RESEARCH LETTER

Bleeding and thrombotic complications in patients with severe COVID-19: A prospective observational study

Mina A. Helmy | **Lydia M. Milad** | **Ahmed Hasanin** | **Eman A. Elsayed** | **Omnia Y. Kamel** | **Maha Mostafa** | **Shaimaa Fathy** | **Mohamed Elsayad**

Department of Anesthesia and Critical Care Medicine, Cairo University, Cairo, Egypt

Correspondence: Ahmed Hasanin, Department of Anesthesia and Critical Care Medicine, Faculty of Medicine, Cairo University, Cairo 7654, Egypt.
Email: ahmedmohamedhasanin@gmail.com

1 | INTRODUCTION

The hypercoagulable state plays an important role in the pathophysiology of Coronavirus disease-2019 (COVID-19).[1] The clear association between COVID-19 and hypercoagulable state resulted in extensive use of anticoagulant drugs worldwide. However, due to the frequent bleeding events with liberal doses,[2] the current recommendations restrict anticoagulant drugs to the prophylactic dose when thrombotic events are not present.[3] Yet the benefit of the use of anticoagulant drugs in doses higher than the ordinary prophylactic doses still shows conflicting evidence.[4,5] Hence, reaching the appropriate anticoagulation regimen requires extensive reports for the prevalence of bleeding and thrombosis and identifying possible tools for risk stratification for bleeding. Furthermore, currently, there is no validated score to assess bleeding risk in patients with COVID-19. We aimed in this study to evaluate the prevalence of thrombosis and bleeding in patients with severe COVID-19 and to assess the ability of the International Medical Prevention Registry on Venous Thromboembolism Bleeding risk assessment model (IMPROVE bleed RAM) to predict major bleeding in this population.

2 | METHODS

This prospective observational study was conducted in a university hospital after the institutional Ethics Committee approval (N-124-2021). Written informed consent was obtained from the patient's next-in-kin before the enrollment. We included adult patients (>18 years) with severe COVID-19[6] within 12 h of admission. Exclusion criteria were age <18 years, patient on anticoagulant therapy before hospital admission, pregnancy, and/or expected death or discharge within 48 h from admission.

Demographic (age, sex, body mass index, and Charlson Comorbidity Index), clinical (heart rate, mean arterial pressure, respiratory rate, temperature, peripheral oxygen saturation, Acute Physiology and Chronic Health Evaluation II [APACHE II] score) and laboratory data (Platelet count, international normalizing ratio, C-reactive protein, D-dimer) were collected on admission. Data for the IMPROVE bleed RAM were collected and the score was calculated.[7] Anticoagulation therapy was prescribed as follows; Patients with no documented venous thromboembolism were given prophylactic dose of anticoagulation (subcutaneous enoxaparin 40 mg once daily if body mass index < 40 kg/m² and twice daily if the body mass index > 40 kg/m²). Confirmed venous thromboembolism, arterial thrombotic events, patients who developed atrial fibrillation, and patients on extra-corporeal membrane oxygenation (ECMO), therapeutic anticoagulation was implemented (subcutaneous enoxaparin 0.8 mg/kg twice daily if the body mass index > 40 kg/m², enoxaparin 1 mg/kg twice daily if creatinine clearance > 30 ml/min, and enoxaparin 1 mg/kg once daily if creatinine clearance < 30 ml/min).[3]

2.1 | The study outcomes

The primary outcome was the incidence of thrombotic events. Secondary outcomes included the incidence of major bleeding

TABLE 1 Demographic, clinical, and outcome data

Age (years)	65 (54, 72)
Male sex (%)	53 (46.5)
Body mass index (kg)	25 (22, 28)
Baseline heart rate (bpm)	96 (19)
Baseline mean arterial pressure (mmHg)	90 (16)
Baseline respiratory rate (breath per minute)	26 (21, 32)
Baseline Temperature (°C)	37.5 (37.0, 38.2)
SpO$_2$ (%)	84 (73,89)
APACHE II score	10 (6, 13)
IMPROVE Bleed RAM	6 (5, 8)
Charlson Comorbidity Index	1 (0, 3)
Comorbidity (%)	
Diabetes mellites	43 (37.7)
Hypertension	47 (41.2)
Ischemic heart disease	12 (10.5)
Atrial fibrillation	3 (2.6)
Stroke	4 (3.5)
Liver cirrhosis	5 (4.4)
Chronic kidney disease	19 (16.7)
Active malignancy	11 (9.6)
Chronic pulmonary disease	5 (4.4)
Hypothyroidism	3 (2.6)
Platelet count (*10^3/μl)	233 (152, 303)
INR	1.1 (1.0, 1.2)
C-reactive protein (mg/dl)	73 (34.4, 123.3)
D-dimer (μg/ml)	1.8 (0.6, 4.1)
In-hospital mortality (%)	50 (43.9)
All thrombotic events (%)	15 (13.2)
Venous thrombotic events (%)	10 (8.8)
- Deep venous thrombosis (%)	8 (7)
- Pulmonary embolism (%)	2 (1.8)
Arterial thrombotic events (%)	5 (4.4)
- STEMI (%)	2 (1.8)
- Ischemic stroke (%)	1 (0.9)
- MVO (%)	1 (0.9)
Acute lower limb ischemia (%)	1 (0.9)
All Bleeding events (%)	18 (15.8)
Tracheostomy site (%)	1 (0.9)
Oropharyngeal (%)	3 (2.6)
Peptic ulcer (%)	3 (2.6)
Variceal (%)	1 (0.9)
Epistaxis (%)	2 (1.8)
Rectus sheath (%)	1 (0.9)
Retroperitoneal (%)	1 (0.9)
Anorectal (%)	1 (0.9)
Melena (%)	1 (0.9)
Basal ganglia hemorrhage (%)	1 (0.9)
Hemorrhagic transformation of stroke (%)	1 (0.9)
Surgical site hematoma (%)	1 (0.9)
Central line-related hematoma (%)	1 (0.9)

Note: Data presented as mean (standard deviation), median (quartiles), and frequency (%).

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; IMPROVE bleed RAM, International Medical Prevention Registry on Venous Thromboembolism bleeding Risk Assessment Method; INR, international normalized ratio; MVO, mesenteric vascular occlusion; SpO2, peripheral oxygen saturation; STEMI, ST-elevation myocardial infarction.

events[8] during hospital stay, risk factors for bleeding, and ability of IMPROVE bleed RAM to predict bleeding events.

2.2 | Statistical analysis

The sample size was planned to detect an incidence of thrombotic disorders of 15% with null hypothesis of 5%. A minimum number of 103 patients would achieve a study power of 95% and an alpha error of 0.05. The number of patients was increased by 110 to compensate for possible dropouts.

Categorical data we presented as frequency (percentages) and continuous data are presented as means (standard deviations) or medians (quartiles) as appropriate. Adjusted odds ratio (OR) and their 95% confidence intervals (CIs) for risk factors for bleeding events were identified using the logistic regression analysis. Multivariate analysis included variables with p-value < 0.2 in the univariate analysis. The area under the receiver operating characteristics curve (AUC) was calculated to evaluate the ability of IMPROVE bleed RAM to predict bleeding event. A p-value < 0.05 was significant. Statistical packages for social science software version 21 and MedCalc version 14 were used for data analysis.

3 | RESULTS

One-hundred twenty-four patients were screened for eligibility and 10 patients were excluded (5 patients for failure to obtain consent, 4 patients for being already on anticoagulation and 1 patient was pregnant), and 114 patients were included in the final analysis. Baseline characteristics are summarized in Table 1.

All patients were initially provided with oxygen via nonrebreathing mask, and the flow was adjusted to maintain $SpO_2 > 94\%$, 58% required high flow nasal oxygen and/or noninvasive mechanical ventilation, 55.3% of patients required mechanical ventilation, and three patients were placed on a veno-venous ECMO.

Venous thromboembolic and arterial thrombotic events were observed in 10 (8.8%) and 5 (4.4%), respectively; while, bleeding occurred in 18 (15.8%) patients, 10 (8.8%) patients were classified as major (Table 1).

The risk factors for bleeding events were IMPROVE bleed RAM and D-dimer through the univariate analysis (Table 2). However, the multivariate analysis showed that IMPROVE bleed RAM was the only risk factor for major bleeding (Table 2).

The AUC (95% CI) of IMPROVE bleed RAM score for predicting bleeding: 0.76 (0.67–0.84), sensitivity: 78 (52–94)%, specificity: 69 (59–78)%, positive predictive value: 32 (24–41)%, negative predictive value: 94 (87–98)%, and a cutoff value > 6.5.

4 | DISCUSSION

In patients with severe COVID-19, we found a considerable prevalence of bleeding events (15.5%) with major bleeding in 8.8% of cases while thrombotic arterial and venous, events were observed in 13.2% of patients. This high prevalence of bleeding was reported despite the conservative use of anticoagulation.

Current evidence shows that bleeding in patients with severe COVID-19 pneumonia is not only due to anticoagulation treatment, but also due to microvascular damage.[9] In line with our findings, some previous reports showed major bleeding events in critically ill patients with COVID-19 which ranged between 4.8% and 18%.[10,11]

In comparison to recent reports,[12,13] current study showed a lower prevalence of thrombotic events. The prevalence of serious thrombotic events (pulmonary embolism and ST-elevation myocardial infarction) was lower than major bleeding events.

We evaluated the possible risk factors for bleeding in our patients and found that IMPROVE bleed RAM score was the only independent risk factor. Furthermore, the score showed moderate predictive ability and excellent negative predictive value for bleeding. supporting our findings, Wang et al.[14] reported higher IMPROVE bleed RAM score in critically ill patients with COVID-19 in comparison to non-critically ill patients. Our study is the first study to prospectively evaluate the predictive ability to IMPROVE bleed RAM score in patients with severe COVID-19 using univariate, multivariate, and AUC analyses.

The optimum dose of anticoagulants for patients with severe COVID-19 is not yet settled, and it is essential to report the prevalence and risk factors of both thrombosis and bleeding to reach the appropriate regimen for anticoagulation in these patients. According to our findings, we suggest that the use of anticoagulant drugs should be judicious as the risk of bleeding might be relatively higher than the risk of thrombosis. IMPROVE bleed RAM score might help in deciding whether to use anticoagulants or not.

TABLE 2 Univariate and multivariate analysis for bleeding risk

	Odds ratio (95% CI)	p Value
Univariate		
Age (years)	0.99 (0.96–1.02)	0.617
Male sex	0.65 (0.24–1.79)	0.403
SpO₂ (%)	1.00 (0.95–1.04)	0.876
HR (bpm)	1.01 (0.99–1.04)	0.357
RR (breath per minute)	1.02 (0.95–1.09)	0.588
APACHE II	1.05 (0.97–1.15)	0.233
CCI	1.23 (0.97–1.56)	0.094
IMPROVE bleed RAM	1.40 (1.12–1.75)	0.003*
Platelet count	1.00 (1.00–1.01)	0.879
INR	1.02 (0.25–4.22)	0.974
CRP (mg/dl)	1.01 (1.00–1.01)	0.061
D-Dimer (µg/mL)	1.14 (1.01–1.28)	0.029*
Multivariate		
CCI	0.99 (0.73–1.35)	0.959
IMPROVE bleed RAM	1.34 (1.03–1.75)	0.031*
CRP (mg/dl)	1.00 (1.00–1.01)	0.241
D-dimer (µg/ml)	1.06 (0.92–1.21)	0.423

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; HR, heart rate; IMPROVE bleed RAM, International Medical Prevention Registry on Venous Thromboembolism bleeding Risk Assessment Method; INR, international normalized ratio; RR, respiratory rate; SpO2, peripheral oxygen saturation.
*Denotes statistical significance.

The current study has some limitations, first, it was conducted in one university; however, we collected the data from three separate units that were handled by different teams of intensivists; this provides more generalizability for our findings. Second, we did not follow up with the patients after discharge from hospital.

In conclusion, despite the judicious use of anticoagulant drugs, the risk of bleeding in patients with severe COVID 19 is still considerable and should not be ignored. Being the independent risk factor for bleeding, IMPROVE bleed RAM score could help in guiding anticoagulation plan in these patients. IMPROVE bleed RAM score less than 6.5 can rule out the risk of bleeding with a negative predictive value of 94%.

AUTHOR CONTRIBUTIONS

Conceptualization: Mina A. Helmy, Ahmed Hasanin, and Maha Mostafa. *Data Curation*: Mina A. Helmy, Lydia M. Milad, and Maha Mostafa. *Formal Analysis*: Mina A. Helmy, Ahmed Hasanin, and Maha Mostafa. *Investigation*: Mina A. Helmy, Lydia M. Milad, Eman A. Elsayed, Omnia Y. Kamel, Shaimaa Fathy, and Mohamed Elsayad. *Methodology*: Mina A. Helmy, Lydia M. Milad, Ahmed Hasanin, Eman

A. Elsayed, Omnia Y. Kamel, Maha Mostafa, Shaimaa Fathy, and Mohamed Elsayad. *Project Administration*: Ahmed Hasanin. *Resources*: Mina A. Helmy, Lydia M. Milad, Eman A. Elsayed, Omnia Y. Kamel, Shaimaa Fathy, and Mohamed Elsayad. *Supervision*: Mina A. Helmy and Maha Mostafa. *Visualization*: Mina A. Helmy, Ahmed Hasanin, and Maha Mostafa. *Writing – original draft preparation*: Mina A. Helmy, Lydia M. Milad, and Ahmed Hasanin. *Writing – review and editing*: Eman A. Elsayed, Omnia Y. Kamel, Maha Mostafa, Shaimaa Fathy, and Mohamed Elsayad. All authors have read and approved the final version of the manuscript. The corresponding author, Ahmed Hasanin, had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The corresponding author, Ahmed Hasanin, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Ahmed Hasanin http://orcid.org/0000-0001-9947-5863

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