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

Running Title: VTE risk in non-severe COVID-19 patients.

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HIGHLIGHTS

- The risk of VTE in patients with mild and moderate COVID-19 remains under debate
- COVID-19 patients presenting to ED and not having VTE were prospectively followed.
- They had a higher risk of subsequent VTE than similar patients without COVID-19
- The independent risk factors of VTE were a moderate COVID-19 form and an age over 65 years.

BACKGROUND

The coronavirus disease 2019 (COVID-19) viral pneumonia leads to hypoxia, a hyper-inflammatory state and immunothrombosis. A complex interaction between coagulopathy, thrombocytopenia and endotheliopathy contributes to COVID-19-associated thromboinflammation¹. 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 patients⁴⁻⁶. The incidence of VTE was estimated at 9-47% in COVID-19 patients hospitalized in intensive care units⁴⁻¹⁰ 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 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.

METHODS

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).

COVID-19 Cohort

The first cohort of COVID-19 patients came from the HOME-CoV study¹⁷. The HOME-CoV study was a pragmatic prospective multicenter before/after design trial which aimed to validate the HOME-CoV rule¹⁸ 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 rule¹⁸. 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” facilities¹⁷. 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 were 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 were recorded to allow analysis over time. Data on the prescription of preventive anticoagulants were collected.

Comparison cohort

The comparison cohort came from the PERCEPIC study¹⁹. 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.

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 $age \times 10$ ruling-out VTE in patients aged of fifty or more²⁰. Patients for whom the diagnosis of VTE was established during the initial workup in the ED or within the 24 hours following ED presentation, and patients lost to follow up at Day 28 were excluded.

Outcome measure

The outcome was the rate of symptomatic VTE occurring within the 28 days following ED presentation. The diagnostic strategy was left 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).

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.

Statistical analysis

For descriptive analysis, quantitative variables were reported as mean \pm 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 Figure 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 nonproportionality 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, Weighlt packages and Survey and plotted by Kaplan–Meier curves.

Ethical Considerations

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

RESULTS

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.

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 hours and day 7 following ED presentation. Among 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 (\pm 6.2) days and 79/1426 (5.5%) of the outpatients with a mean duration of 6.4 (\pm 3.4) days.

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%).

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

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 (Figure 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) (Figure 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) (Figure 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 Figure 3.

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 a significant risk of VTE in patients with severe COVID-19 who require intensive care ^{5,6,8-10,23,5,6,8-10,23}. This risk is 9 times higher when compared with patients with Acute Respiratory Distress Syndrome (ARDS) due to influenza ²⁴. Two main thromboembolic mechanisms have been described: alveolar capillary microthrombi and thrombus migrations in the pulmonary arteries. In severe COVID-19 patients, an 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 informal 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-19²⁶. Moreover, as compared to usual prophylactic regimens, therapeutic anticoagulation was recently proven to improve survival of moderate COVID-19 patients²⁷. 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 Figure S1). We chose the ATO method which is the most reliable but requires a large population which we had available³⁰.

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.

LIST OF 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

DECLARATIONS

Author contribution:

Copyright: This study has not previously been published or submitted elsewhere.

Conflict of interest: The authors report no conflicts of interest relevant to this work.

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

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Conflict of interest: The authors declare that they have no competing interests.

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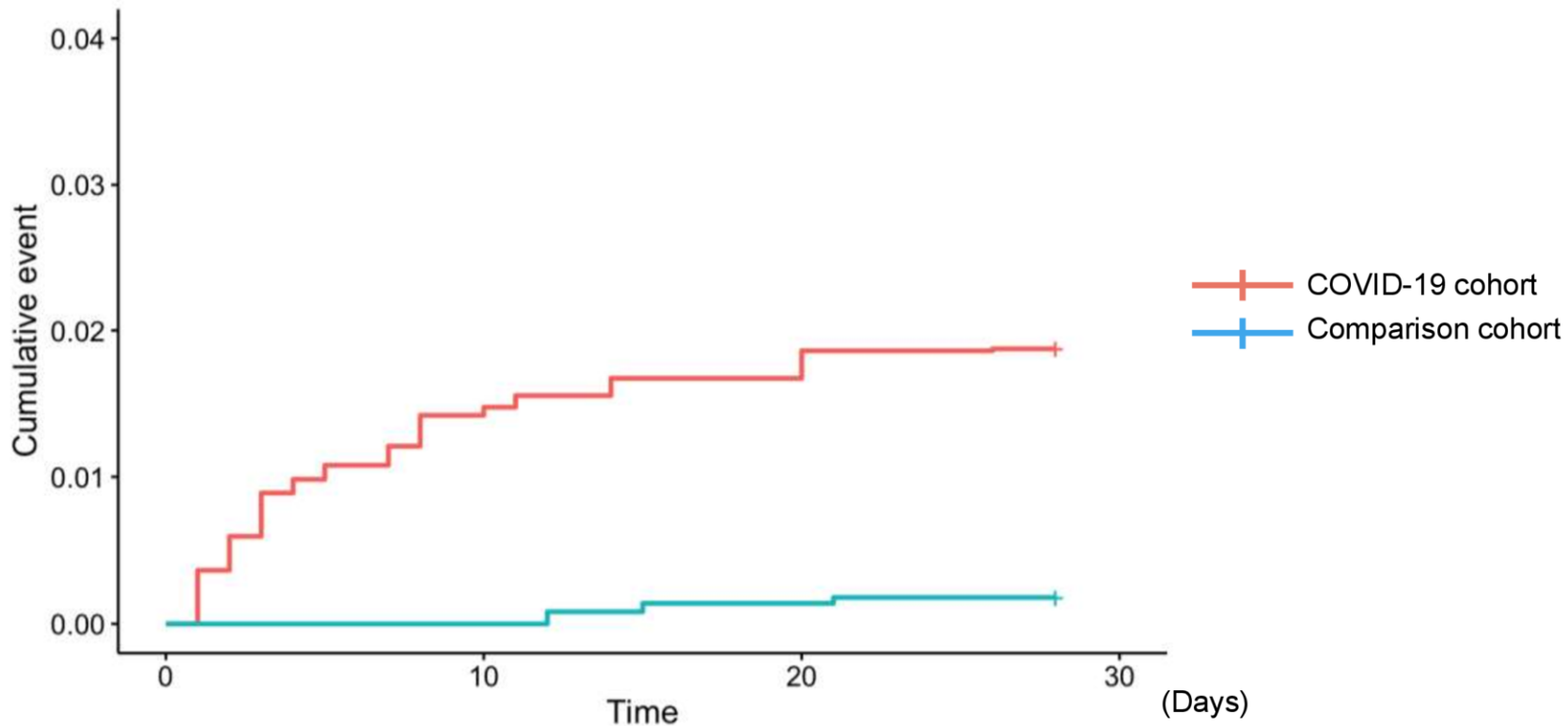


Figure 1. Kaplan-Meier cumulative VTE rate for the primary outcome.

Kaplan-Meier curves are shown for the first occurrence of the primary outcome of symptomatic venous thromboembolism (VTE) — a composite of deep-vein thrombosis or pulmonary embolism — within 28 days.

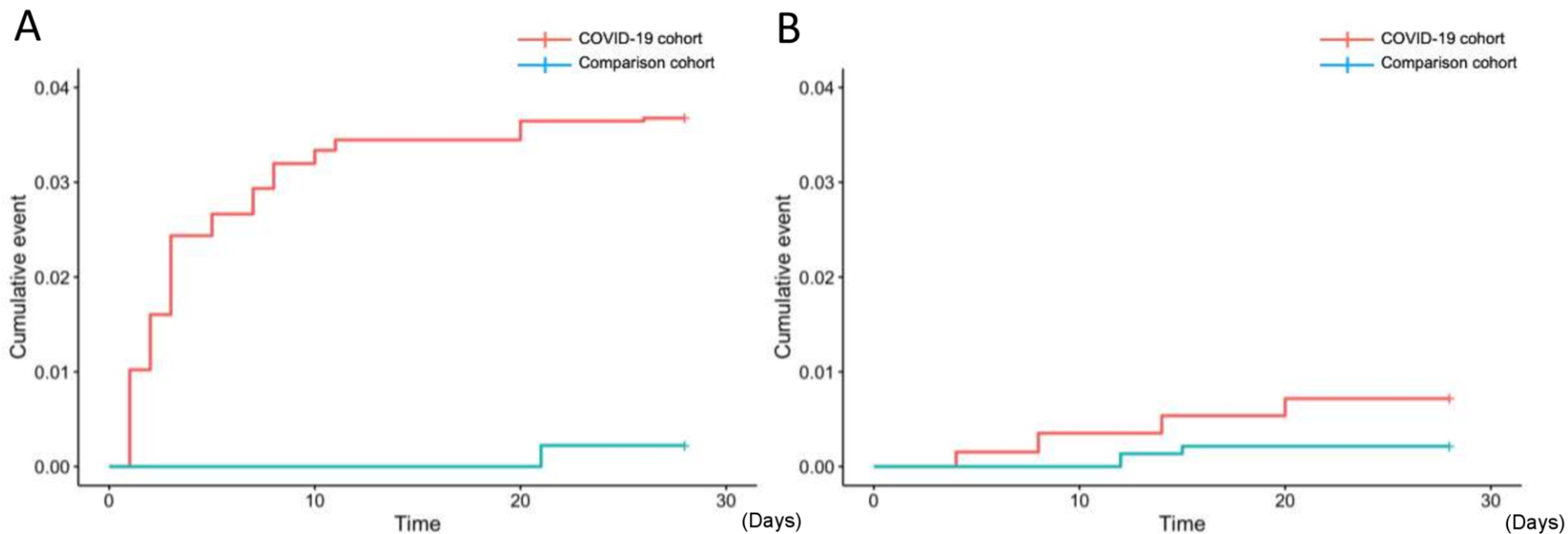


Figure 2. Kaplan-Meier cumulative VTE rate for the primary outcome in the two subgroups:

A. Hospitalised patients

B. Outpatients

Kaplan-Meier curves are shown for the first occurrence of the primary outcome of symptomatic venous thromboembolism (VTE) — a composite of deep-vein thrombosis or pulmonary embolism — within 28 days.

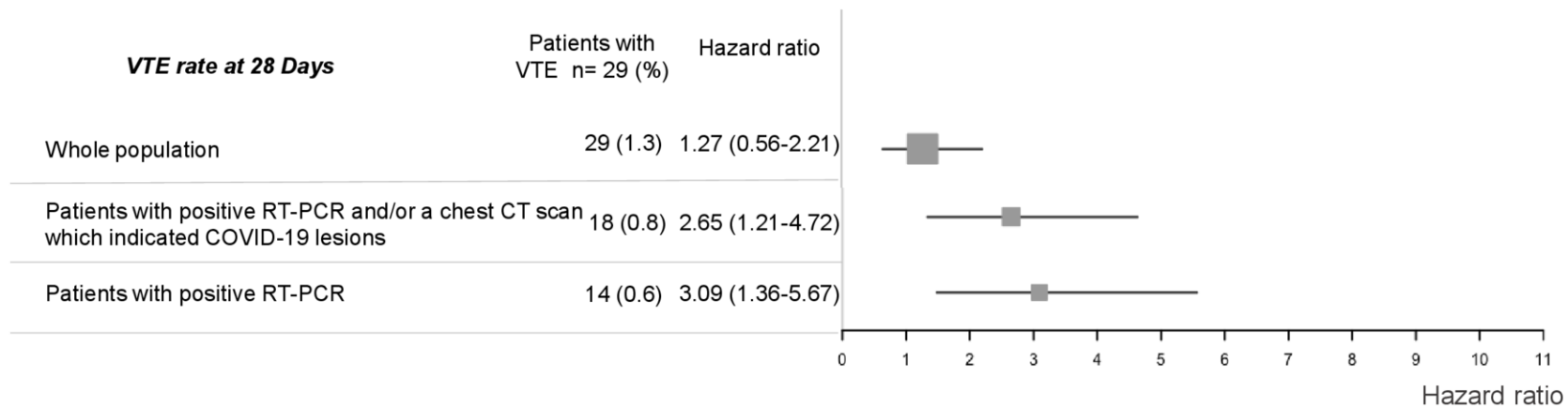


Figure 3. Hazard Ratios for the venous thromboembolism rate within 28 days in different subgroups according to different levels of COVID-19 probability.

VTE: Venous Thromboembolism, RT-PCR: Reverse Transcriptase –Polymerase Chain Reaction, CT-Scan: Computed-Tomography Scan, COVID-19: Coronavirus Infectious Disease 2019.

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

<i>Patient characteristics</i>	Baseline score		Weighting-based propensity score	
	COVID-19 cohort n=2292	Comparison cohort n= 1539	COVID-19 cohort n= 550	Comparison cohort n= 550
<i>Demographic characteristics</i>				
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)
<i>Medical history – no. (%)</i>				
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 < 30ml/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)
<i>Signs and symptoms – no. (%)</i>				
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 < 90mmHg	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.				

Table 2. Risk factors in developing VTE in the COVID-19 cohort.					
			<i>Univariate</i>	<i>Multivariate</i>	
	No VTE n=2263 (%)	VTE n= 29 (%)	p-value	p-value	OR (95%CI)
<i>First model</i>					
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. (%)*	227/2263 (10.0)	1/29 (3.4)	0.39		
Chronic cardiac failure — no. (%)**	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)			
<i>Second model</i>					
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. (%)*	227/2263 (10.0)	1/29 (3.4)	0.39		
Chronic cardiac failure — no. (%)**	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		
Hospitalisation	1406/1426 (98.6)	20/1426 (1.4)	< 0.01	0.05	3.5 (1.1-13.8)
*Including COPD stage III and IV and respiratory failure requiring daily oxygen therapy;					
** Chronic cardiac failure including stage NYHA III-IV					
VTE: Venous Thromboembolism, IQR: interquartile Range; OR: Odds Ratio; 95%CI: 95% Confidence Interval; NS: Not Significant					