Original article

Incidence of venous thromboembolism in hospitalized patients with COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) can lead to systemic coagulation activation and thrombotic complications. We investigated the incidence of objectively confirmed venous thromboembolism (VTE) in 198 hospitalized patients with COVID-19 in a single-center cohort study. Seventy-four patients (37%) were admitted to the intensive care unit (ICU). At time of data collection, 58 (29%) were still hospitalized and 14% had died. During a median follow-up of 5 days (IQR, 3-9), 33 patients (17%) were diagnosed with VTE of whom 22 (11%) had symptomatic VTE, despite routine thrombosis prophylaxis. The cumulative incidences of VTE at 7 and 14 days were 15% (95% CI, 9.3-22) and 34% (95% CI, 23-46), respectively. For symptomatic VTE, these were 11% (95% CI, 5.8-17) and 23% (95% CI, 14-33). VTE appeared to be associated with death (adjusted HR, 2.9; 95% CI, 1.02-8.0). The cumulative incidence of VTE was higher in the ICU (25% at 7 days 95% CI, 15-36, and 48% at 14 days, 95% CI, 33-61) than on the wards (any VTE and symptomatic VTE 6.5 % at 7 days (95% CI, 1.5-17) and 10% at 14 days (95% CI, 2.9-24)).The observed risk for VTE in COVID-19 is high, particularly in ICU patients, which should lead to a high level of clinical suspicion and low threshold for diagnostic imaging for DVT or PE. Future research should focus on optimal diagnostic and prophylactic strategies to prevent VTE and potentially improve survival.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and can lead to systemic coagulation activation. Initial studies from China report increased D-dimers (0.5 mg/L or higher) in 46-63% of patients, as well as other signs of coagulation activation including mild thrombocytopenia and a moderately prolonged prothrombin time.[1,2] Additionally, more pronounced coagulation activation seems to be correlated with a severe disease course, including admission to the intensive care unit (ICU) and death. For example, patients who died of COVID-19 had higher D-dimers on admission compared with those who survived, while D-dimer levels increased further during hospital stay in patients who died but not in survivors.[3] In another study, patients with D-dimers of 1.0 µg/L or higher had an 18-fold increased risk of death.[2] One study used the International Society on Thrombosis and Haemostasis (ISTH) definition of disseminated intravascular coagulation (DIC) and found that a score of ≥5 points was present in 71% of those who died compared with 0.6% in survivors.[4] None of these studies reported on the number of patients with thrombotic complications.

Since the pandemic spread of SARS-CoV-2, there have been several anecdotal reports from colleagues on a high incidence of thrombotic complications, including thrombosis of extracorporeal circuits for continuous veno-venous hemofiltration (CVVH), central venous catheter associated thrombosis, and deep venous thrombosis (DVT) and pulmonary embolism (PE). Most but not all of these complications occurred in patients admitted to the ICU, with most patients receiving routine thrombosis prophylaxis.

Diagnosis of DVT and PE may be particularly challenging in patients with COVID-19. Symptoms of PE overlap with symptoms of COVID-19 and mild symptoms may be overlooked in a patient already suffering from shortness of breath. Similarly, clinical signs and symptoms of DVT may be harder to detect, especially in ICU patients, especially when treating clinicians primarily focus on respiratory status and do not systematically assessing lower extremities for signs of DVT.

Early April 2020, a large number of venous thromboembolic events were diagnosed in COVID-19 patients admitted to our ICU, based on a clinical suspicion of DVT in the lower extremities. These observations have led us to intensify the dose of low-molecular-weight heparin (LMWH) to prevent VTE in COVID-19 patients in the ICU. In the present study, we report on the incidence and risk factors of VTE in COVID-19 patients admitted to the ICU or general ward.

Methods

Patients

We identified consecutive patients with COVID-19 admitted to the Amsterdam University Medical Centers, location Academic Medical Center, until April 12th, 2020. COVID-19 was confirmed by a reverse transcription polymerase chain reaction (RT-PCR) test on a nose/throat swab or sputum sample positive for SARS-CoV-2. Given the sensitivity of RT-PCR of only 50-80%,[5] a daily multidisciplinary team also considered COVID-19 confirmed in patients with a negative RT-PCR but with symptoms and disease course consistent with COVID-19, the absence of an alternative diagnosis, as well as a CT-scan of the chest showing abnormalities highly suspicious of typical pulmonary involvement of COVID 19 (CO-RADS 4 or 5 as per the Dutch Radiology Society).[6] We did not include patients who were diagnosed with COVID-19 during hospital stay for other medical conditions.

Hospitalized patients were categorized as ICU patients or as ward patients. Patients were categorized as ward patients if they had not been transferred to the ICU at any time during the course of their disease. All ICU patients were mechanically ventilated during the course of their disease.

Thrombosis prophylaxis was part of standard of care in all COVID-19 patients. From April 3 onwards, patients in ICU received a double dose of nadroparin as compared to patients on the wards, which was nadroparin 2,850 twice-daily (bid) for patients with a body weight <100 kg and 5,700 IU bid for those ≥100 kg.

Outcomes

The primary outcome was an objectively confirmed diagnosis of distal or proximal DVT, PE or venous thrombosis at other sites including catheter-related thrombosis. The secondary outcome was symptomatic VTE, excluding events detected by bilateral leg ultrasound screening. All outcomes were adjudicated by two of the authors (M.C. and N.v.E.). We did not adjudicate deaths to identify fatal PE, as almost all deaths were due to hypoxemic respiratory failure which can be indistinguishable from fatal PE, while autopsies were very rarely performed in COVID-19 patients.

Data collection

Patients were retrospectively followed from the day of admission to our hospital (also in case a patient was transferred from another hospital) until death, hospital discharge, transfer to another hospital, or end of data collection (between April 10 and 14, 2020). We collected data on

demographics and blood tests on admission. D-dimer levels were included if measured on or within 72 hours of admission.

Statistical analysis

Patient characteristics were compared between ward and ICU patients using standard descriptive statistics. The proportion of ICU and ward patients with VTE was assessed, as well as the rate of first VTE per 100 hospital days. In addition, the cumulative incidence, overall and for symptomatic VTE only, was calculated using a competing risk approach considering death as a competing risk. Risk factors for VTE were evaluated by calculating subdistribution hazard ratios (SHR) in a Fine & Gray competing risk regression model. The association between VTE and mortality and between ICU stay and VTE were analyzed by calculating a time-varying hazard ratio in Cox proportional hazards model. Analyses were performed in R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). Formal approval from the Medical Ethics Review Committee was not required as the Medical Research Involving Human Subjects Act (WMO) does not apply for this observational study.

Results

Between March 2 and April 12 2020, 199 patients who were hospitalized because of COVID-19 were included. One patient was excluded because he was immediately transferred to another hospital from the emergency department. Of the remaining 198 patients, 148 (75%) were hospitalized after an emergency department visit, while 50 (25%) were transferred from another hospital. Seventy-four patients (37%) were admitted to the ICU after being transferred from the ICU of another hospital (n=44), our general ward (n=19), or directly from the emergency department (n=11). COVID-19 was confirmed by a positive RT-PCR in 173 patients (87%) and by clinical features consistent with COVID-19 in combination with a CT chest with suspicious or typical features (CO-RADS 4 or 5) and no alternative diagnosis in 25 (13%).

Characteristics

Patient characteristics are shown in Table 1. Mean age was 61 years (SD, 14) and 130 (66%) were male. Median body mass index (BMI) was 27 kg/m^2 (interquartile range [IQR], 24-31). Compared to ward patients, ICU patients were more often male (77% vs 59%; P=0.014) and had higher D-dimer levels on admission (median 2.1 mg/L vs. 1.1 mg/L; P=0.006). The median time between symptom onset and admission to our hospital was 7 days (IQR, 5-10) for patients presenting at the emergency

department and 11 days (IQR, 6-14) for those transferred from another hospital. Thrombosis prophylaxis was initiated in 167 patients (84%) while 19 (9.6%) continued therapeutic anticoagulation.

At the end of data collection (14 April 2020), 108 patients (55%) had been discharged, 5 (2.5%) transferred to another hospital, 27 had died (14%), and 58 (29%) were still hospitalized. The median times from admission to discharge or death were 5 days (IQR, 2-7) and 6 days (IQR, 4-10, respectively. Nine patients (4.5%) were re-hospitalized after a median of 7 days (IQR, 4-8) after discharge.

Venous thromboembolism

During a median follow-up of 5 days (IQR, 3-9; range, 1-39), 33 patients (17%) were diagnosed with VTE and 1 (0.5%) with extensive thrombophlebitis for which therapeutic anticoagulation was initiated. Type of VTE was PE with or without DVT in 11 (5.6%), proximal DVT in 13 (6.6%), distal DVT in 8 (4.0%), and upper extremity DVT in 1 (0.5%). VTE was symptomatic in 22 patients (11%) and detected incidentally or by screening in 11 (5.6%). Of note, screening for lower extremity DVT was performed randomly in 52 patients (27%) during hospital stay (ICU, n=34; ward, n=18), while CT pulmonary angiography for PE was only performed on indication (e.g. sudden worsening hypoxemia). VTE was diagnosed after a median of 6 days after admission (IQR, 4-9). The VTE incidence rate was 2.4 per 100 hospital days (95% CI, 0.7-7.6). In the competing risk model, the cumulative incidences of VTE at 7 and 14 days were 15% (95% CI, 9.3-22) and 34% (95% CI, 23-46). When only considering symptomatic VTE, the cumulative incidences were 11% (95% CI, 5.8-17) and 23% (95% CI, 14-33) at 7 and 14 days, respectively. All VTE were diagnosed in patients receiving thrombosis prophylaxis. When analyzed as a time-varying variable, VTE was significantly associated with death (HR, 3.3; 95% CI, 1.2-8.9), also when adjusted for age, sex, and ICU stay as time-varying variable (adjusted HR, 2.9; 95% CI, 1.02-8.0).

ICU versus ward patients

The proportion of patients with VTE was significantly higher in the ICU s (29 of 74; 39%) than in the general wards (4 of 124; 3.2%), corresponding to a SHR of 7.3 (95% CI, 2.5-21). The cumulative incidence of any VTE in ICU patients was 25% at 7 days (95% CI, 15-36) and 48% at 14 days (95% CI, 33-61). Symptomatic VTE was detected in 18 ICU patients (24%) and 4 ward patients (3.2%; SHR, 3.8; 95 CI, 1.3-12). The cumulative incidence of symptomatic VTE in ICU patients was 15% at 7 days (95% CI, 7.8-25) and 31% at 14 days (95% CI, 19-44). The cumulative incidences of any VTE and

symptomatic VTE in ward patients were both 6.5 % at 7 days (95% CI, 1.5-17) and 10% at 14 days (95% CI, 2.9-24).

Findings were comparable when ICU stay was modelled as a time-varying variable (HR, 6.9 for any VTE; 95% CI, 2.8-17). The higher risk in ICU patients was somewhat attenuated in the sensitivity analysis excluding patients transferred from another hospital (34% vs. 3.4%; SHR, 5.6; 95% CI, 1.6-19).

Risk factors for venous thromboembolism

Besides ICU stay, other risk factors associated with VTE in univariable regression analyses were a lower lymphocyte count (SHR, 0.59 for every 1 x 10^9/L increase; 95% CI, 0.37-0.93), higher neutrophil-to-lymphocyte ratio (SHR, 2.4 for every unit increase; 95% CI, 1.5-3.7), and a higher D-dimer level (SHR, 1.8 for every 1 mg/L increase; 95% CI, 1.3-2.4) (Table 3). These associations remained materially unchanged when adjusted for age, sex, and ICU stay (Table 3) and when excluding patients transferred from another hospital (data not shown). Notably, none of the 19 patients (0%) who continued therapeutic anticoagulation developed VTE compared to 33 of 179 of the remaining patients (33%; SHR, not estimable; Fisher's exact test P=0.048).

Discussion

We observed a very high risk of VTE in patients with COVID-19. Although the profound coagulopathy associated with COVID-19 has been described soon after start of the pandemic, only few data on clinical VTE have been reported. In a cohort of 81 ICU patients in China, in which routine thromboprophylaxis was not standard of care, the proportion of patients who were diagnosed with DVT was 25%; a follow-up duration or cumulative incidence was not reported.[7] In a study of 184 ICU patients in three Dutch hospitals, where routine LMWH prophylaxis was applied, 28 (15%) patients had VTE, with a cumulative incidence of 31% after 14 days.[8] In our hospital, where thrombosis prophylaxis in patients admitted with COVID-19 is standard of care, VTE was observed in 29 of 74 (39%) ICU patients, with a cumulative incidence of 48% after 14 days. The high incidence in the present study may partially be explained by the initiation of a screening approach, although the risk remained very high if only symptomatic VTE was considered (24% of patients; cumulative incidence 31% after 14 days). In non-ICU COVID-19 patients admitted to the regular ward, 4 of 124 patients (3%) were diagnosed with symptomatic VTE despite thrombosis prophylaxis.

Some issues warrant comment. First, this was a single-center cohort study with a modest sample size, and 29% of patients were still hospitalized at the time of data collection. Second, including patients transferred from other hospitals may lead to immortal time bias as they need to survive until transfer, thereby potentially biasing the VTE cumulative incidence. However, restricting the analysis to patients admitted directly from our own emergency department did not substantially affect the results. Although immortal time bias could also have been introduced by placing patients who were transferred from the ward to the ICU in the ICU group, results were consistent when analyzing ICU stay in a time-varying model. There appeared to be a large difference between the crude proportion of patients with VTE and the cumulative incidence estimate from the survival model, despite the use of a competing risk model to mitigate the influence of death. Likely explanations include the relatively short median follow-up duration, large number of patients still hospitalized, and the (informative) censoring of patients when discharged from the hospital; the risk of VTE in the latter group is likely to be lower than that of patients remaining in the cohort. Finally, based on concerns of a high risk of (fatal) VTE following early observations, we changed our practice during the follow-up period by performing screening compression ultrasound in the ICU every 5 days, while also performing a single cross-sectional round of compression ultrasounds at the ward in the 10 days prior to data collection. This screening led to diagnosis of asymptomatic DVT, all in the ICU group, which may be clinically less relevant than symptomatic DVT. Strengths of our study are that the cohort consists of consecutive patients, follow-up is complete, and that VTE was objectively confirmed.

How should the present results be interpreted? It is not clear whether coagulopathy in COVID-19 stands on itself or whether it is largely driven by inflammation. Among patients with severe sepsis, approximately 35% develop DIC.[9] In DIC, coagulation activation leads to micro- and macrovascular thrombosis that contributes to organ failure and death. Estimates of thrombosis are up to 40% in patients with DIC due to sepsis.[9] Coagulation activation in turn can lead to exhaustion of coagulation factors and platelets, thus to an increased risk of major bleeding with an estimated incidence of 5-12%.[9] The coagulopathy observed in COVID-19 patients partly resembles the coagulation activation seen in severe sepsis and overt DIC, but seems to be less pronounced in terms of coagulation factor consumption and platelet depletion.[4] More than in DIC, the high D-dimer levels seen in COVID-19 patients could reflect macrovascular thrombosis, like PE or DVT, rather than microthrombosis.

It is currently not known whether VTE contributes to respiratory deterioration or death in COVID-19 pneumonia, although VTE during the course of disease appeared to be associated with mortality in an exploratory analysis in our cohort. Whether the high incidence of VTE observed in the ICU justifies higher or therapeutic doses of pharmacological prophylaxis at an acceptable bleeding risk, and

whether this would improve the outcome of severe COVID-19 pneumonia is unknown. One observational study from China that included 449 hospitalized COVID-19 patients suggested that thrombosis prophylaxis was associated with a 56-63% reduction in mortality in patients with sepsis-induced coagulopathy, but not in other patients.[10] It is important to note that this analysis was not adjusted for potential confounders, immortal time bias could have been introduced by only considering patients who received heparin for 7 days or longer, and that only 22% of COVID-19 patients received thrombosis prophylaxis, which is much less than expected according to guidelines on thrombosis prophylaxis in medical patients.[11] Currently, several randomized controlled trials are being planned in which the optimal dose of thrombosis prophylaxis will be investigated. Interestingly, in our cohort, none of the patients who were receiving therapeutic anticoagulation at admission developed VTE. The present findings suggest that D-dimer levels or lymphocyte counts may be used to identify patients at higher risk of VTE.

The 3% risk of VTE among patients who were not admitted to ICU is considerable, despite the standard use of thrombosis prophylaxis. The risk may be somewhat higher than expected in medical hospitalized patients. In a study of 1,099 Chinese patients with COVID-19, 40% were considered at high risk with a Padua score of 4 points or higher.[12] Such a score corresponds to a risk of symptomatic VTE while using thrombosis prophylaxis of 2.2%.[11,13] Likewise, in a large observational validation study that evaluated the IMPROVE risk assessment model in medical patients, the rate of in-hospital VTE while using prophylaxis ranged from 0.85 to 2.89% in high-risk patients.[14] Of note, although thrombosis prophylaxis decreases the risk of VTE by about half, it does not decrease mortality.[11] It is unknown whether anticoagulants improve survival in a procoagulant and inflammatory disease like severe COVID-19 pneumonia.

Based on the present findings, we believe the threshold of suspicion of VTE in COVID-19 patients should be low and elicit appropriate diagnostic testing and treatment if VTE is diagnosed. The clinical value of ultrasound screening of the lower extremities in ICU patients with COVID-19 is a matter of debate. However, given the high risk of symptomatic VTE in ICU patients, screening followed by initiating therapeutic anticoagulation may be justified in patients diagnosed with asymptomatic (proximal) DVT to prevent extension and embolization. It is possible that a higher intensity of thrombosis prophylaxis, both in ICU and ward patients, not only decreases VTE but also decreases mortality, although the bleeding risk needs to be acceptable. Obviously, our findings need confirmation in larger cohorts and different settings. Future research should focus on optimal diagnostic and prophylactic strategies and assessing the risk of VTE in post-discharge and non-hospitalized patients with COVID-19.

Author contributions

All authors contributed substantially to the study design, acquisition, analysis or interpretation of the data. S. Middeldorp, M. Coppens and N. van Es drafted the first version of the manuscript. All authors revised the manuscript critically and approved the final version.

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Disclosures

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The other authors have no disclosures.

References

1. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020:1-13.

2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.

3. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA - J Am Med Assoc*. 2020;323(11):1061-1069.

4. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;(February):844-847.

5. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA*. March 2020.

6. Ai T, Yang Z, Xia L. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease. *Radiology*. 2020;2019:1-8.

7. 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.

8. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. April 2020:100632.

9. Levi M, Scully M. How I treat disseminated intravascular coagulation. *Blood*. 2018;131(8):845-854.

10. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. March 2020.

11. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018;2(22):3198-3225.

12. Wang T, Chen R, Liu C, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. *Lancet Haematol*. 2020;2019(20):2019-2020.

13. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost*. 2010;8(11):2450-2457.

14. Rosenberg D, Eichorn A, Alarcon M, McCullagh L, McGinn T, Spyropoulos AC. External validation of the risk assessment model of the international medical prevention registry on venous thromboembolism (IMPROVE) for medical patients in a tertiary health system. *J Am Heart Assoc*. 2014;3(6):1-7.

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Legends

Figure 1A: Cumulative incidence of venous thromboembolism

Figure 1B: Cumulative incidence of symptomatic thromboembolism

Figure 2A: Cumulative incidence of venous thromboembolism in ICU and non-ICU patients

Figure 2B: Cumulative incidence of symptomatic venous thromboembolism in ICU and non-ICU patients

Table 1. Baseline characteristics

	All patients N=198	Patients admitted to ICU N=74	Patients admitted to regular ward N=124	P-value
Mean age, yr (SD)	61 (14)	62 (10)	60 (15)	0.28
Male sex, n (%)	130 (66)	57 (77)	73 (59)	0.014
Body weight ≥100 kg, n (%)	22/157 (14)	12/72 (17)	10/85 (12)	0.52
Median body mass index, kg/m^2 (IQR)	27 (24-31)	27 (24-30)	28 (25-31)	0.19
History of venous thromboembolism, n (%)	11 (5.6)	2 (2.8)	9 (7.5)	0.30
Active cancer, n (%)	7 (3.5)	3 (4.2)	4 (3.4)	1.0
Anticoagulant therapy at admission	19 (9.6)	7 (9.5)	12 (9.7)	1.0
Antiplatelet therapy at baseline	29 (15)	8 (11)	21 (17)	0.12
Platelet count				
Mean, x 10^9/L (SD)	239 (93)	250 (89)	231 (95)	0.18
<150 x 10^9/L, n (%)	27/196 (14)	7 (9.5)	20/122 (16)	0.25
D-dimer				
Median, mg/L (IQR)	1.1 (0.7-2.3)	2.1 (0.8-9)	1.1 (0.7-1.6)	<0.001
>0.5 mg/L, n (%)	110/131 (84)	39/47 (83)	71/84 (85)	1.0
>1.0 mg/L, n (%)	75/131 (57)	30/47 (64)	45/84 (54)	0.10

Table 2 Clinical outcomes

	All patients (N=198) n (%)	ICU patients (N=74) n (%)	Patients in wards (N=124) n (%)
Venous thromboembolism	33 (17)	29 (39)	4 (3.2)
Pulmonary embolism	11 (5.6)	9 (12)	2 (1.6)
Central or lobar	0	0	0
Segmental	9 (4.5)	8 (11)	1 (0.8)
Subsegmental	2 (1.0)	1 (1.4)	1 (0.8)
Deep-vein thrombosis	22 (11)	20 (27)	2 (1.6)
Proximal leg DVT	12 (6.1)	12 (16)	0
Distal leg DVT	9 (4.5)	7 (9.5)	2 (1.6)
Upper-extremity DVT	1 (0.5)	1 (1.4)	0
Symptomatic VTE	21 (11)	17 (23)	4 (3.2)
Pulmonary embolism	11 (5.6)	9 (12)	2 (1.6)
Proximal DVT	8 (4.0)	8 (11)	0
Distal DVT	2 (1.0)	0	2 (1.6)

Table 3. Risk factors for venous thromboembolism

	VTE (N=33)	No VTE (N=165)	Univariable SHR (95% CI)***	Multivariable SHR (95% CI)****
Mean age, years (SD)	62 (9)	60 (15)	1.04 (0.85-1.3)*	1.09 (0.86-1.4)
Male sex	22 (67)	108 (66)	0.68 (0.33-1.4)	0.46 (0.22-0.97)
Intensive care unit	29 (88)	45 (27)	7.3 (2.5-21)	8.4 (3.0-24)
Median body weight, kg/m^2 (IQR)	84 (74-96)	94 (75-95)	1.2 (0.29-5.4)**	2.8 (0.52-15)
History of venous thromboembolism	3 (9.1)	8 (4.8)	0.98 (0.27-3.5)	2.2 (0.46-11)
Anticoagulant use at admission	0 (0)	19 (12)	Not estimable	Not estimable
Mean hemoglobin, mmol/L (SD)	7.8 (1.2)	8.1 (1.3)	0.97 (0.74-1.3)**	1.002 (0.72-1.4)
Median white blood cell count, x 10^9/L (IQR)	7.8 (6.1-11)	6.7 (5.4-8.8)	1.6 (0.97-2.8) **	1.5 (0.73-3.3)
Median neutrophil count, x 10^9/L	5.7 (4.4-7.9)	5.1 (3.8-7.1)	2.0 (0.98-4.1) **	1.7 (0.72-4.0)
Median lymphocyte count, x 10^9/L	0.68 (0.47-0.96)	1.0 (0.77-1.3)	0.59 (0.37-0.93) **	0.59 (0.39-0.90)
Median neutrophil-to-lymphocyte ratio	9.5 (5.9-13)	5.0 (3.5-7.9)	2.4 (1.5-3.7)**	2.0 (1.3-3.2)
Mean platelet count, x 10^9/L	250 (89)	232 (95)	1.02 (0.99-1.1)*	1.004 (0.97-1.05)
Median D-dimer, mg/L (IQR)	2.1 (0.76-9.0)	1.1 (0.68-1.6)	1.8 (1.3-2.4)**	1.5 (1.14-2.0)***

Abbreviations: SD, standard deviation; SHR, subdistribution hazard ratio.

* Per 10 units increase.

** Per 1 unit increase.

*** Variables with a non-normal distribution (i.e. body weight, white blood cell count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, and D-dimer) were analyzed log-transformed.

**** Multivariable analysis adjusted for age, sex, and intensive care unit admission.

Figures

Figure 1A. Cumulative incidence of venous thromboembolism

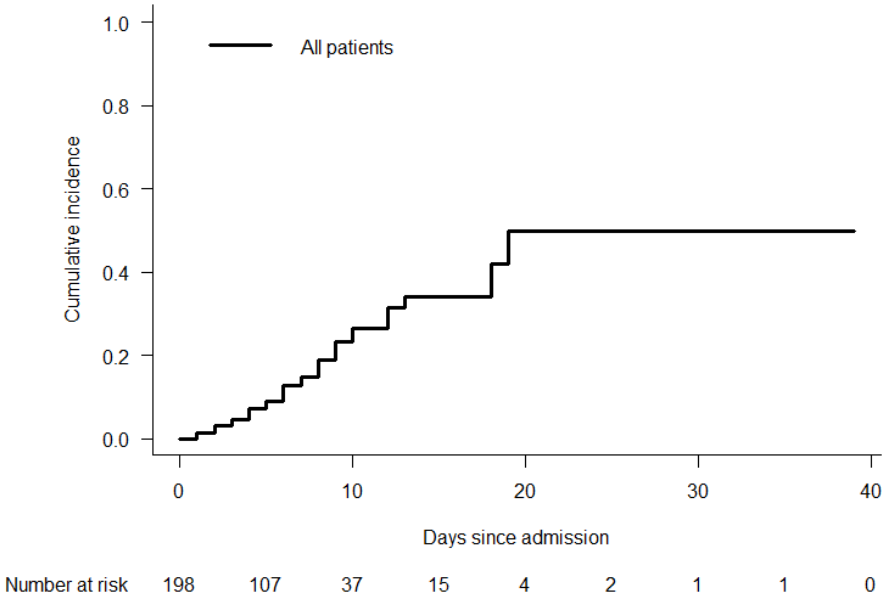


Figure 1B. Cumulative incidence of symptomatic venous thromboembolism

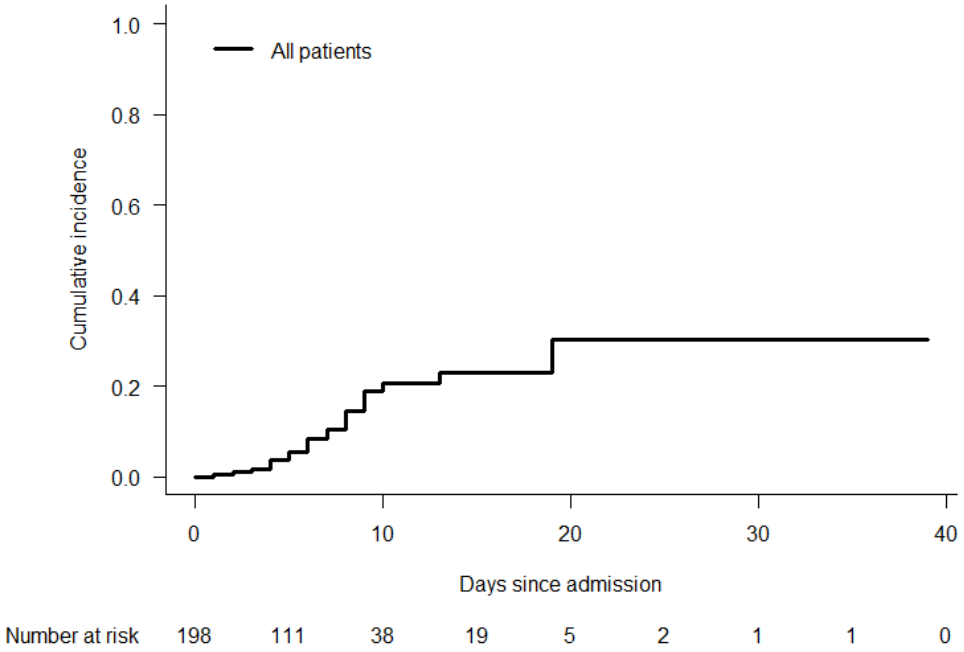


Figure 2A. Cumulative incidence of venous thromboembolism in ICU and non-ICU patients

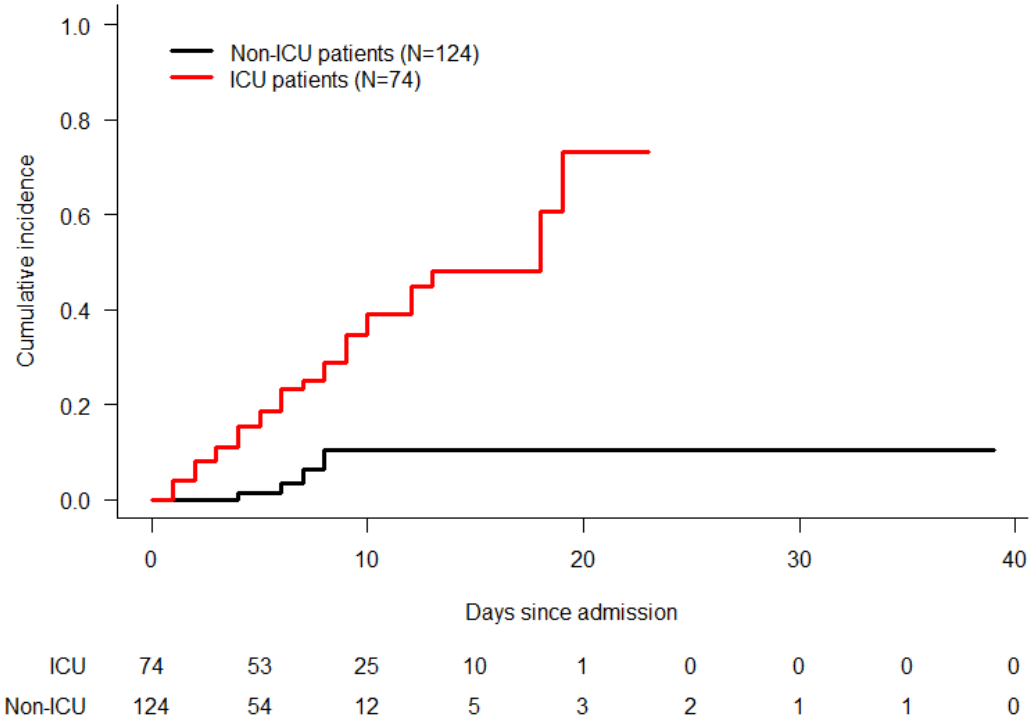
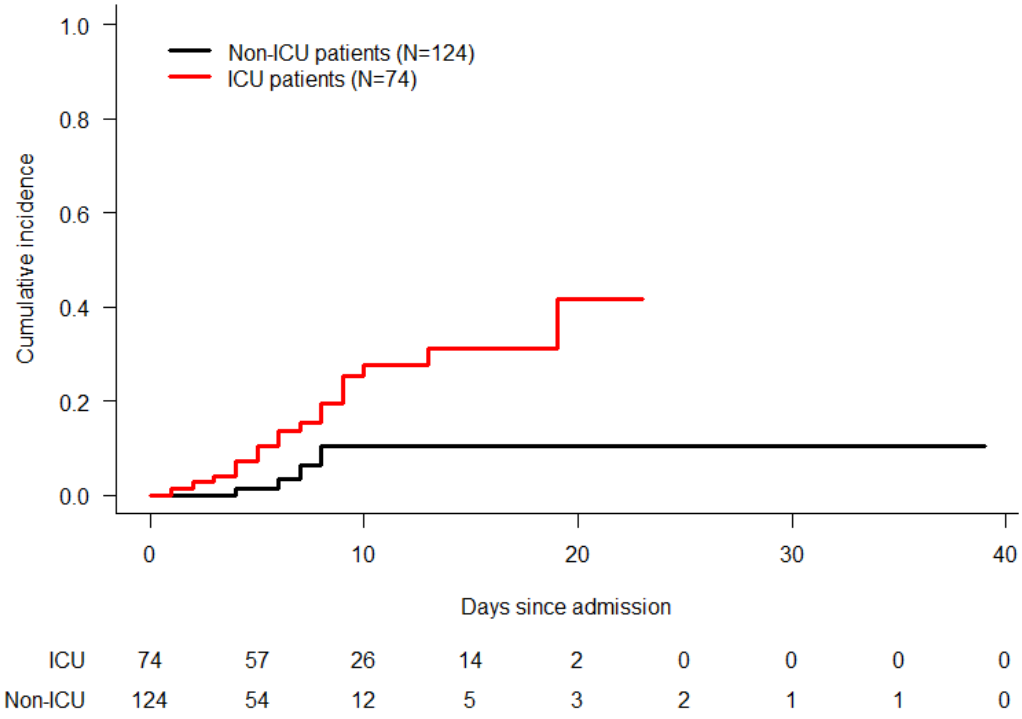


Figure 2B. Cumulative incidence of symptomatic VTE in ICU and non-ICU patients



ICU	74	57	26	14	2	0	0	0	0
Non-ICU	124	54	12	5	3	2	1	1	0