 (29.8)	255 (16.6)	133 (24.2)	133 (24.2)
Diabetes	286 (12.5)	88 (5.7)	50 (9.1)	50 (9.1)
History of thromboembolism	148 (6.5)	175 (11.4)	46 (8.4)	46 (8.4)
History of cancer or active cancer	210 (9.1)	122 (7.9)	37 (6.7)	37 (6.7)
Signs and symptoms – no. (%)				
Dyspnoea	1961 (85.6)	922 (59.9)	466 (84.7)	351 (63.8)
Chest pain	1118 (48.8)	1096 (0.7)	286 (52.0)	401 (72.9)
Confusion, impaired alertness	110 (4.8)	15 (1.0)	8 (1.5)	8 (1.5)
Heart rate ≥ 120 beats/min	119 (5.2)	69 (4.5)	28 (5.1)	41 (7.5)
Systolic blood pressure < 90 mmHg	16 (0.7)	4 (0.3)	3 (0.5)	2 (0.4)
Temperature, mean ± SD, °C	37.0 ± 0.9	36.9 ± 2.1	37.0 ± 0.88	36.9 ± 0.72
Weight, mean ± SD, °C	75.8 ± 18.3	76.3 ± 19.9	74.9 ± 17.9	76.6 ± 20.3
Pulse oxygen saturation ≤ 94% in ambient air or necessity of oxygen therapy	472 (20.6)	334 (21.7)	99 (18.0)	106 (19.3)
Respiratory rate ≥ 25/min	444 (19.4)	155 (10.1)	115 (20.9)	117 (21.3)

COVID-19: Coronavirus disease 2019, SD: standard deviation, IQR: interquartile range, COPD: chronic obstructive respiratory disease, GFR: glomerular filtration rate, NYHA: New York Heart Association Classification.

patients who developed VTE, 14/29 (48.3%) patients received thromboprophylaxis as compared to 592/2263 (26.2%) of non-VTE patients (Table S2). In hospitalized patients, 527/866 (60.9%) received thromboprophylaxis with a mean duration of 10.1 (±6.2) days and 79/1426 (5.5%) of the outpatients with a mean duration of 6.4 (±3.4) days.

3.3. Risk factors of VTE in the COVID-19 cohort

Table 2 summarizes the VTE risk factors. In the univariate model, respiratory issues, cardiac issues, personal VTE and cancer history were not significantly associated with VTE events. Lack of thromboprophylaxis was not a VTE risk factor. In the multivariate analysis, because the hospitalization and the D-dimer were collinear variables, they could not be taken together in the same model. Two models were developed (Table 2). In the first model, only an age over 65 was significantly associated with VTE. The D-dimer level was not a VTE risk factor. In the second model, an age over 65 was considered just about significant and the severity of the COVID-19 (moderate versus mild) was independently correlated to the VTE occurrence. Of 515 patients over 65 years of age with moderate COVID-19, 14 developed a VTE (14/515, 2.7%) including 5 patients who were receiving thromboprophylaxis treatment. Of the 184 patients with an age over 65 treated at home, 2 developed a VTE (2/184, 1.1%).

3.4. VTE risk in COVID-19 patients versus similar patients presenting to the ED

3.4.1. Description of the comparison cohort

A total of 1539 patients were included in the comparison cohort (Table 1). From the initial PERCEPIC study population ($n = 1757$ patients), a total of 218 patients were excluded: 11 did not have dyspnea or/and chest pain, 9 did not have a D-dimers assays or/and a CTPA, 198 patients were excluded because of a confirmed PE during the initial workup at the ED (11.3%) and 2 were lost to follow-up at D28. A total of 1068/1539 (69.5%) patients were treated at home.

In the adjusted populations, the rate of VTE within 28 days was 1.87% (95%CI: 0.95 to 3.24) in the COVID-19 cohort and 0.18% (95% CI: 0.01 to 1.63) in the comparison cohort. The absolute difference was +1.69 (95%CI: 0.88 to 2.51) (p-value <0.001). Most events take place within the first 10 days after ED presentation: 72.4% in the COVID-19 cohort and 81.5% in the comparison cohort (Fig. 1). In the COVID-19 cohort, 24.1% of the VTE events were DVT (7/29) and 75.9% were PE (22/29) and among them 10.3% were fatal PE (3/29). In the comparison cohort, 9.5% of the VTE events were DVT (2/21) and 90.5% were PE (19/21), and, among them, 9.5% were fatal PE (2/21).

In the subgroup of hospitalized patients, the rate of VTE at Day 28 was 3.68% (95%CI: 1.53 to 7.17) in the COVID-19 cohort (i.e., moderate COVID-19) and 0.22% (95%CI: 0.01 to 4.37) in the comparison cohort ($p < 0.001$). The absolute difference was +3.45 (95%CI: 1.80 to 5.11) (Fig. 2). In patients treated at home, the rate of VTE at 28 days was 0.72% (95%CI: 0.15 to 1.99) in the COVID-19 cohort (i.e., mild COVID-19) and 0.21% (95%CI: 0.01 to 5.71) in the comparison cohort. The absolute difference was +0.50 (95%CI: - 0.22 to 1.23) (Fig. 2).

In the subgroup of patients with positive SARS-CoV-2 RT-PCR, the VTE rate within 28-days was 3.10% (95%CI: 1.48 to 5.57) and 0.12% (95%CI: 0.01 to 2.25) in the adjusted comparison cohort. The absolute difference was +2.98 (95%CI: 1.33 to 4.63). In patients with positive SARS-CoV-2 RT-PCR and/or who had a chest CT-scan which indicated COVID-19 lesions, the VTE rate was 2.66% (95%CI: 1.33 to 4.63) and 0.14% (95%CI 0.01 to 1.89) in the adjusted comparison cohort. In the COVID-19 cohort, the different hazard ratio in developing a VTE in each subgroup according to the probability of SARS-CoV-2 infection is summarized in Fig. 3.

Table 2
Risk factors in developing VTE in the COVID-19 cohort.

	No VTE	VTE	Univariate	Multivariate	
	n = 2263 (%)	n = 29 (%)	p-Value	p-Value	OR (95% CI)
First model					
Male sex	1025/2263 (45.3)	11/29 (37.9)	0.23		
Age, years — median (IQR)			0.45		
<65	1608/2263 (71.1)	13/29 (44.8)	0.61		
≥65	655/2263 (28.9)	16/29 (55.2)	<0.01	0.03	6.2 (1.4–45.5)
Chronic respiratory failure — no. (%)[a]	227/2263 (10.0)	1/29 (3.4)	0.39		
Chronic cardiac failure — no. (%)[b]	166/2263 (7.3)	3/29 (10.3)	1.00		
History of personal VTE — no. (%)	147/2263 (6.5)	1/29 (3.4)	0.62		
History of cancer or active cancer — no. (%)	209/2263 (9.2)	1/29 (3.4)	1.00		
Dyspnoea — no. (%)	1934/2263 (85.5)	27/29 (93.1)	0.50		
Thromboprophylactic treatment — no. (%)	592/2140 (27.7)	14/29 (63.6)	0.78		
D-dimers, ng/mL — no. (%)			0.50		
<500	871/1639 (53.1)	10/22 (45.5)			
500–1000	365/1639 (22.3)	2/22 (9.1)			
>1000	403/1639 (24.6)	10/22 (45.5)			
Second model					
Male sex	1025/2263 (45.3)	11/29 (37.9)	0.23		
Age, years — median (IQR)			0.45		
<65	1608/2263 (71.1)	13/29 (44.8)	0.61		
≥65	655/2263 (28.9)	16/29 (55.2)	<0.01	0.08	2.7 (0.9–8.7)
Chronic respiratory failure — no. (%)[a]	227/2263 (10.0)	1/29 (3.4)	0.39		
Chronic cardiac failure — no. (%)[b]	166/2263 (7.3)	3/29 (10.3)	1.00		
History of personal VTE — no. (%)	147/2263 (6.5)	1/29 (3.4)	0.62		
History of cancer or active cancer — no. (%)	209/2263 (9.2)	1/29 (3.4)	1.00		
Dyspnoea — no. (%)	1934/2263 (85.5)	27/29 (93.1)	0.50		
			0.78		

(continued on next page)

Table 2 (*continued*)

	No VTE	VTE	Univariate	Multivariate	
	n = 2263 (%)	n = 29 (%)	p-Value	p-Value	OR (95% CI)
Thromboprophylactic treatment — no. (%)	592/2140 (27.7)	14/29 (63.6)			
Hospitalization	1406/1426 (98.6)	20/1426 (1.4)	<0.01	0.05	3.5 (1.1–13.8)

VTE: venous thromboembolism, IQR: interquartile range; OR: odds ratio; 95% CI: 95% confidence interval; NS: not significant.

[a] Including COPD stage III and IV and respiratory failure requiring daily oxygen therapy.

[b] Chronic cardiac failure including stage NYHA III-IV.

4. Discussion

In this prospective cohort of patients with confirmed or suspected mild and moderate COVID-19, 1.29% of patients experienced symptomatic VTE within the 28 days following ED presentation. The risk of developing VTE was greater than in a comparable population outside of the pandemic period, the higher the likelihood of having a SARS-CoV-2 infection and the higher the COVID-19 severity, the higher the VTE risk. An age over 65 years and a moderate form of COVID-19 requiring hospitalization were independent risk factors of VTE, whether the patients received thromboprophylaxis or not.

Several previous studies have proven an significant risk of VTE in patients with severe COVID-19 who require intensive care [5,6,8–10,23]. This risk is 9 times higher when compared with patients with Acute Respiratory Distress Syndrome (ARDS) due to influenza [24]. Two main thromboemboembolic mechanisms have been described: alveolar capillary microthrombi and thrombus migrations in the pulmonary arteries. In severe COVID-19 patients, a hypercoagulable state may mostly lead to diffuse pulmonary microthrombosis and have a dramatic impact on prognosis and mortality [25]. However, the risk of symptomatic VTE in patients with mild or moderate COVID-19 (managed as outpatient or hospitalized in medical wards), and if these patients have a higher VTE risk than similar patients without COVID-19 were unknown.

The results of this study confirm that hospitalized patients with a mild and moderate COVID-19 have a 1-month VTE risk upper than 2%, corresponding to a significant over-risk than similar patients without COVID-19. The risk of VTE seems correlated to the severity and the evolution of the disease, the majority of VTE events occurring in patients with moderate COVID-19 who get worse and required admission in an intensive care unit. This increased risk occurred while most patients received preventive anticoagulation. Indeed, among hospitalized patients, 61% were receiving antithrombotic prevention and 20 patients (2.3%) developed VTE. Furthermore, among moderate COVID-19 patients over 65 years of age, approximately 3% developed VTE, almost half of whom were receiving thromboprophylaxis treatments. In this study, preventive anticoagulation was not associated with a lower risk of VTE. This unexpected result may be explained, at least partly, by an

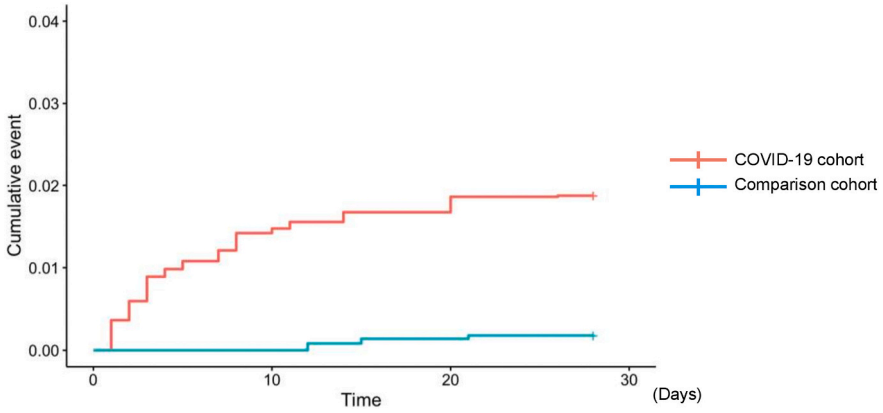

Fig. 1. Kaplan-Meier cumulative VTE rate for the primary outcome.
Kaplan-Meier curves are shown for the first occurence of the primary outcome of symtomatic venous thromboembolism (VTE) - a composite of deep-vein thrombosis or pulmonary embolism - within 28 days.

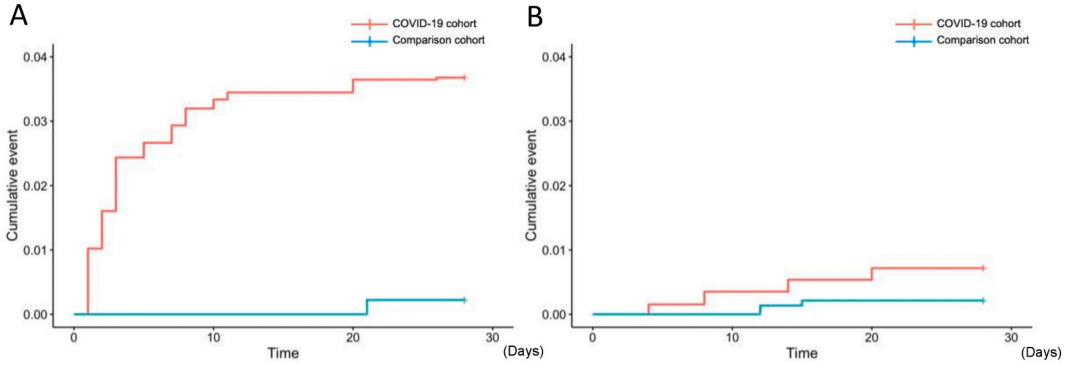

Fig. 2. Kaplan-Meier cumulative VTE rate for the primary outcome in the two subgroups: A. Hospitalized patients. B. Outpatients.
Kaplan-Meier curves are shown for the occurence of the primary outcome of symptomatic venous thromboembolism (VTE) - a composite of deep-vein thrombosis or pulmonary embolism - within 28 days.

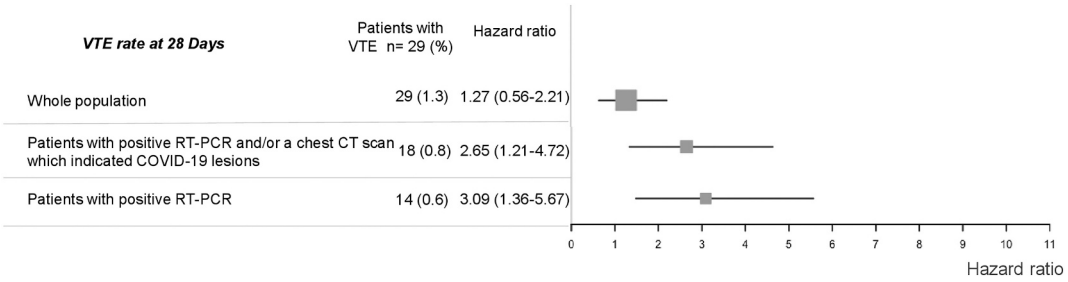

Fig. 3. Hazard Ratios for the venous thromboembolism rate within 28 days in different subgroups according to different levels of COVID-19 probability.
VTE: venous thromboembolism, RT-PCR: reverse transcriptase-polymerase chain reaction, CT-Scan: computed-tomography scan, COVID-19: Coronavirus Infectious Disease 2019.

unformal selection of patients with a high VTE risk by the physicians prescribing thromboprophylaxis and does not preclude the usefulness of thromboprophylaxis. Indeed, recent studies confirm the benefit of thromboprophylaxis in hospitalized patients with moderate COVID-19 [26]. Moreover, as compared to usual prophylactic regimens, therapeutic anticoagulation was recently proven to improve survival of moderate COVID-19 patients [27]. Further studies are needed to assess the effectiveness of thromboprophylaxis in mild COVID-19 patients managed at home.

Conversely, the incidence in mild COVID-19 patients treated on an outpatient basis was low, below 1%, leaving no scope for systematic preventive anticoagulation. The challenge lies in defining which of them are at risk and require treatment. In this study, the two risk factors were hospitalization and an age over 65 years. Age is therefore both a risk factor for venous thrombosis and mortality in the case of COVID-19 [3,8,28]. High levels of D-dimer did not correlate with the occurrence of VTE while this has been shown to be a prognostic factor in other studies [8,29]. In any case, it is essential to assess the existence of a VTE concurrent with COVID-19 and to assess the thrombotic risk individually.

Our study is a post-hoc comparison of two large prospective multicentric cohorts. The primary endpoint is relevant by considering only clinically symptomatic events. However, there are some limitations to be discussed. Firstly, not all participants had confirmation of their COVID-19 by RT-PCR. We included patients with confirmed or highly suspected COVID-19, corresponding to the real daily ED population. Moreover, the same results were observed in the overall population and in the subgroup of patients with a positive RT-PCR for SARS-CoV2 reinforcing their validity. Secondly, the rate of patients lost to follow-up is significant in the COVID-19 study (7%), which could have led to an underestimation of thromboembolic events in this population. Thirdly, we did not record the local protocols for routine preventive anticoagulation at standard or intermediate doses in the participating centers. Finally, it was a retrospective comparison based on prospective data collected at different periods (2016 and 2020). To limit the differences between these two populations, we used strict inclusion criteria, i.e., only patients with dyspnea and/or chest pain, who had an initial diagnostic strategy for pulmonary embolism or deep vein thrombosis (i.e., at least D-dimer or CTPA) and in whom the hypothesis of VTE was ruled out were included. Thanks to a propensity score which considers a high number of variables, the adjusted populations were similar (Table S1 and Fig. S1). We chose the ATO method which is the most reliable but requires a large population which we had available [30].

5. Conclusions

In conclusion, this study highlights that the risk of VTE in mild and moderate COVID-19 patients should be considered, especially in patients with moderate COVID-19 requiring hospitalization. Further studies are to be carried out to define if patients with mild COVID-19 require thromboprophylactic treatment and with which molecule and dosage.

Abbreviations

95%CI	95% confidence Interval
ACCP	American College of Chest Physician
ARDS	Acute Respiratory Distress Syndrome
COVID-19	Coronavirus 2019
CTPA	Computed Tomography Pulmonary Angiogram
CUS	compression ultra-sonography
DOAC	Direct Oral Anticoagulant
DVT	deep vein thrombosis
ED	Emergency Department
ISTH	International Society of Thrombosis and Haemostasis
LMWH	Low-Molecular-Weight-Heparin
PE	pulmonary embolism
VTE	venous thrombo-embolism

Copyright

This study has not previously been published or submitted elsewhere.

Ethics approval and consent to participate

Trial registration: ethics committee of the CHU of Angers (N°2020/87). All participants gave their consent.

Consent for publication

Yes.

Availability of data and materials

Data available on special request from the authors.

Funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank the University Hospital of Angers and specifically the “Délégation pour la Recherche Clinique et Innovation” for

having made this research possible in the context of the pandemic. We would also like to thank all the members of HOME-CoV and PERCEPIC study groups and the research assistants, secretaries, physicians, and residents of the emergency departments for their invaluable help and collaboration. The PERCEPIC study was supported by the French Clinical Research Infrastructure Network on Venous Thromboembolism (F-CRIN INNOVTE).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2021.10.001.

References

[1] S.X. Gu, T. Tyagi, K. Jain, Thrombocytopathy and endotheliopathy: crucial contributors to COVID-19 thromboinflammation, Nat Rev Cardiol. (2020), https://doi.org/10.1038/s41569-020-00469-1. Published online November 19.
[2] W. Guan, Z. Ni, Y. Hu, Clinical characteristics of coronavirus disease 2019 in China, N Engl J Med. (2020), NEJMoa2002032, https://doi.org/10.1056/NEJMoa2002032. Published online February 28.
[3] F. Zhou, T. Yu, R. Du, Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, The Lancet (2020), S0140673620305663, https://doi.org/10.1016/S0140-6736(20)30566-3. Published online March.
[4] A. Di Minno, P. Ambrosino, I. Calcaterra, M.N.D. Di Minno, COVID-19 and venous thromboembolism: a meta-analysis of literature studies, Semin. Thromb. Hemost. 46 (07) (2020) 763–771, https://doi.org/10.1055/s-0040-1715456.
[5] F.A. Klok, M.J.H.A. Kruip, N.J.M. van der Meer, et al., Incidence of thrombotic complications in critically ill ICU patients with COVID-19, Thromb. Res. 191 (2020) 145–147, https://doi.org/10.1016/j.thromres.2020.04.013.
[6] S. Cui, S. Chen, X. Li, S. Liu, F. Wang, Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia, J. Thromb. Haemost. 18 (6) (2020) 1421–1424, https://doi.org/10.1111/jth.14830.
[7] M. Criel, M. Falter, J. Jaeken, et al., Venous thromboembolism in SARS-CoV-2 patients: only a problem in ventilated ICU patients, or is there more to it? Eur. Respir. J. 56 (1) (2020) 2001201, https://doi.org/10.1183/13993003.01201-2020.
[8] C. Lodigiani, G. Iapichino, L. Carenzo, et al., Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in MilanItaly 191 (2020) 9–14, https://doi.org/10.1016/j.thromres.2020.04.024.
[9] G. Chi, J.J. Lee, A. Jamil, et al., Venous thromboembolism among hospitalized patients with COVID-19 undergoing thromboprophylaxis: a systematic review and meta-analysis, JCM. 9 (8) (2020) 2489, https://doi.org/10.3390/jcm9082489.
[10] S. Middeldorp, M. Coppens, T.F. van Haaps, Incidence of venous thromboembolism in hospitalized patients with COVID-19, Published online May 5, J Thromb Haemost. (2020), https://doi.org/10.1111/jth.14888. jth.14888.
[11] J.B. Hill, D. Garcia, M. Crowther, et al., Frequency of venous thromboembolism in 6513 patients with COVID-19: a retrospective study, Blood Adv. 4 (21) (2020) 5373–5377, https://doi.org/10.1182/bloodadvances.2020003083.
[12] H. Al-Samkari, R.S. Karp Leaf, W.H. Dzik, et al., COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection, Blood 136 (4) (2020) 489–500, https://doi.org/10.1182/blood.2020006520.
[13] Y. Freund, M. Drogrey, Ò. Miró, Association between Pulmonary Embolism and COVID-19 in ED patients Undergoing CTPA: the PEPCOV international retrospective study, Published online July 30, Acad Emerg Med. (2020), https://doi.org/10.1111/acem.14096. acem.14096.
[14] A.C. Spyropoulos, J.H. Levy, W. Ageno, 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. 18 (8) (2020) 1859–1865, https://doi.org/10.1111/jth.14929.
[15] S. Schulman, Y. Hu, S. Konstantinides, Venous thromboembolism in COVID-19, Thromb. Haemost. (2020;(12):332:227–234.), https://doi.org/10.1016/j.ijcard.2021.03.063.
[16] COVID-19 and VTE-Anticoagulation - Hematology.org. https://www.hematology.org:443/covid-19/covid-19-and-vte-anticoagulation. (Accessed 19 December 2020).
[17] D. Douillet, A. Penaloza, R. Mahieu, Outpatient management of patients with COVID-19: multicenter prospective validation of the HOME-CoV rule to safely discharge patients, Chest (2021), S0012369221008990, https://doi.org/10.1016/j.chest.2021.05.008. Published online May.
[18] D. Douillet, R. Mahieu, V. Boiveau, Outpatient management or hospitalization of patients with proven or suspected SARS-CoV-2 infection: the HOME-CoV rule, Intern Emerg Med (2020), https://doi.org/10.1007/s11739-020-02483-0. Published online September 4.
[19] A. Penaloza, C. Soulié, T. Moumneh, et al., Pulmonary embolism rule-out criteria (PERC) rule in European patients with low implicit clinical probability (PERCEPIC): a multicentre, prospective, observational study, Lancet Haematol. 4 (12) (2017) e615–e621, https://doi.org/10.1016/S2352-3026(17)30210-7.
[20] L. Roncon, M. Zuin, P. Zonzin, Age-adjusted D-dimer cut-off levels to rule out venous thromboembolism in COVID-19 patients, Thromb. Res. 190 (2020) 102, https://doi.org/10.1016/j.thromres.2020.04.021.
[21] F. Li, F. Li, Li F, Li F., arXiv:180805339 [stat]. Published online June 28, in: Propensity Score Weighting for Causal Inference With Multiple Treatments, 2019, http://arxiv.org/abs/1808.05339. (Accessed 10 December 2020).
[22] F Li KL Morgan AM Zaslavsky. Balancing Covariates via Propensity Score Weighting. 33.
[23] S. Nopp, F. Moik, B. Jilma, I. Pabinger, C. Ay, Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis, Res. Pract. Thromb. Haemost. 4 (7) (2020) 1178–1191, https://doi.org/10.1002/rth2.12439.
[24] M. Ackermann, S.E. Verleden, M. Kuehnel, et al., Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19, N. Engl. J. Med. 383 (2) (2020) 120–128, https://doi.org/10.1056/NEJMoa2015432.
[25] H. Xu, A. Martin, A. Singh, et al., Pulmonary embolism in patients hospitalized with COVID-19 (froma New York health system), Am. J. Cardiol. 133 (2020) 148–153, https://doi.org/10.1016/j.amjcard.2020.07.036.
[26] C.A. Gómez, C.-K. Sun, I.-T. Tsai, et al., Mortality and risk factors associated with pulmonary embolism in coronavirus disease 2019 patients: a systematic review and meta-analysis, Sci. Rep. 11 (1) (2021) 16025, https://doi.org/10.1038/s41598-021-95512-7.
[27] A.C.T.I.V.-4a The ATTACC and REMAP-CAP Investigators, Therapeutic anticoagulation with heparin in noncritically ill patients with covid-19, N Engl J Med. (2021), NEJMoa2105911, https://doi.org/10.1056/NEJMoa2105911. Published online August 4.
[28] G.T. Gerotziafas, M. Catalano, M.-P. Colgan, et al., Guidance for the management of patients with vascular disease or cardiovascular risk factors and COVID-19: position paper from VAS-European independent foundation in angiology/vascular medicine, Thromb. Haemost. 120 (12) (2020) 1597–1628, https://doi.org/10.1055/s-0040-1715798.
[29] S. Bilaloglu, Y. Aphinyanaphongs, S. Jones, E. Iturrate, J. Hochman, J.S. Berger, Thrombosis in hospitalized patients with COVID-19 in a New York City health system, JAMA 324 (8) (2020) 799, https://doi.org/10.1001/jama.2020.13372.
[30] R.J. Desai, J.M. Franklin, Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners, BMJ 367 (2019), l5657, https://doi.org/10.1136/bmj.l5657.