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Incidence and determinants of venous thromboembolism over 90 days in hospitalized and nonhospitalized patients with COVID-19

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Abstract. Tholin B, Ghanima W, Selle ML, Stavem K. Incidence and determinants of venous thromboembolism over 90 days in hospitalized and nonhospitalized patients with COVID-19. *J Intern Med.* 2023;**294**:721–729.

Introduction. COVID-19 is associated with an increased risk of venous thromboembolism (VTE), but there is great variation among reported incidence rates. Most previous studies have focused on hospitalized patients with COVID-19, and only a few reports are from population-based registries.

Methods. We studied the 90-day incidence of VTE, associated risk factors and all-cause mortality in hospitalized and nonhospitalized patients with COVID-19 in a nationwide cohort. Data on hospitalizations and outpatient visits were extracted from two national registries with mandatory reporting linked by a unique national identification number carried by all Norwegian residents. We performed Cox proportional hazards regression to determine risk factors for VTE after infection with SARS-CoV-2.

Results. Our study included 30,495 patients with positive SARS-CoV-2 polymerase chain reaction with a mean (SD) age of 41.9 (17.3) years, and 53% were males. Only 2081 (6.8%) were hospitalized. The 90-day incidence of VTE was 0.3% (95% CI: 0.21–0.33) overall and 2.9% (95% CI: 2.3–3.7) in hospitalized patients. Age (hazard ratio [HR] 1.28 per decade, 95% CI: 1.11–1.48, $p < 0.05$), history of previous VTE (HR 4.69, 95% CI: 2.34–9.40, $p < 0.05$), and hospitalization for COVID-19 (HR 23.83, 95% CI: 13.48–42.13, $p < 0.05$) were associated with risk of VTE.

Conclusions. The 90-day incidence of VTE in hospitalized and nonhospitalized patients with COVID-19 was in the lower end compared with previous reports, with considerably higher rates in hospitalized than nonhospitalized patients. Risk factors for VTE were consistent with previously reported studies.

Keywords: COVID-19, epidemiology, risk factors, venous thromboembolism

Introduction

After the discovery of SARS-CoV-2 in 2019 and the COVID-19 pandemic, the disease has received enormous attention all over the world. The spectrum of symptoms and course of illness are well-described [1–3]. Acute COVID-19 is associated with an increased risk of thrombotic complications. However, studies have reported wide variation in the incidence of venous thromboembolism (VTE) following COVID-19, ranging from 3% to 85% in smaller early studies [4–7]. Clinical and methodological properties of the studies have varied greatly, including study designs, populations, and analytic methods. Most studies describe the incidence during or immediately after hospitalization, and only a few studies have explored the difference in incidence of VTE between hospitalized and nonhospitalized patients [8, 9].

A recent study showed that among 287,683 patients hospitalized with COVID-19, 5.2% developed VTE [5]. The incidence of inhospital VTE decreased during the year 2020 but then rebounded during the second epidemic wave.

Several reports have pointed out a possible overlap between risk factors for VTE during COVID-19 and other acute illnesses and infections [10, 11]. In addition to the known general risk factors of VTE, such as high age or a history of previous VTE, black race is associated with a higher risk of VTE in patients with COVID-19 [12].

It is important to have reliable estimates of the incidence of VTE in patients with COVID-19, as guidelines on prophylactic anticoagulation are influenced by these estimates. This study aimed to determine the 90-day incidence of VTE in hospitalized and nonhospitalized patients in a national cohort and to determine associated risk factors.

Materials and methods

Study design and data collection

This registry-based cohort study comprises all patients in Norway registered with a positive polymerase chain reaction (PCR) test for SARS-CoV-2 before 1 December 2020. This national COVID-19 cohort includes both hospitalized and nonhospitalized patients, identified through the Norwegian Surveillance System for Communicable Diseases (MSIS) registry of the Norwegian Institute of Public Health (NIPH). COVID-19 is considered a mandatory notifiable disease in Norway. Thus, there is a legal mandate for Norwegian microbiology laboratories and physicians ordering the tests to report all positive SARS-CoV-2 PCR cases to MSIS [13, 14].

The Norwegian Patient Registry (NPR) comprises dates and ICD-10 (International Classification of Diseases, revision 10) codes from mandatory reports from hospital stays and ambulatory visits in all publicly financed Norwegian hospitals [15, 16]. As of 2008, reporting to the NPR has included the national personal identification code (PIN), which all Norwegian residents carry, enabling follow-up of patients over time and linkage with other registries. Therefore, hospitalized patients and outpatients can be followed back to 2008 in this registry.

The patients in this study were identified in MSIS through their PIN and cross-linked with data from NPR on hospital visits, giving data on hospitalization and outpatient visits before and after testing positive for COVID-19. The linkage between registries was done by the NPR. Therefore, the project only received anonymous data.

This study was approved by the Regional Ethics Committee (REK) South-Eastern Norway (no 2020/149384), and patient consent was waived according to the Health Research Act §35. Data from MSIS and NPR were available upon application after approval from REK. Approval from data protection officers and privacy officers were also obtained.

Study population

Hospitalized patients with COVID-19 were defined as patients with a positive SARS-CoV-2 PCR test within 14 days prior to or during hospitalization. According to NIPH, 1697 patients were hospitalized with COVID-19 as the main diagnosis before December 2020 [17]. Because some patients also were discharged with COVID-19 as a secondary diagnosis, the total number of hospitalized COVID-19 patients could possibly have been larger. The Norwegian Intensive Care and Pandemic Registry (NIPaR) was established in the beginning of the pandemic and contains data on all hospitalized COVID-19 patients in Norway with a coverage rate of 90% [18]. NIPaR reported 2086 patients admitted for COVID-19 in total during 2020 [19]. The number of included patients in our study between February 21, 2020 to November 30, 2020 (n = 2081) are comparable with the numbers reported from both NIPH and NIPaR.

Nonhospitalized COVID-19 patients were defined as those having a positive SARS-CoV-2 PCR without admission to hospital within 14 days after the test date. Episodes of reinfections were not included. Therefore, if several episodes were noted, only the first episode was selected. One patient was excluded because of several VTE-related hospitalizations in which the first event was dated prior to the positive PCR for SARS-CoV-2, thus assessed to be unrelated to COVID-19.

Variables

The following variables were collected from NPR: age, sex, ICD-10 diagnosis codes (up to 20 codes) and procedure codes from hospital visits back to 2008, dates for hospital visits, level of care (outpatient, day treatment, and hospitalization), hospital region, and death dates. Age group (10-year intervals), sex, country of birth (Norway or abroad), date of positive PCR test, and death dates were collected from MSIS. We calculated the Charlson comorbidity index (CCI) from ICD-10 diagnosis codes of previous hospital stays and outpatient visits from

Table 1. Descriptive statistics, number (%), unless otherwise stated.

	Inpatients	Outpatients	Total
Patients, *n*	2081	28,414	30,495
Age (years), mean (SD)	60.2 (17.4)	40.5 (16.5)	41.9 (17.3)
Sex, males	1208 (58)	14,971 (53)	16,179 (53)
Norwegian origin[a]	1242 (61)	17,108 (62)	18,350 (62)
Charlson comorbidity index			
0	1151 (55)	24,574 (86)	25,725 (84)
1–2	566 (27)	3059 (11)	3625 (12)
3–4	192 (9)	497 (2)	689 (2)
>4	172 (8)	284 (1)	456 (2)
Hospitalizations last year			
0	1595 (77)	28,288 (99)	29,883 (98)
1–2	366 (18)	101 (0.4)	467 (1.5)
>3	120 (6)	25 (0.1)	145 (0.5)
History of VTE	82 (4)	68 (0.2)	150 (0.5)
Health region			
Western Norway	318 (15)	NA	NA
Central Norway	102 (5)	NA	NA
Northern Norway	76 (4)	NA	NA
Southern and Eastern Norway	1582 (76)	NA	NA
Other, private	3 (0.1)	NA	NA
Wave of the epidemic			
Wave 1 (until July 17, 2020)	1187 (57)	7230 (25)	8417 (28)
Wave 2 (July 18, 2020 and later)	894 (43)	21,184 (75)	22,078 (72)

Abbreviation: VTE, venous thromboembolism.
[a] $n = 29{,}275$.

2008 to the date of the positive PCR test [20, 21]. CCI scores were calculated and categorized as 0, 1–2, 3–4, or >4 (Table 1) [22]. There are no missing data on age, sex, wave, or previous hospital contacts in Norway. Patients with no previous hospital contacts were considered to have a low probability of prior VTE or diseases that constitute the CCI score. For multivariable analysis we reduced the number of categories to three (0, 1–2, ≥3). For the age of patients with no previous hospital contacts, we only had 10-year intervals from MSIS, which we converted to continuous variables using the midpoint of the age group.

The study outcome VTE was captured using the first occurrence of one of the following ICD-10 diagnosis codes: I80.1 (thromboembolism in the femoral vein), I80.2 (thromboembolism in other deep veins the lower extremity), I80.3 (unspecified thromboembolism in the lower extremities), I80.8 (thromboembolism in other specified locations), I80.9 (thromboembolism in unspecified locations), I81 (portal vein thrombosis), I82.2 (thromboembolism in the vena cava), I82.3 (thromboembolism in the renal vein), I82.8 (thromboembolism in other specified veins), I82.9 (thromboembolism in unspecified veins), I26.0 (pulmonary embolism with cor pulmonale), and I26.9 (pulmonary embolism without cor pulmonale).

Norway experienced two main epidemic waves of COVID-19 in 2020. We divided the cases into those occurring during the first (PCR test date until July 17, 2020) or second (from July 18, 2020) epidemic wave of COVID-19. This is in line with definitions used in reports from the NIPH and others on COVID-19 waves in Norway [23, 24].

Statistical analysis

Descriptive statistics are presented as number (percent), mean (SD), or median (25th–75th percentile), as appropriate (Table 1). We calculated crude incidence rates for VTE and estimated 95% confidence intervals using Wilson's method [25].

Graphs of the incidence of VTE events over time were prepared as age-adjusted plots of the Cox models in the overall sample and stratified for wave 1 and wave 2, presented at age = 41.9 years, that is, the mean age of the total sample population.

We performed multivariable Cox proportional hazards regression to determine risk factors for VTE within 90 days after a positive PCR test or hospitalization. The start dates for observations were defined as the earliest date of positive PCR test or date of admission to hospital. We had exact dates of VTE event for patients diagnosed with VTE at the outpatient clinic. However, for inpatients diagnosed with a VTE event during hospitalization, we only had an interval of dates defined by hospital admission and discharge. Therefore, we used the midpoint of this interval to define the time of the event, in line with previous studies [26]. We used time to event as the dependent variable and estimated hazard ratios (HR) with 95% confidence intervals and *p*-values.

Prior to the analysis, we selected CCI (0, 1–2, or ≥3), sex (male or female), age, history of previous VTE (yes or no), hospitalization during the last 12 months prior to COVID-19 (yes or no), and hospitalization for COVID-19 (yes or no) as independent variables based on previous studies and clinical knowledge. We limited the number of variables to maximum one independent variable per 10 events. The proportional hazards assumption was checked by inspection of log–log plots and a test of nonzero slope of Schoenfeld residuals and found to be fulfilled [27].

To ensure our results were valid, we performed sensitivity analyses comparing different definitions of time of event (admission date, discharge date, or the midpoint) in Cox analysis, and whether interval-censored Cox regression analysis gave noteworthy changes in the results. Because death was a possible competing risk of VTE, we also determined the cumulative incidence in a Fine and Gray competing risks analysis [28].

The number of VTE events was considered too small for meaningful multivariable Cox regression analysis in strata according to wave. We used Stata software version 17.0 (StataCorp, College Station) for analysis, choosing a significance level of $p < 0.05$ in two-sided tests. We used OpenEpi [29] exact tests with the mid-*p* value [30].

Results

Study population

Data from record linkage between the two national registries comprised 30,495 patients who tested positive for COVID-19 from February 21, 2020 to November 30, 2020. Of these, 2081 (6.8%) patients were hospitalized; the remaining 28,414 patients were outpatients or had no hospital contact during this period. In total, 30,495 patients were observed with a mean follow-up time of 68.6 days, representing 2092,122 person-days at risk.

The mean age was 60.2 (SD 17.4) years for hospitalized patients and 41.9 (SD 17.3) years for nonhospitalized patients (Table 1). In total, 16,179 (53%) were males, and 18,350 (62%) were born in Norway. Median length of stay was 5 days (25th–75th percentile 2–9 and range 1–111 days) for those hospitalized, and 143 patients (7%) died during hospitalization. In total, 336/2081 (16%) received ventilatory support, of whom 201 (10%) received mechanical ventilation. Median CCI was 2 (25th–75th percentile 1–4) in hospitalized and 0 (0–1) in nonhospitalized patients; however, the median number of hospitalizations during the last 12 months was 0 in both groups. Among hospitalized patients, 82 (4%) had a history of VTE compared to 68 (0.2%) among those not hospitalized.

Outcomes

VTE occurred in 81 of 30,495 patients—that is, 0.3% (95% CI: 0.21–0.33) overall, 60/2081 (2.9%, 95% CI: 2.3–3.7) of hospitalized, and 21/28,414 (0.07%, 95% CI: 0.05–0.11) of nonhospitalized patients (Table 2). The majority (47/81 VTEs) were diagnosed during hospitalization. Pulmonary embolism was more frequent than DVT (0.2% vs. 0.1%). The proportion of lower extremity DVT compared to other types of DVTs was similar in both groups.

In total, 52 (0.62%) of COVID-19 patients were diagnosed with VTE in the first wave and 29 (0.13%) in the second. Among hospitalized patients, the incidence was 3.7% and 2.0%, respectively. When comparing the crude incidence of VTE in the first versus second wave, the 90-day incidence rate ratio was 4.70 (95% CI: 2.30–7.49, $p < 0.001$) for wave 1 versus wave 2 in the total sample, and 1.76 (95% CI: 1.02–3.12, $p = 0.041$)

Table 2. *Incidence of venous thromboembolisms within 90 days after positive test for COVID-19, number of patients with events, and incidence rates with 95% confidence intervals (CI) unless otherwise stated.*

	Inpatients ($n = 2081$)		Outpatients ($n = 28{,}414$)		Total ($n = 30{,}495$)	
	No. of patients	Incidence % (95% CI)	No. of patients	Incidence % (95% CI)	No. of patients	Incidence % (95% CI)
Venous thromboembolism	60	2.9 (2.3–3.7)	21	0.07 (0.05–0.11)	81	0.27 (0.21–0.33)
Pulmonary embolism	45	2.2 (1.6–2.9)	12	0.04 (0.00–0.07)	57	0.19 (0.14–0.24)
Deep venous thrombosis	17	0.8 (0.5–1.3)	10	0.04 (0.02–0.06)	27	0.09 (0.06–0.13)
Lower extremity[a], *n* (%)	5 (29)		3 (30)		8 (30)	
Other[b], *n* (%)	12 (71)		7 (70)		19 (70)	

[a]Distal of the Iliac vein.
[b]Upper extremity, abdominal, or unspecified.

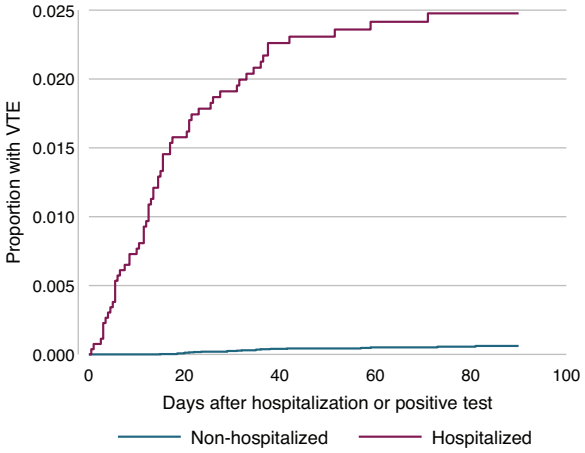

Fig. 1 *The cumulative incidence of venous thromboembolism (VTE) for the total sample according to hospitalization status. Predicted failure curves for patients from separate Cox models for hospitalized and nonhospitalized patients, adjusted for age.*

in hospitalized patients. Figure 1 shows the incidence of VTE in hospitalized and nonhospitalized patients after adjusting for age; and Fig. 2 shows the incidence of VTE during wave 1 and 2 in (A) hospitalized patients and (B) nonhospitalized patients.

The overall all-cause mortality within 90 days of a positive COVID-19 test or hospital admission was 1.5% (450 of 30,495 patients). The highest mortality was observed in the two first months of the pandemic—2.9% by March 2020 and 4.6% by April 2020. Among patients hospitalized for COVID-19, 143 of 2081 (6.9%) died within 90 days of hospitalization.

Risk factors for VTE

In multivariable Cox regression analysis, age per decade (HR 1.28, 95% CI: 1.11–1.47, $p < 0.05$), history of previous VTE (HR 4.69, 95% CI: 2.34–9.40, $p < 0.05$), and hospitalization for COVID-19 (HR 23.84, 95% CI: 13.48–42.13, $p < 0.05$) were associated with risk of VTE (Table 3). The result of the Cox regression analysis was very similar when using admission date, discharge date, or the midpoint as time of event. Similarly, using interval-censored Cox regression did not materially affect the results.

The cumulative incidence from the Fine and Gray competing risks model was not significantly different from the Cox model, with only a marginally higher cumulative incidence function from the Cox model in hospitalized patients. See Supporting Information for results from the Fine and Gray competing risks model (Table S1, Figs. S1 and S2).

Discussion

In this registry-based study that was based on a national cohort of hospitalized and nonhospitalized patients with COVID-19, the 90-day incidence of VTE was low in both hospitalized (2.9%) and nonhospitalized patients (0.07%). The incidence of VTE was higher in wave 1 than wave 2 of the epidemic. The all-cause 90-day mortality was highest among hospitalized patients and in the first 2 months of the pandemic. Age, history of previous VTE, and hospitalization for COVID-19 were associated with an increased risk of VTE.

The incidence rates of VTE in patients with COVID-19 in this study were in the lower end of previous reports [4–7]. In contrast to other studies

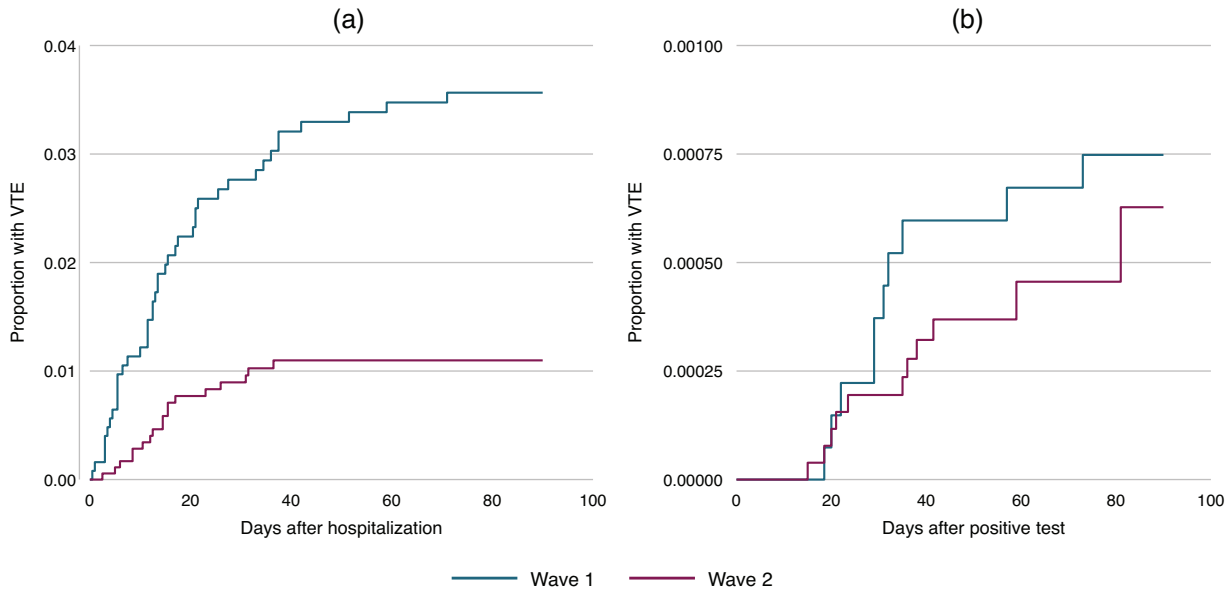

Fig. 2 *The cumulative incidence of venous thromboembolism (VTE) for wave 1 and 2 in (A) hospitalized patients and (B) nonhospitalized patients. Predicted failure curves for patients from separate Cox models for hospitalized and nonhospitalized patients, adjusted for age.*

Table 3. *Results from multivariable Cox regression analysis of risk factors of venous thromboembolism (VTE), n = 81.*

Variables	Hazard ratio	95% CI	*p*-Value[a]
Charlson comorbidity index			
1–2 vs. 0	0.97	0.56–1.70	0.92
≥3 vs. 0	0.97	0.48–1.95	0.92
Age, per decade	1.28	1.11–1.48	**0.001**
Sex, male	1.30	0.83–2.04	0.25
Hospitalization last 12 months	0.79	0.41–1.51	0.47
History of VTE	4.69	2.34–9.40	**<0.001**
Hospitalized for COVID-19	23.84	10.91–42.13	**<0.001**

[a]Bold font indicates significance.

with selected high-risk population—that is, ICU-patients—our study is registry-based and consists of an unselected nationwide cohort of patients with COVID-19. In the beginning of the pandemic, VTE rates as high as 85% were reported [31]. The variations in reported prevalence rates are influenced by the large differences in study designs and populations, including data quality, threshold for hospitalization or transfer to the ICU, use of thromboprophylaxis, patient characteristics, and methods to ascertain the outcome. Thus, comparing incidence rates is difficult [32]. A meta-analysis from 2021 reported a pooled incidence for VTE in hospitalized COVID-19 patients of 17% [33]. However, the incidence was markedly higher in studies intensely screening for VTE (33.1%) compared to when clinical diagnosis was used (9.8%), as well as in prospective (25%) compared to retrospective studies (12%).

Some more recent studies have reported an incidence rate of 5%–10% among hospitalized patients with COVID-19 [5, 8, 34], slightly higher than our rates, but still considerably lower than early reports [31]. In concordance with our study, other reports show far lower rates of VTE in nonhospitalized compared to hospitalized patients [8, 35, 36]. The gradually increasing incidence of VTE from

nonhospitalized patients, to hospitalized patients and those in the ICU, corroborates the close relationship between risk of VTE and severity of COVID-19 [37–39].

The patients included in this study had COVID-19 in Norway in 2020 when two major epidemic waves of COVID-19 were observed. The rate of VTEs decreased considerably throughout the year of 2020. The VTE incidence rate was 4.7 times as high in the first versus the second wave. This could be due to changes in the virus characteristic, test capacity, wider use of thromboprophylaxis, and higher treatment levels, as well as an increased focus on VTEs in the beginning of the pandemic due to reports of very high rates of VTE. According to weekly reports from the NIPH, the genetic line B1 (Pangolin nomenclature) dominated in Norway throughout 2020 with the exception of February 2020 [23]. However, different subgroups (B.1, B.1.1, B.1.5.24, B.1.160, and B.1.177) caused large outbreaks, especially during the second half of 2020. The World Health Organization classifies SARS-CoV-2 subgroups of concern based on increased virulence or disease severity [40]. The occurrence of different subgroups throughout 2020 may explain some of the differences in infection rates, number of deaths, and incidence of VTE over time.

The incidence rates may be underestimated due to conservative use of radiological imaging as part of institutional infection control measures. It is also possible that some patients have been diagnosed with VTE postmortem or died without being diagnosed. Vaccination against COVID-19 started in December 2020 in Norway [41]—that is, after the end of inclusion of patients in the present cohort. Therefore, vaccination status could not have influenced these numbers.

Age, a history of previous VTE, and hospitalization for COVID-19 were associated with the risk of VTE in this study. The lack of association of male sex with an increased risk of VTE contrasts with findings from some recent studies [7, 35]. Although 40% of patients in the national cohort were immigrants, previous reports have described a higher notification and hospitalization rate among immigrants in Norway [42]. In our study, the overall incidence of VTE was similar among patients born in Norway compared to immigrants (0.3% vs. 0.2%). Black race has previously been reported as a risk factor for VTE during COVID-19, but in the present study details on country of origin or ethnicity were not available.

Limitations

This study was a large, observational registry-based study on VTE in a national cohort of patients with COVID-19 identified through two large nationwide registries, which carries some limitations [43]. As SARS-CoV-2 is a fairly new discovery, to our knowledge, data on coverage of virus in MSIS has not yet been validated. However, the MSIS registry has been validated on other communicable diseases—that is, the Legionella bacterium, finding very high internal validity and completeness (>95%) for key variables and an external validity of 83% when compared to reports from NPR [44]. It is important to note that data from NPR cannot be used as a gold standard, and that the lack of a gold standard for comparison is a weakness of these validity estimates. In our opinion, external validity of the diagnosis of SARS-CoV-2 should be high due to the confirmation with PCR tests and extraordinary awareness and high level of priority during the pandemic.

Even though the study was retrospective, the data were reported prospectively to the registries, which reduces the risk of selection bias associated with retrospective studies. Variables, the analysis, and outcomes were limited to available data; however, there was very little missing data. These registries lack data on thromboprophylaxis, which influences the incidence of VTE. All VTEs were diagnosed at hospitals in Norway, eliminating the risks of unreported VTE events from other health services. However, any recurrent VTEs during the 90-day observation period would not be detected because only the first event was counted. This is a limitation with ICD-coding, as it is not possible to discriminate between primary or recurrent episodes when there are several hospital stays or transfers between hospitals for a patient. The ICD-10 code for cerebral vein thrombosis (G08) was not included among the events in this study; however, only one of the patients had this diagnosis following COVID-19. Registry data are subject to potential misclassification due to ICD-10 coding errors. Coding errors rarely occur at diagnosis-levels but rather at secondary subgroups. For instance, the reporting of VTE, DVT, and PE is unlikely to possess coding errors, but the most detailed coding level—such as type of DVT—are more prone to errors [15].

Conclusion

The 90-day incidence of VTE was in the lower end of previous reports for both hospitalized and nonhospitalized patients with COVID-19. Risk factors for VTE were hospitalization, age, and history of VTE. Identifying risk factors might be useful in future risk stratification.

Author contributions

Conceptualization; data curation; formal analysis; investigation; methodology; project administration; visualization; writing—original draft; writing—review and editing: Birgitte Tholin. *Conceptualization; data curation; funding acquisition; methodology; supervision; writing—review and editing*: Waleed Ghanima. *Formal analysis; writing—review and editing*: Maria Lie Selle. *Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; supervision; validation; visualization; writing—review and editing*: Knut Stavem.

Conflict of interest statement

Birgitte Tholin and Maria Lie Selle have no conflicts of interest to report. Knut Stavem reports consulting fees from UCB Pharma and MSD unrelated to this study. Waleed Ghanima reports fees for participation in Advisory board from Amgen, Novartis, Pfizer, Principia Biopharma Inc—a Sanofi Company, Sanofi, SOBI, Grifols, UCB, Argenx, Cellphire. Lecture honoraria from Amgen, Novartis, Pfizer, Bristol Myers Squibb, SOBI, Grifols, Sanofi, and Bayer. Research grants from Bayer, BMS/Pfizer, and UCB.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1: Results from Fine and Gray competing risks analysis of risk factors of venous thromboembolism, n = 81.
Figure S1: The cumulative incidence of venous thromboembolism for wave 1 and 2 in hospitalized and non-hospitalized patients from separate Fine and Gray models adjusted for age.
Figure S2: The cumulative incidence of venous thromboembolism for wave 1 and 2 in hospitalized and non-hospitalized patients from separate Cox models adjusted for age. ■

