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Thromboembolic and bleeding events in intensive care unit patients with COVID-19: results from a Brazilian tertiary hospital

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ABSTRACT

Objectives: To describe the incidence of thromboembolic events in adult patients with severe COVID-19 and identify clinical and laboratory factors associated with these events.

Design: Observational retrospective cohort study of 243 adult patients with severe COVID-19 admitted to an intensive care unit (ICU) at a Brazilian tertiary hospital.

Results: The incidence of all thromboembolic events was 14.8%, in which 3.8% developed deep vein thrombosis, 7.8% pulmonary embolism, 2.5% acute myocardial infarction, 1.2% stroke, and 1.2% peripheral artery occlusion. Risk factors identified were D-dimer at admission >3000 ng/mL ($P < 0.0013$) and major bleeding ($P = 0.001$). The cumulative risk of developing thromboembolic events at day 28 after ICU admission was 16.0%. The rate of major bleeding was 4.1%. After receiver operating characteristic curve analysis, the D-dimer cut-off at admission correlating with thromboembolic events was 1140.5 ng/mL.

Conclusions: The rate of thromboembolic events in our study was lower than previously described. High D-dimer level at admission was the leading risk factor; the optimal cut-off was 1140.5 ng/mL. The occurrence of thromboembolic events did not have an impact on the median overall survival rate. The optimal anticoagulant strategy in this context still needs to be established.

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INTRODUCTION

In December 2019, in Wuhan, China, several pneumonia cases that progressed to severe acute respiratory syndrome (SARS) were reported. SARS-CoV-2 was identified as the aetiological agent of this disease in the following month, later denominated COVID-19 (Chen et al., 2020; Guan et al., 2020). The association between other coronavirus and thromboembolic events was already recognised in both the 2003 SARS and 2012 Middle East Respiratory Syndrome outbreaks (Giannis et al., 2020). Similar thromboembolic events were noted in patients with SARS-CoV-2 after developing a significant inflammatory response, leading to a hypercoagulable state (Connors and Levy, 2020; McGonagle et al., 2020).

In COVID-19 patients, abnormalities in coagulation tests, especially a higher D-dimer level, are associated with worse outcomes (Tang et al., 2020). Moreover, some studies showed that patients with COVID-19 admitted to intensive care units (ICU) have a high incidence of venous thromboembolism (VTE). Some authors report these complications in almost half of the patients (Middeldorp et al., 2020). These events are more frequent in COVID-19 patients than in patients with acute respiratory distress syndrome of other aetiologies (Helms et al., 2020). Of note, a series of autopsies performed in deceased COVID-19 patients showed findings consistent with VTE in 58% of cases, even without prior clinical suspicion (Wichmann et al., 2020).

Most of the published cohorts describing COVID-19 related VTE are from European or US groups (Middeldorp et al., 2020; Helms et al., 2020; Al-Samkari et al., 2020; Llitjos et al., 2020; Bilaloglu et al., 2020; Trigonis et al., 2020; Hippensteel et al., 2020). Our study aimed to describe the incidence of thromboembolic

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events in a retrospective cohort of patients diagnosed with COVID-19 admitted to an ICU of a Brazilian tertiary hospital.

METHODS

Patients

All consecutive patients admitted to the ICU of a Brazilian tertiary hospital between March 17 and June 18, 2020, with a confirmed diagnosis of COVID-19 were included in this retrospective study. SARS-CoV-2 detection in all cases was by polymerase chain reaction. Patients were followed up until the date of hospital discharge or death.

Outcomes

The primary endpoint was the occurrence of thromboembolic events, which were further divided into deep venous thrombosis (DVT), pulmonary embolism (PE), stroke, myocardial infarction, and acute peripheral artery occlusion.

The secondary endpoints were clinical or laboratory risk factors associated with thromboembolic events, overall mortality at day 28 after ICU admission, major bleeding according to the International Society of Thrombosis and Haemostasis, and the correlation between D-dimer levels and thromboembolic events by receiver operating characteristic (ROC) curve (Schulman et al., 2005).

Diagnosis of thromboembolic events

Patients with clinical suspicion of DVT had an ultrasound of extremities performed. Pulmonary embolism was diagnosed by computed tomography (CT) pulmonary angiography or, in unstable patients, a high pulmonary artery systolic pressure observed in an echocardiogram in the absence of other causes. Stroke was defined as central nervous system (CNS) infarction or ischemic stroke diagnosed by CNS imaging. The definition of prophylactic anticoagulant dose in this study was enoxaparin 40 mg every day or unfractionated heparin 5000 IU twice or three times a day according to the patient's body weight.

Statistical analysis

Data were summarised by mean, SD, median, minimum, and maximum when the variables were quantitative, and frequency and percentage for qualitative variables. Simple logistic regression was used to verify the difference between thromboembolic events (Yes / No) and the calculated odds ratio. Multiple model logistic regression was used to determine the effect of combinations of variables. A cut-off value for D-dimer was determined using ROC analysis. The value maximized the sensitivity and specificity of the identification of the patients who experienced thromboembolic events during hospitalization and patients who did not. Previously, a cut-off value of 3000 ng/mL was described as a factor associated with worse outcomes in patients with COVID-19 (Tang et al., 2020). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy and the respective 95% CIs were estimated. A linear mixed-effect model was used to compare evolution for D-dimer in thromboembolic events. Overall survival (death from any cause) and thromboembolic events-free survival rates were estimated using a nonparametric Kaplan-Meier estimator. The log-rank test was used to test the difference between survival (D-dimer and status), and the hazard ratio was calculated by Cox's regression. Data were analyzed with SPSS software (for Windows, v25.0). *P*-value <0.05 was considered statistically significant.

Table 1
Clinical and laboratory characteristics of patients.

	All patients (n=243)
Age- median, interquartile range (IQR)	63 (50–74)
<60 years - n (%)	98 (40.3)
60–80 years - n (%)	97 (39.9)
80 years - n (%)	48 (19.8)
Female - n (%)	97 (39.9)
Baseline Simplified Acute Physiology Score (SAPS) III - median, IQR	49 (41–60)
Body mass index ≥ 35 kg/m ² - n (%)	33 (13.6)
Malignancies	32 (13.2)
D-dimer at admission (ng/mL) - median, IQR	916 (568–1908)
< 3000 ng/mL - n (%)	187 (82.0)
≥ 3000 ng/mL - n (%)	41 (18.0)
Thrombocytopenia - n (%)	49 (20.2)
Baseline anticoagulant treatment - n (%)	222 (91.4)
Prophylactic dosing - n (%)	175 (78.8)
Therapeutic dosing - n (%)	47 (21.2)
Ultrasound of extremities - n (%)	51 (21.0)
Chest computed tomography angiography - n (%)	30 (12.3)
Echocardiogram - n (%)	135 (55.5)
Mechanical ventilation - n (%)	112 (46.1)

RESULTS

A total of 243 consecutive patients admitted to the ICU with a confirmed diagnosis of COVID-19 were included in this study. The clinical and laboratory characteristics of the patients are summarised in Table 1. The median follow-up duration was 10 days (mean, 16.4±18.7 days). The median age of patients was 63 years (range, 20–102), and 97 (39.9%) were female. The median simplified acute physiology score (SAPS) III was 49 points (range 24–100). Thirty-three patients had a body mass index (BMI) >35 kg/m² (13.6%), and 32 (13.2%) had a cancer diagnosis before admission. Median D-dimer at admission was 916 ng/mL (range 215–128 000). Forty-nine patients (20.2%) developed platelet counts lower than 100 000/mm³ during hospitalization. Anticoagulant therapy was employed in 222 patients (91.4%), with 175 (78.8%) receiving prophylactic dosing. Mechanical ventilation was employed in 112 patients (46.1%).

Overall survival

Between ICU admission and day 28, 77 patients (33.5%) died, including 60.7% of patients who underwent mechanical ventilation. The median overall survival (OS) after ICU admission was not reached at day 28. Patients aged ≥ 80 years had a median OS of 11 days after ICU admission, and the median OS was not reached for patients with ages <60 years and 60–79 years (*P*<0.001). Patients who underwent mechanical ventilation had a median OS of 15 days compared with a median OS not reached in those not ventilated (*P*<0.001). The median OS was not reached for both patients who received prophylactic anticoagulant dosing and those who received therapeutic dosing (*P*=0.079). Patients who developed thrombocytopenia during hospitalization had a median OS of 17 days versus not reached for those who did not (*P*<0.001). Patients with a prior history of cancer had a median OS of 27 days versus not reached for those who had not (*P*=0.025). The median OS for both patients who developed thromboembolic events and those who did not, was not reached (*P*=0.995).

Thromboembolic and major bleeding events

During the study period, 51 patients (21%) had an ultrasound of the extremities performed, 30 (12.3%) underwent CT pulmonary angiography, and 135 (55.5%) had an echocardiogram. Thromboem-

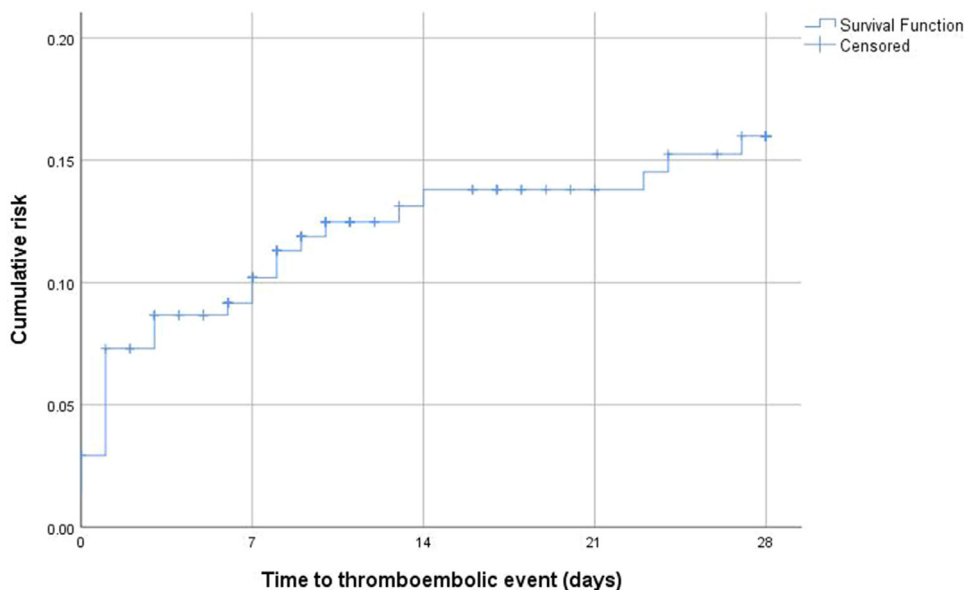


Figure 1. Cumulative risk of thromboembolic events until 28 days after intensive care unit admission.

Table 2
Thromboembolic and major bleeding events.

	All patients (n=243)
Venous thromboembolism - n (%)	27 (11.1)
Deep vein thrombosis - n (%)	9 (3.7)
Pulmonary embolism - n (%)	19 (7.8)
Arterial thrombosis - n (%)	12 (4.9)
Stroke - n (%)	3 (1.2)
Myocardial infarction - n (%)	6 (2.5)
Peripheral artery occlusion - n (%)	3 (1.2)
Major bleeding - n (%)	10 (4.1)

bolic events occurred in 36 patients (14.8%) (Table 2). Venous thromboembolic events were DVT in 9 patients (3.7%) and PE in 19 (7.8%). Cerebral venous thrombosis episodes were not observed. The rate of DVT was 17.6% in patients who had a ultrasound performed. Arterial thromboembolic events were stroke in 3 (1.2%), myocardial infarction in 6 (2.5%), and peripheral arterial occlusion in 3 patients (1.2%). The cumulative risk of thromboembolic events at day 28 after ICU admission was 16.0% (Figure 1). In patients who developed thromboembolic events, the median time to these events occurring was 2 days (range 0–76 days). Major bleeding was observed in 10 patients (4.1%) (Table 2).

Risk factors for thromboembolic events on univariate analysis (Table 3) were D-dimer at admission >3000 ng/mL ($P<0.0013$) and major bleeding ($P=0.001$). These risk factors were also identified by logistic regression (Table 3). For venous thromboembolic events (DVT and PE), D-dimer at admission >3000 ng/mL ($P<0.001$) was the only risk factor identified.

D-dimer levels

The D-dimer cut-off at admission that correlated with thromboembolic events was 1140.5 ng/mL by ROC curve analysis with an area under curve of 0.697 (95% CI 0.599–0.795) (Figure 2), sensitivity 62.5% (95% CI 43.7%–78.9%), and specificity 63.3% (95% CI 56.1%–70.0%). The positive predictive value (PPV) was 21.7% (95% CI 16.7%–27.8%), the negative predictive value (NPV) was 91.2% (95% CI 86.7%–94.2%) and accuracy 63.2% (95% CI 56.5%–69.4%). When analysing the correlation between D-dimer levels >3000 ng/mL with thromboembolic events, the sensitivity was 40.6% (95% CI

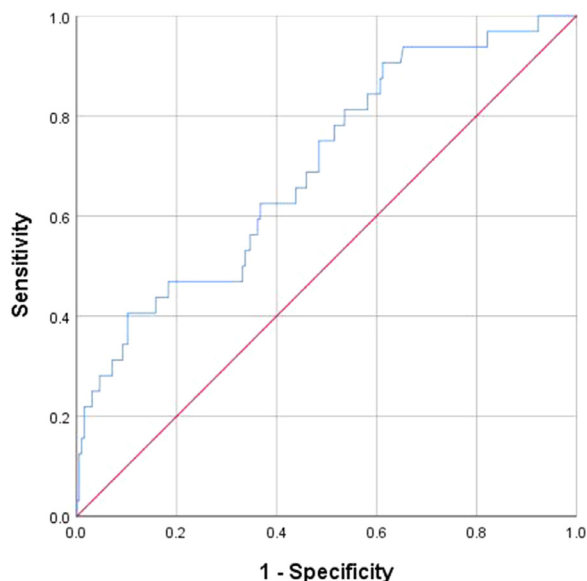


Figure 2. Receiver operating characteristic (ROC) curve of D-dimer levels at admission higher than 1140 ng/mL and occurrence of thromboembolic events.

23.7%–59.4%), specificity 85.7% (95% CI 80.0%–90.3%), PPV 31.7% (95% CI 21.3%–44.4%), NPV 89.8% (95% CI 86.8%–92.2%) and accuracy 79.4% (95% CI 73.6%–84.4%).

Figure 3 summarizes the evolution of D-dimer measurements during follow-up. D-dimer median levels at each time point were higher in patients who developed thromboembolic events ($P=0.001$) and those who died ($P=0.043$).

In patients with baseline D-dimer >1140.5 ng/mL, the median OS was 20 days, and it was not reached for patients with D-dimer <1140.5 ng/mL ($P<0.001$) with a hazard ratio (HR) of 4.091 (CI 95% 2.467–6.785) (Figure 4). The median OS was not reached for both patients with baseline D-dimer >3000 ng/mL and with <3000 ng/mL, with an OS of 53.7% at day 28 after admission versus 71.4%, respectively ($P=0.028$) and HR 1.782 (CI 95% 1.052–3.019).

Table 3
Risk factors for thromboembolic events.

	Patients with thromboembolic events (n=36)	Patients without thromboembolic events (n=207)	Odds ratio (CI 95%)	P value
Mechanical ventilation	20 (55.6%)	92 (44.4%)	1.56 (0.77–3.18)	0.219
Age (years)				
60–80	17 (47.2%)	80 (38.6%)	1.27 (0.59–2.76)	0.537
≥80	5 (13.9%)	43 (20.8%)	0.70 (0.24–2.07)	0.516
Male sex	21 (58.3%)	125 (60.4%)	0.92 (0.45–1.88)	0.816
Body mass index ≥ 35 kg/m ²	6 (16.7%)	27 (13.1%)	1.33 (0.51–3.48)	0.567
Simplified Acute Physiology Score (SAPS) III				
41–60	19 (52.8%)	98 (47.3%)	1.31 (0.54–3.19)	0.554
≥60	9 (25.0%)	55 (26.6%)	1.11 (0.40–3.08)	0.849
D-dimer at admission ≥3000 ng/mL	13 (40.6%)	28 (14.3%)	4.11 (1.82–9.24)	0.001
Thrombocytopenia during the study	7 (19.4%)	42 (20.4%)	1.06 (0.44–2.59)	0.897
Baseline anticoagulant treatment	33 (91.7%)	189 (91.3%)	1.05 (0.29–3.76)	0.943
Major bleeding	6 (16.7%)	4 (1.9%)	10.15 (2.71–38.07)	0.001
Malignancy	4 (11.1%)	28 (13.5%)	0.80 (0.26–2.43)	0.693
Risk factors for thromboembolic events after logistic regression analysis.			Odds ratio (CI 95%)	P value
D-dimer at admission higher than 3000 ng/mL			2.60 (1.16–5.80)	0.02
Major bleeding			12.82 (2.92–56.27)	0.001

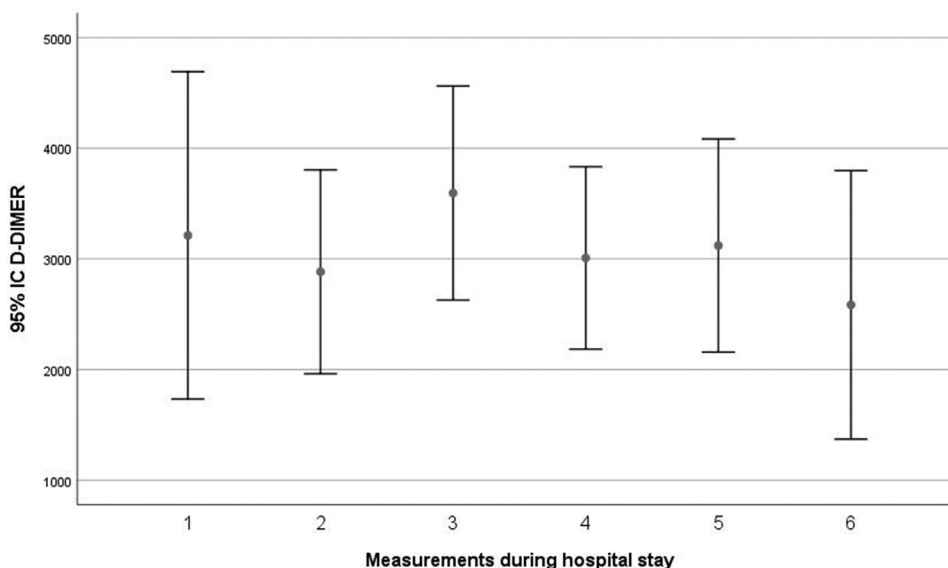


Figure 3. Evolution of D-dimer levels during follow-up in different moments after intensive care unit admission.

DISCUSSION

To the authors’ knowledge, our report is the largest cohort regarding thromboembolic and bleeding events from Latin-American COVID-19 patients to date. We found a mortality rate of 33.5%, and the median OS was not reached at day 28 after ICU admission. Of note, 62.3% of deaths (48 of 77) occurred during the first 10 days. We found a 14.8% incidence of thromboembolic events, further divided into 11.1% of venous thromboembolism and 4.9% of arterial events; the cumulative risk to develop those events at day 28 after ICU admission was 16.0%. These results show a lower incidence of thromboembolic events than previously reported in other ICU cohorts (Table 4) (Middeldorp et al., 2020; Helms et al., 2020; Al-Samkari et al., 2020; Litjós et al., 2020; Bilaloglu et al., 2020; Trigonis et al., 2020; Hippensteel et al., 2020; Yu et al., 2020). The main risk factor identified for thromboembolic events was higher D-dimer levels, both >3000 ng/mL, a parameter already associated with poor prognosis in this group of patients (Tang et al., 2020) and >1140.5 ng/mL, a cut-off identified after ROC curve analysis in our study. This cut-off was also a predictor of shorter overall survival, and patients who had a D-dimer level >1140.5 ng/mL had

a 4.09 higher risk of death. However, the cut-off of 3000 ng/mL described previously (Tang et al., 2020) had better accuracy in predicting patients who developed thromboembolic events. Other studies reported a higher sensitivity when using this cut-off, although with lower accuracy (Artifoni et al., 2020; Gibson et al., 2020). The D-dimer level was consistently higher during follow-up among patients who died and in patients who developed thromboembolic events. It is noteworthy that D-dimer levels seem higher in COVID-19 patients than in patients with bacterial pneumonia or other inflammatory conditions in ICU patients (Yu et al., 2020). Interestingly, mechanical ventilation did not have a significant impact on thromboembolic events, which was unexpected considering the correlation between higher D-dimers and both severity and thromboembolic events. This observation may suggest that D-dimer could be an independent variable of severity in this group of patients and that the optimal D-dimer cut-off with clinical significance needs further study. Our results did not show impact in OS for patients who received therapeutic anticoagulation compared with those who received anticoagulants at prophylactic dosing. Of note, the decision to use therapeutic or prophylactic anticoagulant dosing was at the physician’s discretion. We did not find a correla-

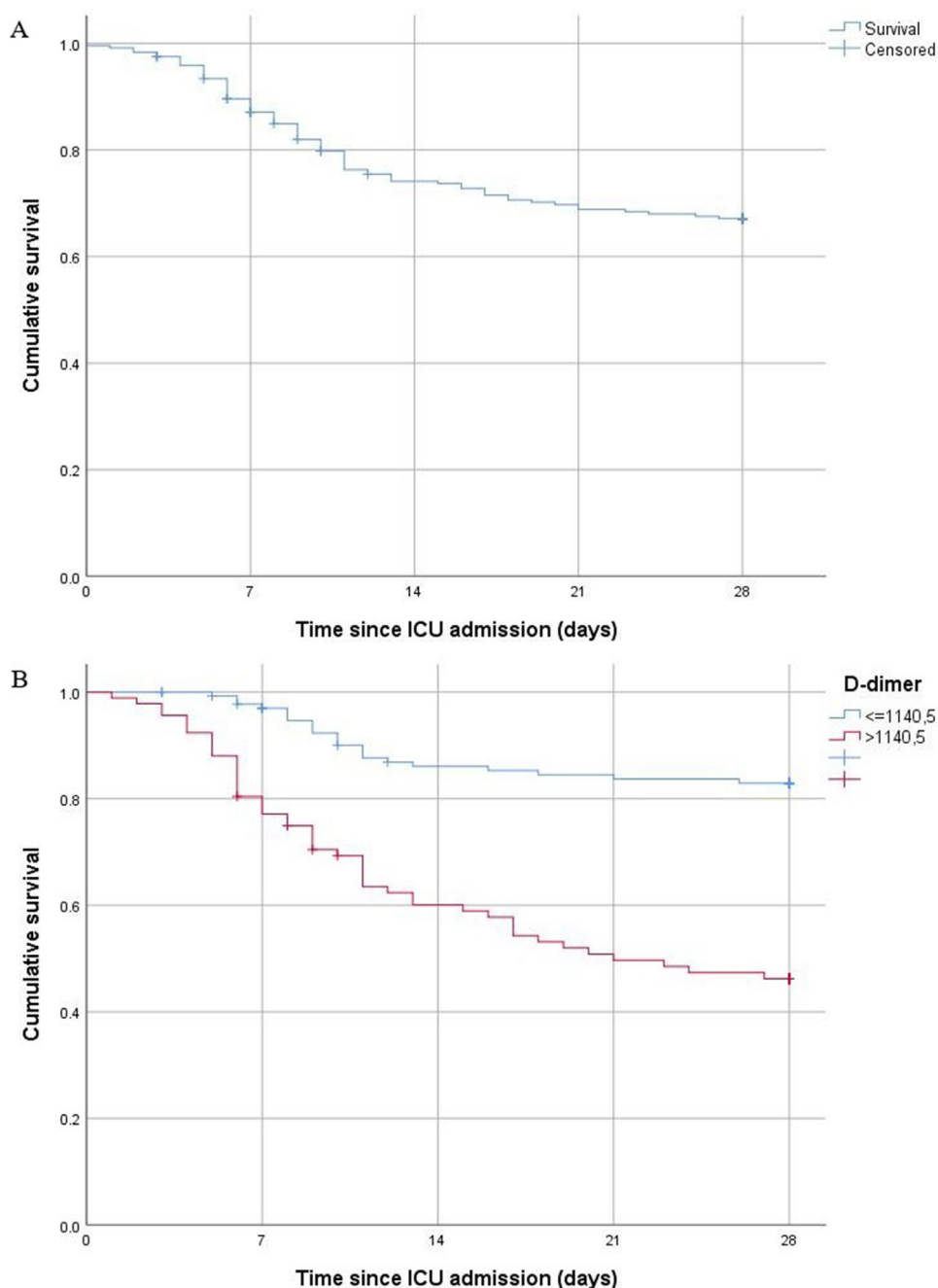


Figure 4. Overall survival by Kaplan-Meier analysis in all patients (A) and according to D-dimer levels higher or lower than 1140.5 ng/mL (B) ($P < 0.001$). Hazard ratio = 4.09 (95% CI 2.47–6.78).

tion between age, gender and obesity with thromboembolic events, and this lack of correlation has been previously reported (Yu et al., 2020).

Major bleeding was also identified as a risk factor for thromboembolic events. A possible reason for this correlation is the inability to administer anticoagulants to these patients due to bleeding events; hence the pharmacological prophylaxis to thromboembolic events could not be used. The major bleeding rate was 4.1%, similar to other cohorts (Wichamann et al., 2020), and relatively low, considering that 91.4% of our patients received anticoagulants. Overall survival was not influenced by the occurrence of thromboembolic events, although this must be addressed cautiously due to the low rate of events.

Our study has limitations since we analysed retrospective data collected from patients from a single centre during “the first wave” of COVID-19 in 2020. Data in the thrombosis risk in the so-called COVID-19 “variants” could differ. We were not able to collect detailed data on patients comorbidities. The incidence of thromboembolic events may have been underestimated due to underdiagnosis as a VTE screening strategy was not employed, such as routine ultrasound; therefore, only patients with symptomatic thromboembolic events were diagnosed. The rate of DVT in patients who underwent ultrasound was low (17.6%); hence a systematic ultrasound policy may not be warranted due to the risk of contamination among health care personnel. On the other hand, the high adhesion to pharmacological prophylaxis of VTE, based on

Table 4
Thromboembolic events in cohorts previously published.

Reference	ICU Patients	Age (years) (median)	D-dimer (median)	Thromboembolic events	Bleeding events
Middeldorp et al.	75	62	2000 ng/mL	47% VTE only	NA
Helms et al.	150	63	2270 ng/mL	18% Venous and arterial thrombosis	2.7% (major)
Al-Samkari et al.	144	65	NA (not reported for ICU patients)	18.1% Venous and arterial thrombosis	5.6% (major)
Llitjos et al.	26	68	1,750 ng/mL	69% VTE only; systematic assessment with ultrasound	NA
Bilaloglu et al.	829	64	648 ng/mL (patients with thrombotic events)	29.4% Venous and arterial thrombosis	NA
Trigoni et al.	45	60.8	4,046 ng/mL	42.2% VTE only; systematic assessment with ultrasound	NA
Hippensteel et al.	91	55 (VTE patients)	1071 ng/mL (VTE patients)	26.1% VTE only	NA
Present study	243	63	916 ng/mL	14.8% Venous and arterial thrombosis	4.1% (major)

ICU: Intensive Care Unit; VTE: Venous thromboembolism; NA: not available.

our institutional protocols, may have favourably contributed to our results. We did not perform a routine anti-Xa assay to evaluate the prophylactic anticoagulation's efficacy, which may identify patients eligible for a more intensive anticoagulation strategy (Dutt et al., 2020). We also did not have access to data regarding thromboembolic events post-discharge. However, we did observe patients who developed thromboembolic events 76 days after admission, suggesting that the thromboembolic risk may persist after ICU and hospital discharge. However, most of the thromboembolic events occurred in the first 2 days after ICU admission.

In conclusion, the correlation between thromboembolic events and severe COVID-19 is striking. The optimal anticoagulant strategy in this context is a matter of debate (Thachil et al., 2020; Moores et al., 2020; Orsi et al., 2020). Two clinical trials (INSPIRATION Investigators et al., 2021; REMAP-CAP Investigators et al., 2021) which evaluated the effect of different anticoagulant doses among patients admitted to the ICU with COVID-19 did not show improved outcomes. Other ongoing randomised clinical trials may provide further evidence to help physicians in managing this clinical issue.

Author Contributions: AAGSB designed the study, collected and analysed the data, drafted and revised the paper. CZO wrote the statistical analysis plan, cleaned and analysed the data, and revised the paper. SOR, AAMO and VMQ collected the data and revised the paper. DLCF and PS designed the study and revised the paper. VCV designed the study, collected and analysed the data, and revised the paper.

Declaration of Competing Interests

Nothing to disclose.

Ethics approval

Approval was not required.

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REFERENCES

- Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood* 2020;136(4):489–500. doi:[10.1182/blood.2020006520](https://doi.org/10.1182/blood.2020006520).
- Artifoni M, Danic G, Gautier G, Gicquel P, Boutoille D, Raffi F, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. *J Thromb Thrombolysis* 2020;50(1):211–16. doi:[10.1007/s11239-020-02146-z](https://doi.org/10.1007/s11239-020-02146-z).
- Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. *JAMA* 2020;324(8):799–801. doi:[10.1001/jama.2020.13372](https://doi.org/10.1001/jama.2020.13372).
- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395(10223):507–13. doi:[10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7).
- Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020;135(23):2033–40. doi:[10.1182/blood.2020060600](https://doi.org/10.1182/blood.2020060600).
- Dutt T, Simcox D, Downey C, McLenaghan D, King C, Gautam M, et al. Thromboprophylaxis in COVID-19: Anti-FXa-the Missing Factor? *Am J Respir Crit Care Med* 2020;202(3):455–7. doi:[10.1164/rccm.202005-1654LE](https://doi.org/10.1164/rccm.202005-1654LE).
- Giannis D, Ziovas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol* 2020;127. doi:[10.1016/j.jcv.2020](https://doi.org/10.1016/j.jcv.2020).
- Gibson CJ, Alqunaibit D, Smith KE, Bronstein M, Eachempati SR, Kelly AG, et al. Pro-bative Value of the D-Dimer Assay for Diagnosis of Deep Venous Thrombosis in the Coronavirus Disease 2019 Syndrome. *Crit Care Med* 2020;48(12):e1322–6. doi:[10.1097/CCM.0000000000004614](https://doi.org/10.1097/CCM.0000000000004614).
- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020;382(18):1708–20. doi:[10.1056/NEJMoa2002032](https://doi.org/10.1056/NEJMoa2002032).
- Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multi-center prospective cohort study. *Intensive Care Med* 2020;46(6):1089–98 <https://doi.org/10.1007/s00134-020-06062-x>.
- Hippensteel JA, Burnham EL, Jolley SE. Prevalence of venous thromboembolism in critically ill patients with COVID-19. *Br J Haematol* 2020;190(3):e134–7. doi:[10.1111/bjh.16908](https://doi.org/10.1111/bjh.16908).
- Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, et al. INSPIRATION Investigators. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. *JAMA* 2021;325(16):1620–30. doi:[10.1001/jama.2021.4152](https://doi.org/10.1001/jama.2021.4152).
- Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 2020;18(7):1743–6. doi:[10.1111/jth.14869](https://doi.org/10.1111/jth.14869).
- McGonagle D, O'Donnell J, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol* 2020;2(7):e437–45. doi:[10.1016/S2665-9913\(20\)30121-1](https://doi.org/10.1016/S2665-9913(20)30121-1).
- Middeldorp S, Coppens M, van 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(8):1995–2002. doi:[10.1111/jth.14888](https://doi.org/10.1111/jth.14888).
- Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, et al. Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report. *Chest*. 2020;158(3):1143–63. doi:[10.1016/j.chest.2020.05.559](https://doi.org/10.1016/j.chest.2020.05.559).

- Orsi FA, De Paula EV, Santos FO, et al. Guidance on diagnosis, prevention and treatment of thromboembolic complications in COVID-19: a position paper of the Brazilian Society of Thrombosis and Hemostasis and the Thrombosis and Hemostasis Committee of the Brazilian Association of Hematology, Hemotherapy and Cellular Therapy. *Hematol Transfus Cell Ther* 2020;42(4):300–8. doi:[10.1016/j.htct.2020.06.001](https://doi.org/10.1016/j.htct.2020.06.001).
- Goligher EC, Bradbury CA, McVerry BJ, et al. REMAP-CAP Investigators; ACTIV-4a Investigators; ATTACC Investigators. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med*. 2021. doi:[10.1056/NEJMoa2103417](https://doi.org/10.1056/NEJMoa2103417).
- Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692–4. doi:[10.1111/j.1538-7836.2005.01204.x](https://doi.org/10.1111/j.1538-7836.2005.01204.x).
- 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;18(4):844–7. doi:[10.1111/jth.14768](https://doi.org/10.1111/jth.14768).
- Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020;18(5):1023–6. doi:[10.1111/jth.14810](https://doi.org/10.1111/jth.14810).
- Trigoni RA, Holt DB, Yuan R, et al. Incidence of Venous Thromboembolism in Critically Ill Coronavirus Disease 2019 Patients Receiving Prophylactic Anticoagulation. *Crit Care Med* 2020;48(9):e805–8. doi:[10.1097/CCM.0000000000004472](https://doi.org/10.1097/CCM.0000000000004472).
- Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med* 2020;173(4). doi:[10.7326/M20-2003](https://doi.org/10.7326/M20-2003).
- Yu B, Li X, Chen J, Ouyang M, Zhang H, Zhao X, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. *J Thromb Thrombolysis* 2020;50(3):548–57. doi:[10.1007/s11239-020-02171-y](https://doi.org/10.1007/s11239-020-02171-y).
- Yu Y, Tu J, Lei B, Shu H, Zou X, Li R, et al. Incidence and Risk Factors of Deep Vein Thrombosis in Hospitalized COVID-19 Patients. *Clin Appl Thromb Hemost* 2020;26. doi:[10.1177/1076029620953217](https://doi.org/10.1177/1076029620953217).