


Incidence of thrombotic complications in hospitalised and non-hospitalised patients after COVID-19 diagnosis

Birgitte Tholin,¹ 
Waleed Ghanima,^{1,2,3} Gunnar Einvik,^{2,4}
Bernt Aarli,^{5,6} Eivind Brønstad,^{7,8}
Ole H. Skjønsberg^{2,9} and
Knut Stavem^{2,4,10}

¹*Clinic of Internal Medicine, Østfold Hospital, Gralum,* ²*Institute of Clinical Medicine, University of Oslo,* ³*Department of Haematology, Oslo University Hospital, Oslo,* ⁴*Department of Pulmonary Medicine, Akershus University Hospital, Lørenskog,* ⁵*Department of Thoracic Medicine, Haukeland University Hospital, Haukeland,* ⁶*Department of Clinical Science, University of Bergen, Bergen,* ⁷*Thoracic Department, St. Olavs Hospital,* ⁸*Department of Circulation and Medical Imaging, Faculty of Medicine and Health Sciences, NTNU, Trondheim,* ⁹*Department of Pulmonary Medicine, Oslo University Hospital Ullevål, Oslo,* and ¹⁰*Health Services Research Unit, Akershus University Hospital, Lørenskog, Norway*

Received 25 January 2021; accepted for publication 7 April 2021

Correspondence: Birgitte Tholin, Clinic of Internal Medicine, Østfold Hospital, Gralum, Norway.

E-mail: birgitte_tholin@hotmail.com

Introduction

During the past year, numerous studies have reported on the incidence and prevalence of venous thromboembolism (VTE) in coronavirus disease-2019 (COVID-19) patients, with incidence rates varying from 3% to 85%, depending on populations, settings and assessment methods.¹⁻⁴ Variations may also be associated with a lack of a consensus on the indication, dosage and duration of prophylactic anticoagulation. The majority of reports are from studies of selected patients or hospital cohorts using intensive case findings. The information on the incidence of VTE after hospital discharge and among those not needing hospital admission is limited.

This study assessed the incidence of VTE in both hospitalised and non-hospitalised patients in two ongoing cohort studies in

Summary

Infection with coronavirus disease-2019 (COVID-19) may predispose for venous thromboembolism (VTE). There is wide variation in reported incidence rates of VTE in COVID-19, ranging from 3% to 85%. Therefore, the true incidence of thrombotic complications in COVID-19 is uncertain. Here we present data on the incidence of VTE in both hospitalised and non-hospitalised patients from two ongoing prospective cohort studies. The incidence of VTE after diagnosis of COVID-19 was 3.9% [95% confidence interval (CI): 2.1–7.2] during hospitalisation, 0.9% (95% CI: 0.2–3.1) in the three months after discharge and 0.2% (95% CI: 0.00–1.25) in non-hospitalised patients, suggesting an incidence rate at the lower end of that in previous reports.

Keywords: coronavirus disease-2019, venous thromboembolism, anticoagulation, epidemiology, incidence.

Norway. Furthermore, we assessed the variation in the use of prophylactic anticoagulation between five hospitals.

Methods

Participants and data collection

PROLUN (patient-reported outcomes and lung function after hospitalisation for COVID-19) is an ongoing multicentre prospective cohort study in six Norwegian hospitals comprising 262 surviving patients hospitalised before June 1, 2020. Patients with a discharge diagnosis of U07.1 (confirmed COVID-19 diagnosis), U07.2 (COVID-19, diagnosis unconfirmed) or J12.x [viral pneumonia, in combination with positive Severe Acute Respiratory Syndrome Coronavirus-2

(SARS-CoV-2) polymerase chain reaction (PCR)] were considered eligible. Consenting patients were invited to a three-month follow-up visit.⁵ At the follow-up, patients were asked if they had been diagnosed with a VTE during the last months, which was subsequently verified by medical record review. Through a re-review of medical records, we also checked if the patients had been prescribed anticoagulation for primary thromboprophylaxis at discharge.

PROTROM (patient-reported outcomes and thromboembolism after COVID-19 without hospitalisation) is another ongoing prospective population-based cohort study assessing non-hospitalised individuals with COVID-19.⁶ Patients from the geographical catchment area of two Norwegian hospitals [Akershus University Hospital (Ahus) and Østfold Hospital (ØH)] with a positive real-time PCR for SARS-CoV-2 before June 1, 2020 were invited. Patients admitted to hospital <22 days after a positive PCR test were excluded, because we considered the probability to be high that this hospital stay was COVID-19-related. In total, 458 of 938 eligible subjects (49%) responded to a survey on average four months after symptom onset; 451 (48%) responded to items on recent VTE. Self-reported VTE events were verified by medical record review in each local hospital.

Statistical analysis

The uncertainty of the incidence rates for VTE was estimated by calculating 95% confidence intervals using the Wilson method. For display of anticoagulation practice, we excluded one hospital, as we only included hospitals with ≥ 20 patients. Data were analysed using Stata software version 16.1 (StataCorp, College Station, TX, USA).

Results and discussion

Among the 262 hospitalised patients (PROLUN), the median (25th to 75th percentile) length of stay was 6 (3–12) days, and 51 patients (19%) were admitted to the intensive-care unit (ICU). At admission, the median clinical frailty scale score was 2 (range: 1–7) and 26/262 (10%) were considered as at least pre-frail (>3). Only (17%) had severe disease according to the COVID-19 ordinal scale for clinical improvement (Table I), i.e. requiring non-invasive ventilation, high-flow oxygen, intubation/mechanical ventilation, or extracorporeal membrane oxygenation (ECMO; only one patient had ECMO). A chest computed tomography (CT) was performed in 39/262 (15%) during the hospital stay. Fifteen of 262 patients (5.7%) had a history of prior VTE.

At the three-month follow-up, 232 responded to items about VTE; 11/232 (5%) patients reported a VTE during or after being discharged from the hospital, and ten of these had the diagnosis confirmed by compression ultrasound or CT pulmonary angiography, as verified by review of medical records. Thus, the incidence rate of verified VTE during

hospitalisation for COVID-19 was 3.9% [95% confidence interval (CI): 2.1–7.2] and 0.9% (95% CI: 0.2–3.1) in the three months after discharge from the hospital (Table I). The incidence rate among those admitted to the ICU was 7.8% (95% CI: 3.1–18.5%).

In non-hospitalised patients (PROTROM), 11/458 patients (2.4%) had a history of VTE, and 1/451 (0.2%, 95% CI: 0.0–1.3%) reported a VTE after COVID-19 that was verified.

In the hospitalised patients, the incidence rate was at the low end of those previously reported.^{1,2} All patients being hospitalised before June 1, 2020, with a positive SARS-CoV-2 PCR were included, although many of these patients were only moderately affected by COVID-19, as shown by the distribution of scores on the COVID-19 ordinal scale for clinical improvement. Norwegian hospitals have not been overwhelmed with COVID-19-related admissions compared to other countries, and so the population hospitalized may have milder disease than in countries with high demand for hospital beds. This might contribute to the low incidence of VTE for the hospitalised patients presented here. In addition, we only obtained data from patients who were discharged alive, which represents a limitation. Two recent meta-analyses reported overall incidence rates of 21% (95% CI: 17–26%) and 26% (95% CI: 6–66%), range 2.6–85.4%, for VTE in hospitalised COVID-19 patients, but it was emphasized that the quality of the evidence was low due to heterogeneity and risk of bias.^{1,2} These variations in incidence rates in previous reports may largely be explained by the variations in sample selection and methods.

In the current study, the rate of chest CT during the hospital stay of 15% was lower than in some other studies. For example, a recent study reported rates of chest CT of 1 042/1 259 (83%).⁷ Yet, the case fatality rate of hospitalised patients in Norway seems similar to that in other countries. In Norway, as of June 21, 2020, 1 142 patients had been hospitalised with COVID-19; 929 with the disease as a primary diagnosis, and 94 hospitalised patients were reported dead with COVID-19, i.e., a case fatality rate in hospitals of 8.2% (95% CI: 6.8–10.0) or 10.1% (95% CI: 8.3–12.2), depending on choice of denominator.⁸ Liberal use of chest CT or compression ultrasonography of the lower extremities has been discouraged in Norway due to both capacity challenges and in the interest of infection control. This practice could possibly have led to underreporting in our setting, and physicians might instead have administered higher doses of low molecular weight heparin (LMWH). The incidence of symptomatic VTE following hospital discharge for COVID-19 has been reported to be 0.2% within 45 days,⁹ suggesting that most VTEs occur during the hospital stay.

The uncertainty associated with the true incidence of VTE in unselected COVID-19 patients might also have influenced the use of thromboprophylaxis. In this study, we observed a wide variation in the practice of prophylactic anticoagulation with LMWH between the participating hospitals (Table II).

Short Report

Table I. Patient characteristics and incidence of VTE in the PROLUN and PROTROM studies.

	PROLUN (hospitalised) (n = 262)	PROTROM (non-hospitalised) (n = 458)
Age (years), mean (SD)	58.6 (14.2)	49.6 (15.3)
Male	151 (58)	202 (44)
Comorbidity		
Hypertension	80* (33)	86 (19)
Asthma	51 (19)	52 (11)
Diabetes	22 (8)	16 (3)
COVID-19 ordinal scale for clinical improvement		
1–2, ambulatory	0	458 (100)
3, hospitalised, no oxygen therapy	91 (35)	0
4, hospitalised, oxygen by mask or nasal prongs	126 (48)	0
5–7, hospitalised, non-invasive ventilation, high flow oxygen, intubation/mechanical ventilation, or ECMO	45 (17)	0
History of VTE	15 (6)	11 (2)
Anticoagulated prior to admission†	19 (7)	NA
Anticoagulation initiated in hospital	154 (59)	NA
Discharged with thromboprophylaxis‡	19 (7)	NA
Follow-up after 3–4 months	232 (89)	NA
Self-reported VTE	11§ (5)	1¶** (0.2)
Verified VTE	10 (4.3, 95% CI: 2.4–7.8)	1¶** (0.2, 95% CI: 0.0–1.3)
VTE during hospital stay	8 (3.9, 95% CI 2.1–7.2)	NA
Verified VTE in ICU patients††	4 (7.8, 95% CI: 3.1–18.5)	NA
VTE after discharge	2‡‡ (0.9, 95% CI 0.2–3.1)	NA

ECMO, extracorporeal membrane oxygenation; VTE, venous thromboembolism; ICU, intensive care unit; CI, confidence interval; NA, not applicable.

*Self-reported, n = 239.

†Direct oral anticoagulants, warfarin or low molecular weight heparin (LMWH).

‡Primary thrombotic prophylaxis in patients not diagnosed with a VTE, n = 262.

§Deep venous thrombosis, four pulmonary embolism.

¶n = 451.

**Pulmonary embolism.

††Three months after discharge.

‡‡n = 51. Data presented as absolute number (%) unless stated otherwise.

Table II. Dosage and use of prophylactic LMWH* initiated in five participating hospitals, number (%).

	Hospital					Total
	A	B	C	D	E	
LMWH dose						
None	45 (42)	23 (34)	5 (16)	20 (69)	15 (75)	111 (42)
2 500 iu	1 (0.9)	2 (3)	0 (0)	2 (7)	5 (25)	10 (4)
5 000 iu	40 (37)	29 (43)	20 (65)	5 (7)	0 (0)	95 (36)
>5 000 iu	22 (20)	13 (19)	6 (19)	2 (7)	0 (0)	46 (17)
Sum	108 (100)	67 (100)	31 (100)	29 (100)	20 (100)	255 (100)

Only hospitals with ≥20 patients are presented. LMWH, low molecular weight heparin; iu, international units.

*Dalteparin.

In Norway, the use of prophylactic anticoagulation was liberal in the early days of the pandemic due to several case reports and smaller studies reporting a high incidence of

VTE in COVID-19 patients.^{10,11} The majority of patients in PROLUN received ≥ 5 000 iu dalteparin as thromboprophylaxis, and in total 66% received anticoagulation, initiated

prior to or during the hospitalisation. Although 5 000 iu dalteparin once daily is the standard thromboprophylactic dosage for immobilisation because of acute illness in Norway, 17% of patients received higher doses, and only 1.9% of those receiving prophylactic anticoagulation during hospitalization were diagnosed with a VTE. This might have influenced the incidence of VTE in this study, although the number of VTE events was considered too small to compare the results between hospitals. It is possible that the variation might be smaller now, after implementation of more recent guidelines on anticoagulation during COVID-19 like the American Society of Hematology suggesting using prophylactic-intensity anticoagulation in patients who do not have suspected or confirmed VTE.¹²

In other studies, a fair proportion of patients have been diagnosed with VTE despite prophylactic anticoagulation.⁷ This can be used as an argument for the use of higher doses of prophylactic anticoagulation than usual, which seems to be practiced at several hospitals.

There is little information available on the incidence of VTE among those not hospitalised for COVID-19, except for some case reports.¹³ We found a low incidence rate of VTEs following COVID-19. This low rate may be explained by a healthier population with a lesser degree of inflammation, immobilization and possibly comorbidities, than in hospitalised patients. Moreover, the sample in this study was population-based with a 48% response to the item on VTE and should therefore be reasonably representative of non-hospitalised COVID-19 patients. It is possible that patients with an increased symptom burden (i.e. if they have a VTE) respond more often than patients without symptoms, although patients with considerable comorbidity or language problems may have a lower propensity to respond. Therefore, responder bias may influence the findings, although it is not evident in what direction this would work. It was not possible to assess the incidence rate of VTEs among non-participants in the survey. There is, however, a possibility that some patients diagnosed with a VTE within 21 days of having a positive COVID-19 test might have been hospitalised and thereby excluded. One may also speculate that some patients may have hesitated to seek medical attention due to the ongoing pandemic. This might contribute to the low incidence rate in our study.

If the incidence of VTE in non-hospitalised patients is as low as these results suggest, large-scale data from population-based studies or studies with record linkage between registries may provide more accurate data, although verification of the events may be more difficult.¹⁴

Reported incidence rates of VTE in COVID-19 may seem high; however, it is not clear if the incidence of VTE is higher in COVID-19 than in other viral or bacterial pneumonias, e.g. community-acquired pneumonia.¹⁵ This may easily be forgotten during the current pandemic.

In conclusion, in this study, we found a low incidence rate of VTEs compared to previous reports in hospitalised

patients. In a population-based study of non-hospitalised COVID-19 patients, the incidence rate was considerably lower (0.2%). These incidence rates are at the low end of previous reports. The study also noticed a wide variation in the practice of prophylactic anticoagulation in the hospitalised patients.

Author contributions

All authors have contributed to drafting, revision and approval of the manuscript. BT and KS are responsible for the final version. KS analysed the data.

Ethics approval

Both studies have approval from the Norwegian Regional Ethics committee (REK).

Conflict of interest

BT, KS, BA, EB and OHS have no conflict of interest to disclose. GE has received unrestricted research grants from Boehringer Ingelheim and Novartis. WG has received honoraria from Amgen, MSD, Novartis and Pfizer, and research funding from Bayer, BMS/Pfizer and Novartis.

References

1. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. *EClinicalMedicine*. 2020;29:100639.
2. Porfida A, Valeriani E, Pola R, Porreca E, Rutjes AWS, Di Nisio M. Venous thromboembolism in patients with COVID-19: systematic review and meta-analysis. *Thromb Res*. 2020;196:67–74.
3. Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS, Syrigos K. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. *Br J Haematol*. 2020;189:846–7.
4. Middeldorp S, Coppens M, Haaps TF, Foppen M, Vlaar AP, Müller MCA, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020;18:1995–2002.
5. Lerum TV, Aaløkken TM, Brønstad E, Aarli B, Ikdahl E, Lund KMA, et al. Dyspnoea, lung function and CT findings three months after hospital admission for COVID-19. *Eur Respir J*. 2020;10:2003448.
6. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Persistent symptoms 1.5-6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. *Thorax*. Published Online First: 03 Dec 2020. 2021;76(4):405–7.
7. Planquette B, Le Berre A, Khider L, Yannoutsos A, Gendron N, de Torcy M, et al. Prevalence and characteristics of pulmonary embolism in 1042 COVID-19 patients with respiratory symptoms: a nested case-control study. *Thromb Res*. 2020;197:94–9.
8. Folkehelseinstituttet. COVID-19 Ukerapport - uke 25. 2020 [cited 2021 Jan 7]. Available from: <https://www.fhi.no/contentassets/8a971e7b0a3c4a06bdbf381ab52e6157/vedlegg/forste-halvar-2020/2020.06.24-ukerapport-uke-25-covid-19.pdf>.
9. Rashidi F, Barco S, Kamangar F, Heresi GA, Emadi A, Kaymaz C, et al. Incidence of symptomatic venous thromboembolism following hospitalization for coronavirus disease 2019: prospective results from a multi-center study. *Thromb Res*. 2021;198:135–8.

Short Report

10. Klok FA, Kruip M, van der Meer N, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;**191**:145–7.
11. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost.* 2020;**18**:1421–4.
12. Cuker A, Tseng EK, Nieuwlaat R, Angchaisuksiri P, Blair C, Dane KE, et al. ASH 2020 guidelines on the use of anticoagulation in patients with COVID-19: Draft recommendations. Washington, DC: American Society of Hematology. Published October 8, 2020. <http://www.hematology.org.ezproxy.uio.no/COVIDguidelines>.
13. Overstad S, Tjonnfjord E, Garabet L, Fronas S, Bergan J, Aballi S, et al. Venous thromboembolism and coronavirus disease 2019 in an ambulatory care setting - a report of 4 cases. *Thromb Res.* 2020;**194**: 116–8.
14. Scierbia FC. COVID-19 Positive Outpatient Thrombosis Prevention in Adults Aged 40-80. [cited 2021 Mar 11]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04498273>.
15. Mei F, Fan J, Yuan J, Liang Z, Wang K, Sun J, et al. Comparison of venous thromboembolism risks between COVID-19 pneumonia and community-acquired pneumonia patients. *Arterioscler Thromb Vasc Biol.* 2020;**40**:2332–7.