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RESEARCH ARTICLE

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Thromboembolic and bleeding events in ICU patients with COVID-19: A nationwide, observational study

Lene Russell[1] | Sarah Weihe[2] | Emilie Kabel Madsen[3] | Christine Lodberg Hvas[3] | Jens Wolfgang Leistner[1] | Jens Michelsen[4] | Anne Craveiro Brøchner[5] | Anders Bastiansen[6] | Frederik Mølgaard Nielsen[7] | Nick Meier[1] | Anne Sofie Andreasen[8] | Niels-Erik Ribergaard[9] | Bodil Steen Rasmussen[7] | Christoffer Grant Sølling[10] | David Levarett Buck[11] | Helle Bundgaard[12] | Helle Scharling Pedersen[13] | Iben Strøm Darfelt[14] | Lone Musaeus Poulsen[2] | Michael Ibsen[15] | Ronni R. Plovsing[16] | Sigurdur T. Sigurdsson[17] | Susanne Iversen[18] | Thomas Hildebrandt[19] | Thomas Mohr[20] | Ulrick Skipper Espelund[21] | Vibeke Jørgensen[22] | Nicolai Haase[1] | Anders Perner[1]

[1]Department of Intensive Care, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

[2]Department of Anaesthesiology, Zealand University Hospital, Roskilde, Denmark

[3]Department of Anaesthesiology and Intensive Care, Aarhus University Hospital, Aarhus, Denmark

[4]Department of Anaesthesiology and Intensive Care, Odense University Hospital, Odense, Denmark

[5]Department of Anaesthesiology and Intensive Care, University Hospital of Southern Denmark, Kolding, Denmark

[6]Department of Anaesthesiology and Intensive Care, Bispebjerg Hospital, Copenhagen, Denmark

[7]Department of Anaesthesiology and Intensive Care, Aalborg University Hospital, Aalborg, Denmark

[8]Department of Anaesthesiology and Intensive Care, Herlev Hospital, Herlev, Denmark

[9]Department of Anaesthesiology and Intensive Care, Hjørring Regional Hospital, Hjørring, Denmark

[10]Department of Anaesthesiology and Intensive Care, Viborg Regional Hospital, Viborg, Denmark

[11]Department of Anaesthesiology and Intensive Care, Holbæk Hospital, Holbæk, Denmark

[12]Department of Anaesthesiology and Intensive Care, Randers Regional Hospital, Randers, Denmark

[13]Department of Anaesthesiology and Intensive Care, Nykøbing Falster Hospital, Nykøbing Falster, Denmark

[14]Department of Anaesthesiology and Intensive Care, Regionshospitalet Gødstrup, Herning, Denmark

[15]Department of Anaesthesiology and Intensive Care, North Zealand Hospital, Hillerød, Denmark

[16]Department of Anaesthesiology and Intensive Care, Hvidovre Hospital, Hvidovre, Denmark

[17]Department of Neuroanaesthesiology, Neuroscience Centre, Rigshospitalet, Copenhagen, Denmark

[18]Department of Anaesthesiology and Intensive Care, Slagelse Hospital, Slagelse, Denmark

[19]Department of Anaesthesiology and Intensive Care, Zealand University Hospital, Roskilde, Denmark

[20]Department of Anaesthesiology and Intensive Care, Gentofte Hospital, Gentofte, Denmark

[21]Department of Anaesthesiology and Intensive Care, Horsens Regional Hospital, Horsens, Denmark

[22]Department of Cardiothoracic Anaesthesiology, Rigshospitalet, Copenhagen, Denmark

Correspondence
Lene Russell, Department of Intensive Care, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark.
Email: lene.russell@mail.dk

Abstract

Background: Intensive care unit (ICU) patients with Coronavirus disease 2019 (COVID-19) have an increased risk of thromboembolic complications. We describe the occurrence of thromboembolic and bleeding events in all ICU patients with COVID-19 in Denmark during the first and second waves of the pandemic.

Methods: This was a sub-study of the Danish Intensive Care Covid database, in which all patients with SARS-CoV-2 admitted to Danish ICUs from 10th March 2020 to 30th June 2021 were included. We registered coagulation variables at admission, and all thromboembolic and bleeding events, and the use of heparins during ICU stay. Variables associated with thrombosis and bleeding and any association with 90-day mortality were estimated using Cox regression analyses.

Results: We included 1369 patients in this sub-study; 158 (12%, 95% confidence interval 10–13) had a thromboembolic event in ICU and 309 (23%, 20–25) had a bleeding event, among whom 81 patients (6%, 4.8–7.3) had major bleeding. We found that mechanical ventilation and increased D-dimer were associated with thrombosis and mechanical ventilation, low platelet count and presence of haematological malignancy were associated with bleeding. Most patients (76%) received increased doses of thromboprophylaxis during their ICU stay. Thromboembolic events were not associated with mortality in adjusted analysis (hazard ratio 1.35 [0.91–2.01, $p = .14$], whereas bleeding events were 1.55 [1.18–2.05, $p = .002$]).

Conclusions: Both thromboembolic and bleeding events frequently occurred in ICU patients with COVID-19. Based on these data, it is not apparent that increased doses of thromboprophylaxis were beneficial.

KEYWORDS
bleeding, COVID-19, thromboprophylaxis, thrombosis

Editorial Comment

In this nationwide study of thromboembolic and bleeding events in Danish ICU patients with COVID-19 that were mostly treated with intermediate dose thromboprophylaxis, the incidence of thrombosis was 12% and the incidence of bleeding was 23%. The occurrence of bleeding was associated with higher mortality. This suggests that caution and vigilance are needed when prescribing higher dose of thromboprophylaxis based on presumed hypercoagulable state. Furthermore, this highlights the need for careful follow-up for adverse effects after implementing national patient management guidelines.

1 | INTRODUCTION

The risk of thromboembolic complications in patients with Coronavirus disease 2019 (COVID-19) has been widely discussed since the first early reports, which indicated that coagulopathy was common in COVID-19 patients[1] and that prolonged prothrombin time and increased D-dimer levels were associated with the need for intensive care unit (ICU) treatment and increased mortality.[1,2] Reports followed suggesting that a high proportion of ICU patients with COVID-19 developed thromboembolic complications, although rates varied greatly among reports,[3–6] and autopsy studies of COVID-19 patients confirmed the presence of thrombosis and microangiopathy in the small vessels and capillaries of the lungs.[7,8]

As a result of the high rates of thrombotic events reported in the early studies, several investigators suggested higher dosing of prophylactic anticoagulation for patients with critical COVID-19,[9] which was swiftly followed by guidance statements by some institutions,[10] including The Danish Society of Thrombosis and Haemostasis (DSTH). DSTH was one of the first national societies to recommend the routine use of intermediate doses of low molecular weight heparin (LMWH) (enoxaparin 40 mg/tinzaparin 4500 units/dalteparin 5000 units twice daily) in patients with critical COVID-19. Other

institutions chose more moderate thromboprophylaxis strategies, and a review of published guidelines for the management of coagulopathy and thrombosis in patients with critical COVID-19, published in September 2020, found marked differences in the major societies' recommendations and strategies for thrombosis prevention.[11]

After the online publication of the Danish national guidelines during the first pandemic wave (Supplement 1), most COVID-19 ICU patients in Denmark were likely to receive intermediate dosing of LMWH. We are here able to describe the presence of clinically important bleedings and thromboembolic events in an entire, unselected cohort of all ICU patients with COVID-19 in Denmark during the first and second waves of the pandemic.

2 | METHODS

This was a sub-study of the Danish Intensive Care Covid database, in which all patients at the 29 ICUs in the 27 Danish hospitals which treated patients with COVID-19 were prospectively screened. All ICU patients with laboratory-confirmed Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were entered into the database.[12] All patients admitted within the timeframe 10th March 2020 to 30th June 2021 were included in this sub-study. The Danish Patient Safety Authority granted access to the patient files and waived consent from the individual patients due to the study's retrospective design (ref. no. 31-1521-293 and R-21004283).

Medical staff manually searched the electronic patient files and obtained the following information: haematological variables (haemoglobin value and platelet count), coagulation variables (International Normalised Ratio and D-dimer) and level of C-reactive protein at baseline, daily use of antiplatelet or anticoagulant agents before ICU admission (definition: warfarin, direct oral anticoagulants, fondaparinux, clopidogrel, ticagrelor or similar) and daily dose of thrombosis prophylaxis during the first 7 ICU-days.

We registered all bleeding events and thrombotic events during the entire ICU admission. Only thromboembolic events that were confirmed radiographically or ultrasonographically were registered. Bleeding events were categorised as (1) any bleeding event or (2) major bleeding events, defined as bleeding requiring transfusion of at least two units of red blood cells (RBCs) and/or intracranial bleeding and/or bleeding resulting in the need for a major therapeutic intervention.

We also registered transfusion data (Blood group [A, AB, B, 0]), number of transfusions of RBCs, fresh frozen plasma (FFP) and platelet concentrate during the entire ICU admission. The size of blood product units in Denmark is approximately: one unit of RBC = 245 ml, one unit of FFP = 275 ml and one unit of platelet concentrate = 180 ml or 360 ml, depending on geographical region.

In addition, we obtained the following baseline values as per the national database: age, sex, body mass index (BMI), comorbidities, including the presence of haematological malignancy or solid tumour cancer, use of mechanical ventilation or renal replacement therapy during ICU admission and outcome data at Day 90.

3 | STATISTICAL ANALYSIS

Study data were managed using REDCap electronic data capture tools hosted at the Capital Region of Denmark.[13] The rates of thrombosis and bleeding were computed with Wilson score confidence limits. Qualitative data were analyzed using Mann–Whitney test for non-parametric data. For categorical data, the Chi-square test was used unless the expected data was less than 5%, in which case Fisher's exact test was used. We analyzed the association between baseline variables with thrombosis and bleeding using competing Cox regression models. The associations between time to bleeding and time to thrombosis were analyzed with a maximum follow-up time of 90 days. A positive hazard ratio indicates that an event was more likely, and a negative hazard ratio indicates that an event was less likely. Death without prior bleeding/thrombosis was treated as a competing event. Covariates were included in the multivariable model if the p-value was <.10 in the univariate analysis. Interaction analysis was performed before computing the final multivariable model. In case of missing data for a specific variable, these patients were not included in the analysis including this same variable. No imputation was performed. Survival analysis of thrombosis and bleeding within the first 7 days in the ICU was conducted using the Kaplan–Meier method, and the log-rank test was used to compare the survival curves. Survival analyses were adjusted for age and the presence of any malignancy (haematological or solid tumour cancer). SAS Enterprise Edition 3.8, SAS Institute Inc., was used for all analyses.

4 | RESULTS

A total of 1377 patients with laboratory-confirmed SARS-CoV-2 infection were admitted to Danish ICUs during the study period and registered in the National Covid database. In eight patients, the presence of the SARS-CoV-2 virus was a chance-finding and not the cause of hospital or ICU admission; these patients were excluded from this study, leaving 1369 included patients. Their baseline characteristics and use of organ support during the ICU stay are presented in Table 1.

4.1 | Thrombotic events

One-hundred and fifty-eight patients (12%, 95% confidence interval [CI] 10–13) experienced at least one thrombotic event during ICU stay; 11 patients had more than one thrombotic event registered during ICU stay. The median number of ICU days before the thrombotic event was 5 (IQR 1–11). The most frequently registered events were pulmonary embolisms (121 patients [9%, 7.5–10]). Deep-venous thrombosis was registered in 17 patients (1.2%, 0.7–2.0). Other thrombotic events were stroke (12 patients, 1%), acute myocardial infarction (4 patients, 0.3%) and "other thrombotic events" (17 patients, 1.2%). Increased D-dimer at admission and use of mechanical ventilation were associated with thrombosis in multivariable analysis (Table 2).

TABLE 1 Baseline and clinical characteristics of Danish intensive care unit patients with Coronavirus disease 2019 stratified by thrombosis and bleeding

	All patients	Patients with thrombosis	Patients with bleeding	Missing
No.	1369	158	309	
Age	68 (58–75)	66 (58–73)	68 (59–75)	0
Female	443 (32)	37 (23)	87 (28)	0
Days from hospital admission to ICU admission	1 (0–4)	1 (0–4)	1 (0–4)	0
Co-morbidities				
Body Mass Index	28 (25 – 33)	28 (25–32)	29 (25–33)	141
Hypertension[a]	733 (54)	73 (46)	161 (52)	0
Ischemic heart disease[b]	197 (14)	18 (11)	42 (14)	0
Heart failure[c]	65 (5)	4 (3)	13 4	0
Diabetes[d]	325 (24)	30 (19)	64 (21)	0
Chronic obstructive pulmonary disease[e]	260 (19)	20 (13)	60 (19)	0
Liver disease[f]	12 (1)	1 (1)	4 (1)	0
Renal disease[g]	198 (14)	19 (12)	53 (17)	0
Haematological malignancy[h]	74 (5)	9 (6)	24 (8)	0
Solid tumour cancer[i]	46 (3)	4 (3)	15 (5)	0
Immunocompromised patient[j]	154 (11)	19 (12)	48 (16)	0
Use of antithrombotic medications prior to admission[k]	410 (31)	45 (29)	102 34	57
Laboratory parameters at ICU admission				
Haemoglobin (mmol/L)	8.0 (7.1–8.7)	8.2 (7.3–8.8)	7.9 6.7–8.6)	24
Platelets ($\times 10^9$/L)	236 (177–317)	238 (178–337)	214 (155–290)	61
INR	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	106
D-dimer (mg/L)	1.4 (0.8–3.3)	2.3 (1.1–16)	1.7 (1.0–4.2)	398
CRP (mg/L)	120 (71–196)	140 92–222)	124 (73–200)	35
Blood type				97
A	595 (47)	68 (45)	146 (48)	
AB	69 (5.4)	10 (6.6)	16 (5.3)	
B	147 (12)	16 (11)	32 (11)	
0	461 (36)	58 (38)	109 (36)	
Organ support during ICU stay				
Mechanical ventilation	873 (64)	131 (83)	282 (91)	0
Renal replacement therapy	223 (16)	40 (25)	203 (66)	0

Note: Data are in median Interquartile range (IQR) or no. (%).
Abbreviations: CRP: C-reactive protein; ICU: intensive care unit; INR: International Normalised Ratio.
[a]Here defined as the use of antihypertensive medication.
[b]One or more of the following: previous myocardial infarction coronary stenting, stable or unstable angina.
[c]Left-ventricular ejection fraction <40% or New York Heart Association Functional classification 3 or 4.
[d]Here defined as the use of any antidiabetic drug (oral or injection).
[e]Here defined as the use of inhalation drugs.
[f]Presence of liver cirrhosis.
[g]Defined as estimated glomerular filtration rate < 60 ml/min/1.73 m^2.
[h]Here defined as the presence of any type of leukaemia, lymphoma or myeloma.
[i]Here defined as the presence of active cancer disease.
[j]Defined as one of the following: congenital immunodeficiency, human immunodeficiency virus or use of radiotherapy, chemotherapy or systemic prednisolone or another immunosuppressive agent within the last 6 months.
[k]Defined as daily usage of antiplatelet or antithrombotic agents before ICU admission (Definition: warfarin, DOACs, fondaparinux, clopidogrel, ticagrelor or similar. Low-dose aspirin not included).

TABLE 2 Variables associated with thrombosis in intensive care unit patients with Coronavirus disease 2019

	HR (95% CI)	*p* Value
Age	1.00 (0.99–1.01)	.94
Female	0.62 (0.43–0.89)	**.01**
BMI[a]	1.00 (0.97–1.02)	.82
Haematological malignancy	1.12 (0.52–2.05)	.77
Cancer	0.87 (0.27–2.06)	.78
Renal disease	0.91 (0.54–1.43)	.70
Prior antithrombotic medication	1.01 (0.70–1.42)	.96
CRP (increase by 10)[b] **	1.03 (1.01–1.42)	**<.01**
D-dimer[c]	1.02 (1.01–1.02)	**<.01**
Log2 INR[d]	1.16 (0.66–1.95)	.60
Platelet count (increase by 10)	1.00 (0.99–1.01)	.95
Blood type (Blood type 0 = reference)		.84
Blood type A	0.92 (0.645–1.307)	
Blood type AB	1.20 (0.575–2.250)	
Blood type B	0.90 (0.488–1.494)	
Mechanical ventilation ICU-day 1	1.61 (1.18–2.21)	**<.01**
*Adjusted analyses***		
Female	0.710 (0.46–1.07)	.11
D-dimer[c] **	1.012 (1.00–1.02)	**.010**
Mechanical ventilation ICU-day 1	1.843 (1.28–2.66)	**<.001**

Note: Bold values indicate results with $p < .05$.
Abbreviations: BMI, Body Mass Index; CRP, C-reactive protein; HR, hazard ratio; ICU, intensive care unit; INR, International Normalised Ratio.
[a]HR for each increase in BMI by 1 (kg/m^2).
[b]HR for each increase in CRP by 10 units (mg/L).
[c]HR for each increase in D-dimer by 1 unit (mg/L).
[d]Log2 INR; indicates that every time INR doubles, then the risk increases by 16%.
**CRP not included in adjusted analyses due to interaction with D-dimer; *p*-value for interaction effect = .06. As D-dimer was missing for 398 patients, this analysis only includes 971 patients of which 120 (12%) had a thrombotic event.

4.2 | Bleedings

Three-hundred-and-nine patients (23%, 20–25) experienced at least one bleeding episode during the ICU stay. The median number of ICU days before a bleeding event was 7 (Interquartile range (IQR) 2–13). Most patients with bleeding had more than one bleeding event; the median number of bleeding events in each patient was 2 (1–3). One or more major bleeding episodes were seen in 81 patients (6%, 4.8–7.3); the total number of registered major bleeding events was 133. Twenty-one patients died within 24 h of their major bleeding episode. Patients with minor bleedings were more likely to develop subsequent major bleeding than patients without minor bleedings ($p < .0001$); minor bleedings were seen in 32 patients (40%) in the days leading up to a major bleeding event.

The most common sites of bleeding were the airways (141 patients (10%, 8.8–12)) and the gastrointestinal tract; (108 patients (8%, 6.6–9.4)) (Supplement 2, Table S1). Mechanical ventilation, low platelet count at admission and haematological malignancy were associated with bleeding (Table 3).

4.3 | Thromboprophylaxis

Before the 20th of April 2020 (the date of publication of the new Danish guidelines [Supplement 1]), most patients received the standard dose of thromboprophylaxis (enoxaparin 40 mg, tinzaparin 4500 units or lower, once daily, or equivalent). After this date, most patients received an increased dose, either intermediate (enoxaparin 40 mg, tinzaparin 4500 units twice daily or equivalent) or therapeutic (weight-adjusted) dose: On ICU Day 2, 75% (210/281 patients) received standard-dose LMWH before publications of the new guidelines, whereas after the publication, only 14% (142/1049 patients) received standard prophylaxis and 81% (850/1049) patients received intermediate or therapeutic doses of LMWH (Supplement 2, Figure S1).

In the entire cohort (10th of March 2020–30th June 2021), 1034 patients (76%) of the patients received either intermediate doses (the equivalent of enoxaparin 40 mg × 2) or therapeutic (weight-adjusted) doses of LMWH during the first 7 days in ICU (Figure 1).

TABLE 3 Variables associated with bleeding in intensive care unit patients with Coronavirus disease 2019

	Bleeding event (any) $n = 309$		Major bleeding $n = 81$	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age	1.01 (1.00–1.02)	**<.01**	1.01 (1.00–1.03)	.13
Female	0.80 (0.62–1.03)	**.08**	1.05 (0.65–1.65)	.83
BMI[a]	1.00 (0.99–1.02)	.63	0.97 (0.94–1.01)	.16
Haematological malignancy	1.66 (1.06–2.48)	**.02**	2.49 (1.16–4.72)	**.01**
Cancer	2.14 (1.21–3.49)	**.005**	2.68 (0.94–6.02)	**.03**
Renal disease	1.47 (1.08–1.97)	**.02**	2.87 (1.72–4.63)	**<.0001**
Prior antithrombotic medication	1.33 (1.05–1.69)	**.02**	1.94 (1.22–3.05)	**<.01**
CRP (increase by 10)[b]	1.01 (1.00–1.02)	.25	1.02 (1.00–1.05)	**.08**
D-dimer[c]	1.01 (1.01–1.02)	**.0005**	1.01 (0.98–1.02)	.49
Log2 INR*	1.76 (1.21–2.47)	**.002**	1.88 (0.89–3.45)	**.07**
Platelet count (increase by 10)	0.97 (0.96–0.98)	**<.0001**	0.99 (0.96–1.01)	.19
Blood type (Blood type 0 = reference)		.83		.44
Blood type A	1.09 (0.85–1.40)		0.67 (0.41–1.09)	
Blood type AB	1.02 (0.58–1.68)		0.77 (0.23–1.92)	
Blood type B	0.92 (0.61–1.35)		0.90 (0.42–1.75)	
Mechanical ventilation[d]	1.54 (1.23–1.93)	**.0002**	1.79 (1.16–2.78)	**.01**
*Adjusted analyses**				
Age	1.01 (1.00–1.02)	.19		
Female	0.95 (0.69–1.30)	.76		
Haematological malignancy	1.79 (1.05–2.88)	**.02**	4.21 (1.69–9.08)	**.0007**
Cancer	1.42 (0.55–3.00)	.40	0.81 (0.05–3.93)	.84
Renal disease	1.25 (0.82–1.85)	.25	2.55 (1.20–5.08)	**.010**
Prior antithrombotic medication	1.15 (0.82–1.58)	.40	1.66 (0.85–3.13)	.12
Platelet count (increase by 10)	0.97 (0.96–0.99)	**.0002**	1.01 (0.99–1.04)	.37
D-dimer	1.01 (1.00–1.02)	**.04**	1.01 (0.98–1.02)	.62
Log2 INR*	1.30 (0.82–2.04)	.26	1.69 (0.67–3.69)	.23
Mechanical ventilation ICU day 1	1.55 (1.16–2.06)	**.003**	4.88 (2.08–14.3)	**.0010**

Note: Bold indicates significant results with $p < .05$.

Abbreviations: BMI, Body Mass Index; CRP, C-reactive protein; HR, hazard ratio; ICU, Intensive Care Unit; INR, International Normalised Ratio.

[a]HR for each increase in BMI by 1 (kg/m^2).

[b]HR for each increase in CRP by 10 units (mg/L).

[c]HR for each increase in D-dimer by 1 unit (mg/L).

[d]HR for Log2 INR indicates that every time INR doubles, the risk increases by 76% (any bleeding, unadjusted analyses).

*Only variables with a *p*-value <.10 in univariate analyses are included in the multivariable analyses; therefore, age and female sex are not included in multivariable analyses for major bleeding.

4.4 | Mortality

We analyzed survival in patients with thrombosis and bleeding within the first 7 days in ICU. As 117 patients (9%) had died before Day 7, they were not included in these analyses. Among the remaining 1250 patients, 149 patients had a bleeding episode and 83 had a thrombotic event. A thrombotic event during ICU stay was not associated with increased mortality in unadjusted or adjusted analyses (Figure 2A). The unadjusted hazard ratios for death in patients who had a thrombotic event within the first week in ICU were 1.17 (0.79–1.73) and 1.35 (0.91–2.01, $p = .14$) when adjusted for age and presence of any cancer, including haematological malignancy.

Mortality was increased in patients with bleeding versus patients with no bleeding (Figure 2B). The hazard ratio for death in patients with bleeding within the first 7 ICU days was 1.77 (95% CI 1.35–2.34, $p < .0001$); when adjusted for age and presence of any cancer, the hazard ratio was 1.55 (1.18–2.05, $p = .002$).

Fifteen patients had both a thrombosis and a bleeding within the first 7 days. Excluding these patients from the analyses did not change the results (data not shown).

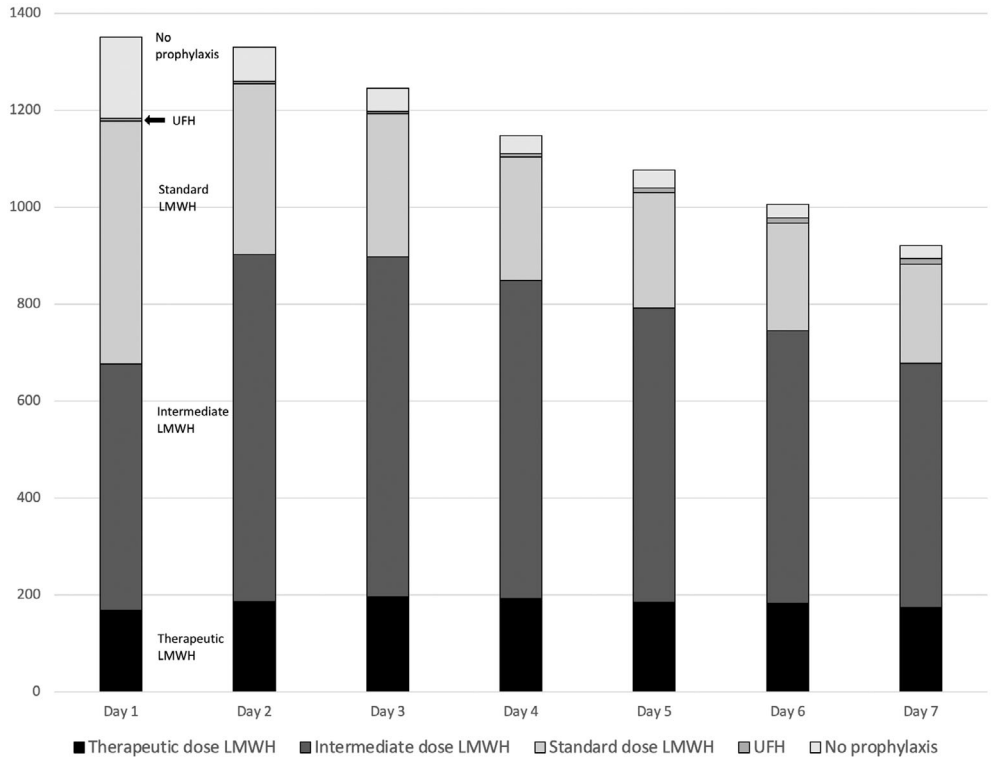

FIGURE 1 Thrombosis prophylaxis in the Danish intensive care unit (ICU) COVID cohort during the first week in ICU. The figure shows the number of patients receiving therapeutic doses of low molecular weight heparin (LMWH), intermediate (twice daily) doses of LMWH or standard thrombosis prophylaxis with LMWH. A small number of patients received unfractionated heparin (UFH) doses unknown. (Therapeutic dose LMWH: Enoxaparin 1 mg/kg/daily or tinzaparin 175 units/kg/daily or equivalent; Intermediate dose LMWH: Enoxaparin 40 mg × 2 or tinzaparin 4500 units × 2 or equivalent; Standard dose LMWH: Enoxaparin 40 mg or lower or tinzaparin 4500 units or lower once daily.)

4.5 | Transfusions

RBC transfusions were given to 338 patients (25%), FFP to 121 patients (9%) and platelet transfusions were given to 75 patients (5%).

Patients with bleeding received more transfusions than non-bleeding patients. Among the 309 patients with bleedings, 183 (59%) received RBC as compared to 15% of non-bleeding patients ($n = 1060$) ($p < .0001$), 74 (24%) received FFP versus 4% of non-bleeders ($p < .0001$) and 56 (18%) received platelet transfusions vs only 19 (2%) of non-bleeders ($p < .0001$). Patients with thrombotic events ($n = 158$) also received more transfusions than patients without thrombotic events ($n = 1211$): RBC 39% versus 23% ($p < .0001$), plasma 13% versus 8% ($p = .07$) and platelet concentrate 9% versus 5% ($p = .05$).

5 | DISCUSSION

In this study, we describe the frequency of thromboembolic and bleeding events in a nationwide ICU cohort of COVID-19 patients during the first and second waves of the pandemic in Denmark. We found an overall high rate of thrombosis and bleeding; 12% of patients experienced a thrombotic event, 23% bled during the ICU stay and 6% experienced a major bleeding episode. Bleeding was associated with mortality, whereas thrombosis was not. Most patients received intermediate doses of LMWH in accordance with the national recommendations at the time.

It is well established that patients admitted to the ICU with COVID-19 are at high risk of thrombotic events, particularly venous thromboembolism (VTE).[14] However, the VTE rates reported have varied considerably, with higher rates generally reported in earlier studies. In a meta-analysis published during the first half of 2020 based on 43 studies reporting on ICU cohorts, the estimated prevalence of VTE was 22.7%.[15] The highest rates were reported in single-centre studies where universal VTE screening was used.[16,17] In more recent studies, the reported rates of VTE have been lower. A large multicentre cohort study in 3239 critically ill patients with COVID-19 found that 6.3% developed VTE; independent predictors were male sex and high D-dimer on ICU admission.[18] The INSPIRATION multicentre trial of intermediate- versus standard-dose heparin-based thromboprophylaxis in 562 critically ill patients found VTE in 3.3% versus 3.5% of patients.[19] A joint analysis combining data from the ACTIV-4a randomised trial and two trials using response-adaptive randomisation (REMAP-CAP and ATTACC) assessed therapeutic-dose heparin or LMWH versus standard thromboprophylaxis in 1098 critically ill patients and found an incidence of major thrombotic events in 6.4% versus 10.4%.[20] In our study, the thrombosis incidence of 12% is higher than described in these large multicentre trials. One may speculate that our population had more severe respiratory failure, as the use of mechanical ventilation in our study was considerably higher (64%) than in the INSPIRATION trial (20%) and the REMAP-CAP/ATTACC trials (27%–30%). As seen in Table 2, mechanical ventilation was associated with an increased risk of thrombosis in our cohort.

While the initial focus might have been primarily on thrombosis, reports on bleedings in COVID-19 patients followed. Al-Samkari and co-authors published an observational study of bleeding and thrombotic manifestations in COVID-19 patients,[21] where the overall

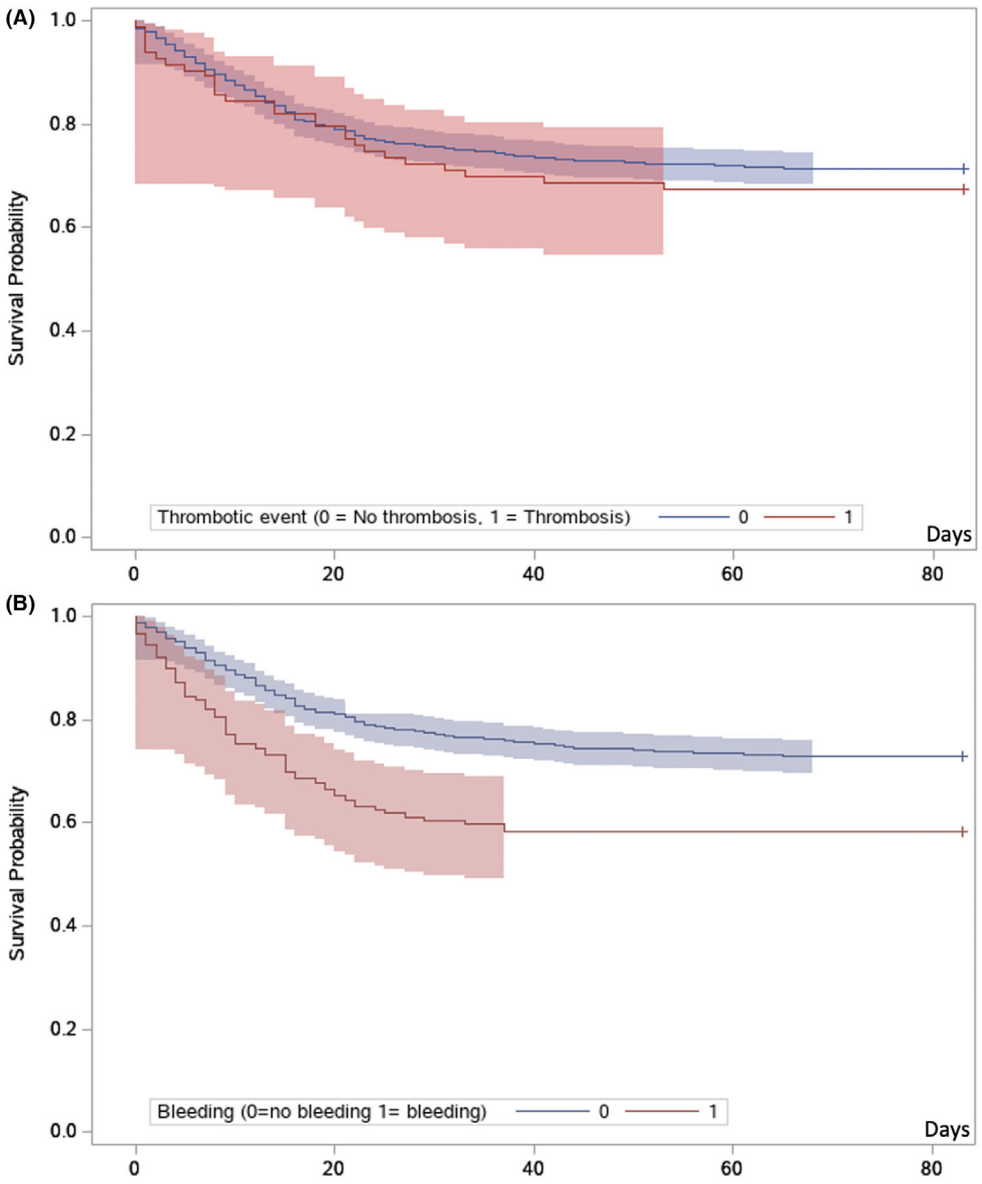

FIGURE 2 Kaplan–Meier curves with 95% confidence intervals showing survival from intensive care unit (ICU) Day 7 and onwards in (**A**) Patients with and without thrombotic events during the first week in the ICU. Log-rank test score 0.59; $p = .44$. (**B**) Patients with and without bleeding during the first week in the ICU. Log-rank test score 17.2; $p < .0001$. Exactly 117 patients died during the first week in ICU and were not included in the survival analyses, leaving 1250 patients in the analyses. The follow-up is the same in both groups (thin lines), but the length of confidence intervals (broad markings) differs depending on time of the last event.

bleeding rate was 4.8% (95% CI, 2.9–7.3); however, in critically ill patients the rate was 7.6% (3.9–13.3) and all major bleedings but one occurred in critically ill patients (5.6%; 2.4–10.7). Thrombocytopenia and low fibrinogen, although rare, were associated with major bleedings.[21] This rate is comparable to that of our study, where major bleeding was seen in 6% (4.8–7.3).

The overall bleeding rate of 23% in our study is higher than previously described. There may be several reasons for this; our patients may have been more severely ill, and the higher doses of thromboprophylaxis received by most patients may have contributed. Increased bleeding rates in patients who received intermediate or therapeutic doses were seen in the INSPIRATION[19] trial and the analysis of the ACTIV-4a, REMAP-CAP and ATTACC trials.[20] In line with previous studies,[21] we also found that a low platelet count was associated with bleeding and that major bleeding events were associated with an increased risk of mortality.[18,22] Furthermore, more than one-third of the major bleedings were preceded by minor bleedings, a clear indication that minor bleedings should be taken as a warning sign, as seen in other patient populations.[23]

The underlying mechanisms of the COVID-19 associated coagulopathy and thrombosis have not yet been established. The SARS-CoV-2 itself does not seem to have innate prothrombotic properties.[24] Instead, the coagulopathy seen in critically ill patients is likely a consequence of an overwhelming hyperinflammatory response.[25] It is also well known that severe infections cause systemic inflammation and this includes activation of the coagulation system. Previously, viral pneumonias caused by H1N1 or SARS-CoV-1 have been reported to induce hypercoagulability[26] and increased rates of VTE.[27–29]

Furthermore, as regulation of the coagulation system in critically ill patients is highly complex and closely linked to the inflammatory response, it may be that coagulation activation is a marker of disease severity rather than the cause itself. It is also important to consider that the risk of both bleeding and thrombosis is increased in critically ill patients in general, regardless of COVID-19.[30,31] This has been

confirmed in several randomised trials, although the incidence varies considerably.[32,33] For example, in the Transfusion Requirements in Septic Shock trial, bleeding events were registered in 30% of patients,[33] and in a sub-study of a thromboprophylaxis trial (PROTECT), bleeding occurred in 13%, however, patients with thrombocytopenia at baseline were excluded from this study.[31] In ICU patients with thrombocytopenia, the risk of bleeding is even higher, with rates up to 57%.[23] The increased risk of thromboembolic events in ICU patients is also well-established,[34–36] and VTE rates ranging from 5% to 15% have previously been described[37–39]; the high rates have also been confirmed in autopsy studies.[40,41]

The strength of this study is the complete nationwide cohort of COVID-19 ICU patients during the first and second wave of the pandemic and the high availability of data harvested manually by medical staff (doctors, nurses and senior medical students) directly from patient files. We had few missing data and complete follow-up.

This study has several limitations. Due to the retrospective data registration, there is a risk of underestimating the occurrence of both minor bleedings and minor thrombotic events. We did not collect data on thrombotic events before ICU admission, nor did we collect data on thromboprophylaxis before ICU admission or after Day 7 in the ICU. Our adjusted analyses were data-driven, so the results should be confirmed in independent datasets. Most importantly, we cannot make any inferences about cause and effect because of the observational design.

6 | CONCLUSIONS

The frequencies of thrombotic events and bleedings were high in this nationwide cohort of ICU patients with COVID-19. Based on this data, it is not apparent that the increased doses of thromboprophylaxis were beneficial.

AUTHOR CONTRIBUTIONS

This study was designed by the Danish Covid Thrombosis working group (Lene Russell, Jens Michelsen, Christine Lodberg Hvas, Anne Sofie Andreasen, Jens Wolfgang Leistner and Anders Perner). The study protocol was written by Lene Russell and Jens Wolfgang Leistner and approved by all members of the thrombosis working group; the manuscript was written by Lene Russell and Christine Lodberg Hvas and approved by all authors. The data for this study was collected by Sarah Weihe, Emilie Kabel Madsen, Anne Craveiro Brøchner, Anders Bastiansen, Frederik Mølgaard Nielsen, Jens Michelsen, Jens Wolfgang Leistner, Nick Meier and Lene Russell. Lene Russell performed the statistical analyses. Nicolai Haase is responsible for the overall management of the Danish covid-cohort database. All authors read and approved the final manuscript.

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ORCID

Lene Russell https://orcid.org/0000-0001-7352-8728
Sarah Weihe https://orcid.org/0000-0002-2491-3408
Christine Lodberg Hvas https://orcid.org/0000-0003-0826-4126
Frederik Mølgaard Nielsen https://orcid.org/0000-0002-0071-1203
Bodil Steen Rasmussen https://orcid.org/0000-0003-2190-145X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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