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Bleeding complications in critically ill COVID-19 patients receiving anticoagulation in a tertiary hospital intensive care unit

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Background. Coronavirus disease-2019 (COVID-19) is associated with a heightened inflammatory response, leading to thromboembolic events that influence patient outcomes. Complex anticoagulation strategies are often required to mitigate these complications. However, severe illness combined with such strategies may be associated with bleeding at multiple sites.

Objectives. To describe the incidence of bleeding and venous thromboembolism (VTE) in critically ill COVID-19 patients receiving anticoagulation. Secondary objectives were to determine the incidence of transfusion in bleeding patients, and the association between inflammatory markers, coagulation parameters, and bleeding and/or VTE. Length of intensive care unit (ICU) stay and patient outcomes in the same cohort were also investigated.

Methods. Participants included adult patients with confirmed COVID-19 by positive polymerase chain reaction (PCR), admitted to the ICU from 1 April 2020 to 30 April 2021. A *p*-value of <0.05 was considered statistically significant.

Results. The study population comprised 103 patients. The anticoagulant of choice was low-molecular-weight heparin at therapeutic doses (median 80 mg/day). Bleeding occurred in 39.8% (*n*=41) of patients, predominantly from the oral mucosa (20.4%; *n*=21) and the gastrointestinal tract (13.6%; *n*=14). Of the patients who bled, 46.3% (*n*=19) received blood transfusions. Two patients (1.9%) developed grade 1 deep vein thrombosis. The median length of ICU stay was 7 days. Survival dropped below 50% (*n*=51) after 10 days of admission, and 25% (*n*=25) of patients survived beyond 28 days. Overall mortality was high at 65.0% (*n*=67).

Conclusion. COVID-19-positive critically ill patients receiving therapeutic anticoagulation exhibited an increased incidence of bleeding, accompanied by a high mortality rate.

Keywords. COVID-19, intensive care unit, anticoagulation, bleeding, venous thromboembolism

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Contribution of study

This study provides South African data demonstrating a high burden of bleeding among critically ill patients with COVID-19 receiving therapeutic anticoagulation. Bleeding risk was not explained by anticoagulation intensity alone but was associated with markers of thrombo-inflammatory disease severity. These findings highlight the complex coexistence of thrombotic and haemorrhagic risks in severe COVID-19 and challenge a simplistic approach to anticoagulation based solely on anticoagulant exposure. The study supports the need for individualised, dynamic, risk-stratified anticoagulation strategies that incorporate clinical status, inflammatory markers and platelet trends.

The COVID-19 pandemic has revealed complex challenges in understanding the disease's pathophysiology, notably its association with a hypercoagulable state and an increased risk of thromboembolic events, particularly in critically ill patients.[1] As a result, anticoagulation therapy has become a mandatory component of treatment for these patients, despite the risk of multisite bleeding complications.[2-4] The virus invades human cells via angiotensin-converting enzyme receptors, triggering an inflammatory response across various tissues, including the lungs, heart, brain and kidneys.[5] This response leads to complex interactions between inflammation, endothelial injury and coagulation, involving key biomarkers such as D-dimer, fibrinogen and cytokines, with elevated D-dimer levels predicting higher mortality.[5,6]

Thromboembolic events, especially venous thromboembolism (VTE), occur more frequently in COVID-19, with incidence rates up to three times higher than those in other respiratory infections.[7,8] The pandemic posed challenges for conducting imaging studies to diagnose deep vein thrombosis (DVT) or pulmonary embolism, owing to infection risks.[5] Anticoagulation dosing during the pandemic was contentious, and the role of antiplatelet therapy was not well understood. Despite the benefits of anticoagulation, prolonged partial thromboplastin time (PTT) and low platelet counts were associated with major bleeding complications.[9] The International Society on Thrombosis and Haemostasis defines 'major bleeding' as (*i*) bleeding with symptomatic presentation, (*ii*) fatal bleeding, (*iii*) bleeding in a

critical area or organ, or (*iv*) bleeding causing a fall in haemoglobin levels of at least 2 g/dL (1.24 mmol/L), or leading to transfusion of two or more units of whole blood or red cells. The biphasic evolution of coagulation disorders during COVID-19 suggests that fibrinogen levels may be a useful marker for early detection of bleeding risk, and that thromboprophylaxis intensity may need adjustment based on thrombo-inflammatory kinetics.[10] The American Society of Hematology's 2021 guidelines recommend prophylactic-dose anticoagulation, such as low-molecular-weight heparin, except in patients at high thrombotic risk without significant bleeding risk.[11] Therapeutic-dose anticoagulation in these patients has not consistently been shown to improve patient outcomes or reduce the need for organ support.[11]

At the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in South Africa (SA), the incidence of bleeding complications in critically ill COVID-19 patients receiving anticoagulation has not previously been reported. Healthcare providers faced difficulties in managing and preventing anticoagulation-related complications during the pandemic. This study aimed to determine the incidence of, and describe the occurrence of, bleeding and VTE events in critically ill patients with confirmed COVID-19 admitted to the CMJAH intensive care unit (ICU) while receiving anticoagulation.

Methodology

Approval to conduct this retrospective cross-sectional study was obtained from the University of the Witwatersrand Human Research Ethics Committee (ref. no. M220553). The study included adult patients with PCR-confirmed COVID-19 admitted to the ICU at CMJAH from 1 April 2020 to 30 April 2021 who were receiving anticoagulation. Exclusion criteria included unknown COVID-19 status, COVID-19-negative patients admitted to the ICU during the study period, patients receiving anticoagulation for other medical conditions prior to admission, and ward patients. A convenient consecutive sampling method was used, with data collected from ICU charts and National Health Laboratory Service (NHLS) blood results.

The population size was determined by the number of eligible patients with complete records during the one-year study period. The sample size could not be calculated *a priori*, as COVID-19 was a novel and evolving disease during the study period; therefore, a consecutive sampling method was employed. Based on feasibility, a target sample size of 100 patients was selected to approximate a 95% confidence interval (CI) with a 5% margin of error.

The primary investigator collected the data using a validated tool formatted in REDCap (Research Electronic Data Capture, Vanderbilt University) (Appendix 1). The data collection sheet was adopted and modified with permission from Al-Samkari *et al.*[8] The investigator accessed ICU patient charts via the Oracle electronic database in the CMJAH medical records department. Findings from the charts were recorded on an anonymised data collection sheet using a numerical coding system to ensure patient confidentiality.

Data were analysed using Stata Statistical Software, version 15 (StataCorp, USA). Variables collected included demographics, risk factors for COVID-19, biomarkers, bleeding events, anticoagulation therapy, thromboembolic events, organ dysfunction, organ support, length of ICU stay and mortality.

The Shapiro-Wilk test was used to assess normality of data distribution. Categorical variables are presented as frequency and percentages. Normally distributed data are presented as means and standard deviations (SDs), while non-normally distributed data are presented as medians and interquartile ranges (IQRs). The χ^2 test was used to compare body mass index (BMI) categories between males and females. Fisher's exact test was used to assess associations between normally distributed variables. The Wilcoxon rank-sum test was used to assess associations between non-normally distributed variables. The Kruskal-Wallis test was used to assess the relationship between bleeding, haemoglobin levels, and coagulation and inflammatory markers. The Kaplan-Meier curve was used to assess patient trends post ICU admission. A *p*-value of <0.05 was considered statistically significant.

Results

Of the 152 identified patients, 103 were eligible and included in the analysis (Fig. 1). Of this cohort (*n*=103), 55.9% (*n*=57) were male and the mean age was 49.5 years. Table 1 shows the baseline characteristics of bleeding and non-bleeding patients in the study population.

No statistically significant differences were found in demographics, body habitus or risk factors for severe COVID-19 between bleeding and non-bleeding patients (Table 3). A statistically significant risk factor for bleeding was the presence of cardiovascular disease ($p<0.001$). All patients in the study received a therapeutic dose of enoxaparin. The median (IQR) anticoagulation dose administered was 80 mg (60 - 80 mg), suggesting relatively consistent dosing within the data set. The median anti-Xa level was lower in the bleeding group than in the non-bleeding group (0.1 v. 0.3; $p=0.011$), suggesting that bleeding may be influenced by factors other than anticoagulation intensity.

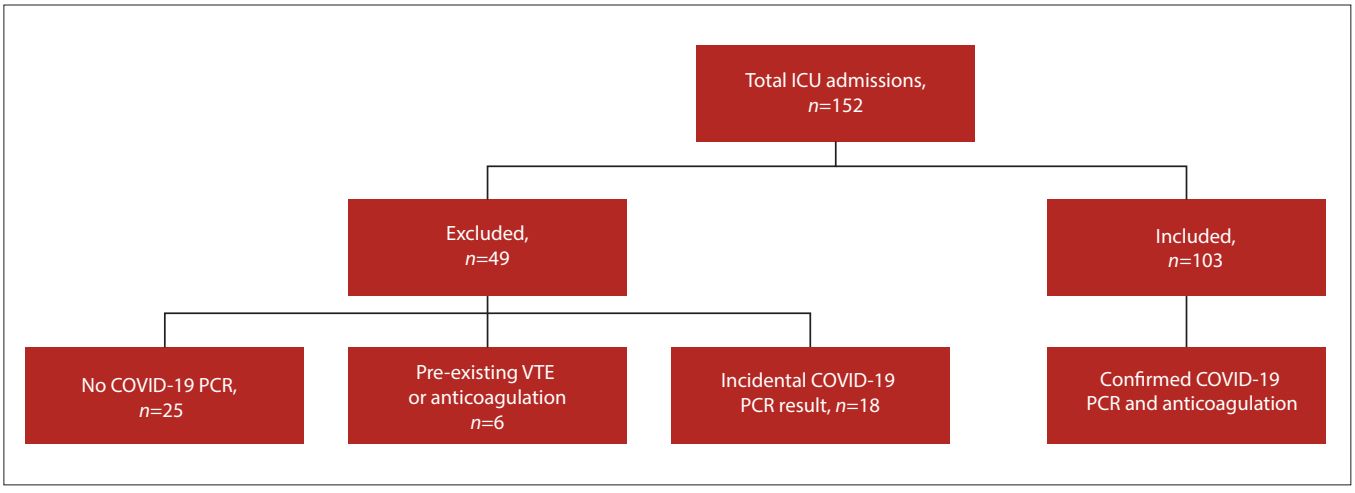


Fig. 1. Study population sampling. (ICU = intensive care unit; PCR = polymerase chain reaction; VTE = venous thromboembolism).

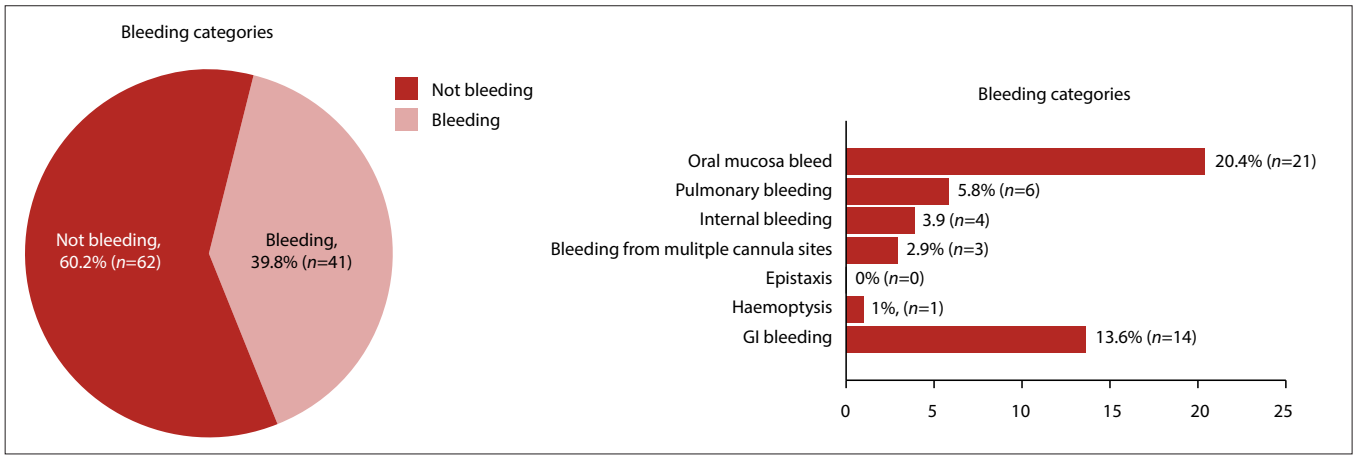


Fig. 2. Bleeding incidence and categories. (GI = gastrointestinal).

Table 1. Baseline characteristics of the study cohort

Patient demographics	Entire study cohort: *N*=103	Not-bleeding group: *n*=62	Bleeding group: *n*=41	*p*-value
Age (years)				0.004
Mean (SD)	49.5 (12.4)			
Median (IQR)		46.0 (38.0, 54.0)	52.0 (45.0, 63.0)	
Sex: frequency (%)				0.581
Male	57 (55.9)	36 (63.2)	21 (36.8)	
Female	45 (44.1)	26 (57.8)	19 (42.2)	
Outcome: frequency (%)				0.008
Discharged to ward	35 (34.0)	28 (80.0)	7 (20.0)	
Deceased	67 (65.0)	33 (49.3)	34 (50.7)	
Other (transfer)	1 (1.0)	1 (100)	0 (0)	
Length of ICU stay in days: median (IQR)	7.0 (4.0 - 12.0)	5.0 (3.0 - 9.0)	10.0 (7.0 - 19.0)	<0.001
Height (metre): median (IQR)	1.6 (1.6 - 1.7)	1.6 (1.6 - 1.7)	1.6 (1.6 - 1.7)	0.710
Weight (kilogram): median (IQR)	90 (80.0 - 100)	90.0 (80.0 - 100)	90.0 (85.0 - 100)	0.216
BMI				0.195
Mean (SD)	34.1 (5.9)			
Median (IQR)		34.6 (30.9 - 35.2)	35.2 (31.2 - 39.1)	
BMI category: mean (SD)				0.764
Normal (18.5 - 24.9)	9 (9.0)	6 (66.7)	3 (33.3)	
Overweight (25.0 - 29.9)	13 (13.0)	8 (61.5)	5 (38.5)	
Class I obesity (30.0 - 34.9)	27 (27.0)	16 (59.3)	11 (40.7)	
Class II obesity (35.0 - 39.9)	39 (39.0)	24 (61.5)	15 (38.5)	
Class III obesity (>40)	12 (12.0)	5 (41.7)	7 (58.3)	
Anticoagulation dose (mg): median (IQR)	80.0 (60.0 - 80.0)	80.0 (60.0 - 80.0)	80.0 (60.0 - 80.0)	0.920
Anticoagulation duration (days): median (IQR)	7.0 (4.0 - 11.0)	5.0 (4.0 - 8.0)	9.0 (6.0 - 13.0)	0.009
Anticoagulation anti-Xa level: median (IQR)	0.2 (0.1 - 0.4)	0.3 (0.1 - 0.5)	0.1 (0.1 - 0.3)	0.011

SD = standard deviation; IQR = interquartile range; ICU = intensive care unit; BMI = body mass index.

Bleeding in this cohort was documented in 39.8% (*n*=41) of patients. Fig. 2 demonstrates the incidence of different categories of bleeding. Two patients (1.9%) developed grade 1 DVT, while 98% of the population had no confirmed VTE event. VTE events were confirmed using bedside ultrasound imaging upon clinical suspicion; no routine ultrasound screening was performed in the ICU. Among bleeding patients, there was no statistically significant difference in transfusion practices. A haemoglobin threshold of <7 g/dL was used to guide blood transfusion. Rotational thromboelastometry (ROTEM) and thromboelastography (TEG) were not available to guide transfusion practices. Fig. 3 shows transfusion patterns between the groups.

Biomarker analysis suggested associations between peak of inflammation, coagulopathy and disease severity. Statistically significant differences between non-bleeding and bleeding patients were observed for C-reactive protein (CRP) peak (168 v. 279; $p<0.001$), minimum platelet count (204 v. 132; $p<0.001$) and D-dimer peak (1.6 v. 4.0; $p=0.025$) (Table 2). D-dimer and fibrinogen were measured daily in the ICU.

The median length of ICU stay was longer in the bleeding than in the non-bleeding group (10.0 v. 5.0 days, respectively). Overall mortality was 65.0% (*n*=67), with similar numbers in the two groups (33 v. 34). Of the patients discharged from ICU (28 v. 7), the non-bleeding group had a higher survival rate.

Kaplan-Meier analysis of ICU survival during the first month showed that >75% (*n*=77) of patients survived the first 4 days after admission. However, survival declined to <50% (*n*=51) after 10 days, and only 25% (*n*=25) of patients survived beyond 28 days.

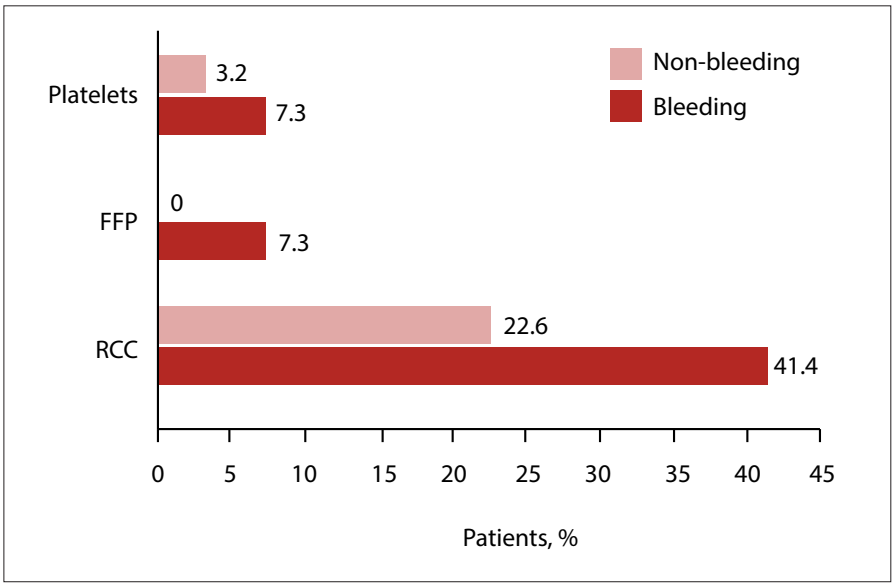


Fig. 3. Transfusion of blood products in bleeding v. non-bleeding patients.

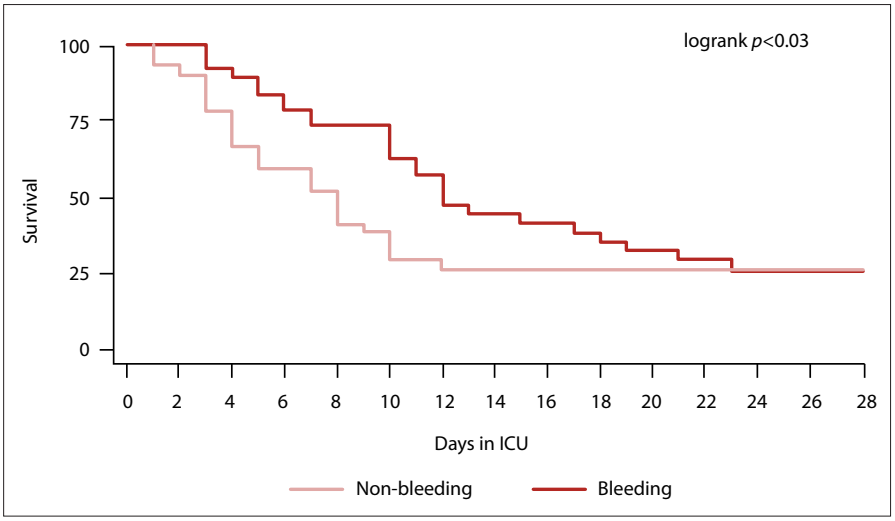


Fig. 4. Survival trends in bleeding v. non-bleeding patients. (ICU = intensive care unit).

Fig. 4 compares the survival trends of bleeding and non-bleeding ICU patients. Although patients in the bleeding group had a higher probability of survival initially, this difference converged with that of the non-bleeding group by day 23. These findings may suggest that prolonged critical illness is associated with an increased risk of bleeding, particularly gastrointestinal tract (GIT) bleeding, possibly related to stress ulceration.

Discussion

This study investigated the incidence of bleeding complications and thrombotic events in critically ill patients with COVID-19 receiving anticoagulation in a tertiary hospital ICU. The high incidence of thromboembolic events reported in COVID-19, together with the poorly understood thrombo-inflammatory response, has led to the widespread clinical use of therapeutic-dose anticoagulation to mitigate this prothrombotic state. Some studies have reported improved survival with the use of therapeutic anticoagulation during the pandemic.[4,12] In this study, the preferred anticoagulant was low-molecular-weight heparin (LMWH), administered at therapeutic doses on admission. However, the use of therapeutic dosing raised concerns regarding an increased risk of clinically significant bleeding in this patient group.

The incidence of bleeding in this study was 39.8%, comparable to the rate of 33.54% reported by Singh *et al.*[13] However, the incidence of severe bleeding in this study was 29.2%, substantially higher than the generally reported 5.02 - 18% in the literature.[4,13] The association between intensive anticoagulation and severe bleeding has been reported by Halaby *et al.*[14] These findings suggest that anticoagulation therapy should be tailored to individual patient risk and guided by risk-stratifying scoring systems. Godier *et al.*[4] also observed that thrombo-inflammatory kinetics change as the disease progresses and suggested that adjusting anticoagulation therapy according to these changes may reduce bleeding risk.

GIT bleeding was the leading cause of major bleeding events in this cohort, likely reflecting severity of illness rather than anticoagulation alone. Critically ill patients may develop mucosal changes within 72 hours of illness onset, and the risk of severe bleeding increases with the duration of critical illness, consistent with the present findings. The bleeding group had a longer ICU stay than the non-bleeding group. Timely stress ulcer prophylaxis and early feeding are essential in preventing severe bleeding.[15]

Inflammatory markers (CRP and D-dimer) were elevated in the bleeding group, while coagulation parameters (international normalised ratio (INR) and PTT) were not. In addition, the bleeding group had lower platelet counts, indicating an increased risk of bleeding. Interestingly, anti-Xa levels did not correlate with bleeding, highlighting the complexity, unpredictability and limited understanding of the pathophysiology of bleeding in this patient group. This underscores the challenge of accurately predicting bleeding risk in critically ill COVID-19 patients during the pandemic.[10]

This study observed a low incidence (1.9%) of thrombotic events in the cohort, contrasting with other studies reporting VTE rates of 20 - 30%.[16,17] This discrepancy may be explained by limited routine VTE screening at our facility during the pandemic, owing to reduced access to radiological services shared with non-COVID-19 patients. As a result, critically ill COVID-19 patients could access these services only after hours to prevent cross-contamination. Furthermore, many patients were too unstable to transport and were often positioned prone to optimise ventilation, complicating VTE screening and diagnosis. This limitation should be considered when interpreting the findings of this study and warrants further investigation in future research.

A mortality rate of 65% was observed, with higher survival rates in the non-bleeding group. This aligns with outcomes reported in literature during the pandemic.[18-20] The finding of increased survival in the non-bleeding group is supported by Singh *et al.*,[13] who similarly reported an association between bleeding and increased mortality.

Table 2. Biomarkers of the study cohort

Biological markers	Entire study cohort: *N*=103	Not-bleeding group: *n*=62	Bleeding group: *n*=41	*p*-value
D-dimer: median (IQR)				
Initial	1.8 (0.8 - 4.8)	1.2 (0.6 - 2.8)	2.4 (1.7 - 7.5)	0.035
Minimum	1.5 (0.8 - 3.0)	1.2 (0.6 - 2.3)	1.8 (0.9 - 4.0)	0.100
Peak	1.9 (0.8 - 7.4)	1.6 (0.7 - 4.3)	4.0 (1.7 - 20.6)	0.025
PTT: median (IQR)				
Initial	15.7 (14.1 - 17.9)	16.0 (14.3 - 17.6)	15.4 (14.0 - 18.1)	0.399
Minimum	15.1 (13.9 - 16.2)	15.7 (14.1 - 16.8)	14.4 (13.7 - 15.4)	0.027
Peak	16.2 (14.8 - 18.7)	16.2 (14.8 - 18.0)	16.3 (14.9 - 19.3)	0.361
INR: median (IQR)				
Initial	1.1 (1.0 - 1.3)	1.1 (1.0 - 1.2)	1.1 (1.0 - 1.3)	0.464
Minimum	1.1 (1.0 - 1.1)	1.1 (1.0 - 1.2)	1.0 (1.0 - 1.1)	0.028
Peak	1.1 (1.1 - 1.3)	1.1 (1.1 - 1.3)	1.2 (1.1 - 1.3)	0.298
Fibrinogen: median (IQR)				
Initial	5.5 (2.9 - 6.6)	5.5 (3.8 - 5.7)	6.2 (1.9 - 39.8)	0.672
Minimum	4.1 (2.2 - 5.7)	4.1 (3.5 - 5.5)	4.1 (1.9 - 6.6)	0.751
Peak	4.1 (3.5 - 5.7)	4.1 (3.5 - 5.6)	4.2 (2.9 - 6.4)	0.700
Platelet count: median (IQR)				
Initial	289.0 (210.0 - 361.0)	281.0 (202.0 - 360.0)	297.0 (216.0 - 361.0)	0.647
Minimum	166.0 (104.0 - 247.0)	204.5 (149.0 - 301.0)	132.0 (66.0 - 177.0)	<0.001
Peak	371.0 (274.0 - 451.0)	361.5 (262.0 - 446.0)	393.0 (293.0 - 453.0)	0.561
CRP: median (IQR)				
Initial	111.0 (49.0 - 208.0)	113.0 (49.0 - 193.0)	104.0 (53.0 - 239.0)	0.642
Minimum	30.0 (10.0 - 66.0)	32.0 (10.0 - 61.0)	27.5 (10.0 - 70.5)	0.697
Peak	226.0 (130.0 - 306.0)	168.0 (111.0 - 237.0)	279.0 (238.5 - 350.0)	0.001
Cardiac troponin: median (IQR)				
Initial	30.0 (11.0 - 85.0)	28.0 (10.0 - 79.0)	40.5 (18.5 - 93.5)	0.385
Minimum	28.0 (11.0 - 79.0)	25.0 (9.0 - 79.0)	39.0 (18.0 - 99.0)	0.294
Peak	55.0 (19.0 - 127.0)	38.0 (15.0 - 121.0)	82.5 (25.0 - 129.5)	0.371
Ferritin: median (IQR)				
Initial	1268.0 (554.0 - 2171.0)	1451.0 (554.0 - 2305.0)	1220.0 (471.0 - 2010.0)	0.456
Minimum	1249.5 (554.0 - 2171.0)	1451.0 (591.0 - 2741.0)	917.5 (471.0 - 2010.0)	0.303
Peak	1249.5 (529.0 - 2171.0)	1451.0 (578.5 - 2741.0)	1025.5 (471.0 - 2010.0)	0.349
Initial Hb: median (IQR)	12.5 (10.8 - 13.6)	12.6 (10.8 - 13.6)	12.2 (11.0 - 13.6)	0.894
Initial HCT: median (IQR)	39.0 (33.3 - 42.4)	38.9 (33.2 - 41.8)	39.3 (34.2 - 43.0)	0.364
Lowest Hb: median (IQR)	9.3 (7.8 - 11.3)	10.0 (8.6 - 11.8)	8.2 (7.5 - 10.2)	0.002
Hb difference: median (IQR)	2.1 (1.1 - 3.9)	1.4 (0.8 - 2.7)	(2.1 - 4.6)	<0.001
Hb difference category: frequency (%)				<0.001
<3	63 (61.8)	48 (76.2)	15 (23.8)	
≥3	39 (38.2)	13 (33.3)	26 (66.7)	
RCC number: frequency (%)				0.136
N/A	68 (66.0)	47 (69.1)	21 (30.9)	
0	4 (3.9)	1 (25.0)	3 (75.0)	
1	11 (10.7)	6 (54.5)	5 (45.5)	
2	9 (8.7)	4 (44.4)	5 (55.6)	
3	3 (2.9)	2 (66.7)	1 (33.3)	
4	5 (4.9)	1 (20.0)	4 (80.0)	
5	3 (2.9)	1 (33.3)	2 (66.7)	
RCC number continuous: median (IQR)	2.0 (1.0 - 3.0)	−1.0 (−1.0 - −1.0)	−1.0 (−1.0 - 2.0)	0.029
FFP number: frequency (%)				0.148
N/A	90 (87.4)	57 (91.9)	33 (80.5)	
0	10 (9.7)	5 (8.1)	5 (12.2)	
1	1 (1.0)	0 (0.0)	1 (2.4)	
4	2 (1.9)	0 (0.0)	2 (4.9)	
Platelets number: frequency (%)				0.477
N/A	88 (85.4)	55 (62.5)	33 (37.5)	
0	10 (9.7)	5 (50.0)	5 (50.0)	
1	5 (4.9)	2 (40.0)	3 (60.0)	

IQR = interquartile range; PTT = partial thromboplastin time; INR = international normalised ratio; CRP = C-reactive protein; Hb = haemoglobin; HCT = haematocrit; RCC = red cell concentrate; FFP = fresh frozen plasma.

Table 3. Risk factors and organ dysfunction of the study cohort

Characteristic: *N* (%)	Entire study cohort: *N*=103	Not-bleeding group: *n*=62	Bleeding group: *n*=41	*p*-value
Risk factors for severe COVID-19				
Cardiovascular disease				0.001
Yes	60 (58.3)	28 (46.7)	32 (53.3)	
No	-	34 (79.1)	9 (20.9)	
Immunocompromised or suppressed				0.251
Yes	18 (17.5)	13 (72.2)	5 (27.8)	
No	-	49 (57.6)	36 (42.4)	
Chronic lung disease				0.043
Yes	12 (11.7)	4 (33.3)	8 (66.7)	
No	-	58 (63.7)	33 (36.3)	
Chronic kidney disease or dialysis				0.373
Yes	23 (22.3)	12 (52.2)	11 (47.8)	
No	-	50 (62.5)	30 (37.5)	
Diabetes mellitus				0.158
Yes	54 (52.4)	29 (53.7)	25 (46.3)	
No	-	33 (67.3)	16 (32.6)	
Chronic liver disease				0.414
Yes	1 (100)	1 (100)	0 (0)	
No	-	61 (59.8)	41 (40.2)	
Resides in a nursing home or long-term				
Yes	0 (0)	0 (0)	0 (0)	
No	-	62 (60.2)	41 (39.8)	
Other risk factors for severe COVID-19				0.209
Yes	27 (26.2)	19 (70.4)	8 (29.6)	
No	-	43 (56.6)	33 (43.4)	
Risk factors for bleeding				
Low platelet count				<0.001
Yes	30 (29.1)	8 (26.7)	22 (73.3)	
No	-	54 (74.0)	19 (26.0)	
Liver failure				0.166
Yes	6 (5.8)	2 (33.3)	4 (9.8)	
No	-	60 (96.8)	37 (90.2)	
Disseminated intravascular coagulopathy				0.040
Yes	10 (9.7)	3 (30.0)	7 (70.0)	
No	-	59 (63.4)	34 (36.6)	
Acute kidney injury				0.113
Yes	74 (71.8)	41 (55.4)	33 (44.6)	
No	-	21 (72.4)	8 (27.6)	
Other risk factors for bleeding				0.217
Yes	1 (100)	0 (0)	1 (100)	
No	-	62 (60.8)	40 (39.2)	
ICU organ dysfunction				
Kidney failure				0.066
Yes	59 (57.3)	31 (52.5)	28 (47.5)	
No	-	31 (70.4)	13 (31.7)	
Kidney failure requiring dialysis				0.169
Yes	-	11 (47.8)	12 (52.2)	
No	-	51 (63.8)	29 (36.3)	
Respiratory failure				0.121
Yes	77 (74.8)	43 (55.8)	34 (44.2)	
No	-	19 (73.1)	7 (26.9)	
Haemodynamic instability				0.006
Yes	41 (39.8)	18 (43.9)	23 (56.1)	
No	-	44 (71.0)	18 (29.0)	
Heart failure				0.170
Yes	10 (9.7)	4 (40.0)	6 (60.0)	
No	-	58 (63.4)	35 (37.6)	
Liver dysfunction				0.217
Yes	1 (100)	0 (0)	1 (100)	
No	-	62 (60.8)	40 (39.2)	

ICU = intensive care unit.

It is well established that major bleeding in critically ill patients contributes to an elevated risk of mortality, even in non-COVID-19 patients.[21] Bleeding patients also had a longer ICU stay, consistent with existing literature. This may reflect increased organ support requirements and the need for interventions to manage bleeding, further prolonging ICU stay compared with non-bleeding patients.[22]

Limitations

This study has several limitations that affect the generalisability of its findings, including its small sample size and single-centre design. By including only patients with PCR-confirmed positive COVID-19, the study may have excluded clinically relevant cases with inconclusive test results. Furthermore, the retrospective design makes it challenging to establish causality, as temporal relationships between exposures and outcomes cannot be clearly defined. There may also be unmeasured confounding variables influencing the observed associations between anticoagulation, VTE and bleeding outcomes. Consequently, while the study identifies associations, it cannot definitively establish causal relationships.

Conclusion

This study highlights an increased incidence of bleeding complications in critically ill COVID-19 patients receiving therapeutic anticoagulation. The observed associations between bleeding and inflammatory markers in this patient group, including D-dimer, CRP and platelet counts, reflect the complex interplay between coagulation, inflammatory responses and disease severity. While statistical associations were identified, these did not establish causality and should be interpreted with caution. Bleeding in this patient group was associated with increased mortality, underscoring the importance of careful anticoagulation management. Predictive scoring systems should be adopted to tailor individualised anticoagulation strategies. The observed reduction in the incidence of severe disease and VTE following vaccination suggests that disease severity may influence thrombo-inflammatory kinetics.

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