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Research Article

Assessment of Peripheral Thromboembolic Events Risk Factors Among Covid-19 Patients in Suez Canal University Hospital

Micheal Naseem El Abd*, Mamdouh M Almezaien, Sherif A Reffat, Hatem H Mohamed and Meera Refaat

Department of Surgery, Vascular Surgery Unit, Suez Canal University Hospital, Ismailia, Egypt

***Corresponding Author:** Micheal Naseem El Abd, Department of Surgery, Vascular Surgery Unit, Suez Canal University Hospital, Ismailia, Egypt.

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Abstract

This study aims to assess thrombotic risk, laboratory markers, and clinical outcomes in patients with and without COVID-19 presenting with peripheral thromboembolic events (TEs), focusing on COVID-19-associated coagulopathy (CAC). A prospective observational comparative study was conducted at Suez Canal University Hospital, Ismailia, Egypt, between January and June 2023. The patients were divided into three groups: those with recent PCR-confirmed COVID-19 and TEs, those with COVID-19 but no TEs, and those with TEs without COVID-19. Demographics, symptoms, comorbidities, laboratory parameters, imaging data, and clinical outcomes were collected. Patients in the COVID-19 with TEs group demonstrated significantly higher rates of diabetes mellitus (60%), obesity (69.3%), and ICU admission (42.7%) compared to other groups ($p < 0.05$). D-dimer levels >9.4 µg/mL showed excellent predictive performance for TEs (AUC = 0.999, sensitivity = 100%, specificity = 97.33%, $p < 0.001$), whereas fibrinogen levels demonstrated moderate predictive capacity. Among therapeutic interventions, 53.3% of COVID-19 patients with TEs and 56% of non-COVID-19 patients with TEs received anticoagulation; however, 24% of COVID-19-associated TE patients ultimately required limb amputation. Despite comparable treatment protocols, clinical outcomes were notably worse among COVID-19 patients with TEs. The study highlights the severity of peripheral thromboembolic complications in COVID-19 patients, highlighting the importance of aggressive risk stratification and intensified anticoagulation strategies. It suggests further multicentric studies to refine anticoagulation protocols and investigate long-term vascular outcomes post-COVID-19, highlighting the need for further research.

Keywords: COVID-19; Thromboembolic Events; Coagulopathy; D-Dimer; Anticoagulation

Abbreviations

CAC: COVID-19-Associated Coagulopathy; ICU: Intensive Care Unit; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; TEs: Thromboembolic Events; DVT: Deep Vein Thrombosis

Introduction

Rapid transmission, substantial morbidity, and significant death are the hallmarks of the COVID-19 pandemic, which has caused an unparalleled worldwide health disaster. Along with other extremely

virulent coronaviruses like SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), the causal pathogen, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a member of the Coronaviridae family.

Given its widespread impact, the management of COVID-19 requires a multidisciplinary approach, particularly in critical care settings where complications such as coagulopathy have emerged as a significant concern [3].

A growing body of evidence has established an association between SARS-CoV-2 infection and a hypercoagulable state, now termed COVID-19-associated coagulopathy (CAC). Unlike classical disseminated intravascular coagulation (DIC), CAC is characterized by thrombotic rather than hemorrhagic complications, manifesting as venous thromboembolism (VTE), arterial thrombosis, and microvascular dysfunction. Several pathophysiological mechanisms have been proposed, including direct viral endothelial injury via ACE2-mediated entry, an exaggerated inflammatory response leading to a cytokine storm, and dysregulated coagulation pathways [4,5].

Additionally, hospitalised COVID-19 patients are more susceptible to thrombotic events due to previous risk factors as advanced age, obesity, diabetes, hypertension, and cardiovascular disease [6]. A similar pathophysiological foundation for virus-induced hypercoagulability has been suggested by the observation of similar coagulation abnormalities in other viral illnesses, such as SARS-CoV and H1N1 influenza [7].

Despite accumulating clinical data, the optimal approach to thrombosis prevention and management in COVID-19 remains an area of active investigation. Current therapeutic strategies, including anticoagulation protocols, risk stratification, and individualized thromboprophylaxis, are guided by evolving evidence and expert consensus. This study aims to comprehensively review the coagulation abnormalities observed in COVID-19, evaluate the mechanisms contributing to CAC, and explore evidence-based management strategies. By integrating insights from past thrombotic disorders and emerging COVID-19-specific data, this study seeks to contribute to the ongoing discourse on optimizing thrombosis management in affected patients.

Patients and Methods

Between January and June 2023, all patients admitted to Suez Canal University Hospital, Ismailia, Egypt, presenting with COVID-19 infection or thromboembolic complications were prospectively included. Patients were divided into three groups based on clinical characteristics:

- **Group I (n = 75):** Patients with PCR-confirmed COVID-19 infection within the preceding six months who developed thromboembolic complications.
- **Group II (n = 75):** Patients with PCR-confirmed COVID-19 infection within the preceding six months who did not develop thromboembolic complications.
- **Group III (n = 75):** Patients presenting with thromboembolic complications but without history or evidence of COVID-19 infection.

Inclusion criteria

- COVID -19 infection confirmed by PCR in the last six months in both first and second group.
- Thromboembolic complication must be confirmed by clinical examination and duplex and or CT Angiography imaging investigations.

Exclusion criteria

Included refusal to participate, age below 18 years, or presence of pre-existing thromboembolic risk factors, including atrial fibrillation, arterial aneurysms, prior thromboembolic events, prolonged immobilization, trauma, or malignancy.

The required sample size was determined using Dawson's formula (2004), with the parameters set as follows: $Z\alpha/2 = 1.96$ (95% confidence interval), $Z\beta = 0.84$ (80% power), and a correlation coefficient (r) of 0.32 based on previous studies (Katsoularis., *et al*. 2022). Consequently, the calculated sample size was 75 patients per group.

Patient assessment

Each patient underwent a comprehensive clinical assessment, emphasizing the identification of symptoms suggestive of recent or active COVID-19 infection. Collected demographic data included age, sex, occupation, and contact information. Clinical evaluation encompassed systemic symptoms such as fever, fatigue, chills,

myalgia, headache, as well as respiratory and gastrointestinal manifestations. In addition, the presence of peripheral thromboembolic complications was assessed, including signs of acute limb ischemia and unilateral limb tenderness. Risk factors known to increase thrombotic predisposition—such as advanced age, obesity, hypertension, diabetes mellitus, coronary artery disease, and recent admission to an intensive care unit (ICU)—were carefully documented.

The use of medications with known prothrombotic potential was documented based on patient history and medication review. A detailed medical history was obtained for each participant, including prior diagnoses of chronic limb ischemia, vasculitis, dyslipidemia, carotid artery disease, diabetes, hypertension, malignancies, and any history of thromboembolic events. Previous hospital admissions, especially those involving immobilization, surgical interventions, or intensive care, were also recorded to ensure a comprehensive understanding of each patient's baseline risk profile [6].

Statistical analysis

ANOVA and Tukey's post hoc test were used to compare the quantitative variables, which were presented as mean ± standard deviation in the study's data analysis using SPSS v28. The Chi-square or Fisher's exact test was used to analyse the qualitative variables, which were reported as frequencies. To evaluate independent risk variables for thromboembolic events, multivariate logistic regression was employed.

Diagnostic and predictive model analysis comprises analysing diagnostic sensitivity, specificity, positive and negative predictive values, and the Receiver Operating Characteristic (ROC) Curve to evaluate diagnostic accuracy. PPP and NPV quantify the percentage of genuine positives and negatives, respectively, whilst AUC >50% is deemed appropria.

Results

Demographic and clinical characteristics

The patients in Group I (COVID-19 with thromboembolic events) had a higher mean age (57.56 ± 12.94 years) compared to Group III (non-COVID thromboembolic patients) at 52.6 ± 13.22 years. Males predominated across all groups, with the highest percentage observed in Group III (70.67%). The BMI was higher in Group I (29.91 ± 3.08 kg/m^2) compared to Group II (24.1 ± 2.87 kg/m^2) and Group III (24.4 ± 2.95 kg/m^2) as in Table 1.

		Group I (n = 75)	Group II (n = 75)	Group III (n = 75)
Age (years)	Mean ± SD	57.56 ± 12.94	56.7 ± 11.97	52.6 ± 13.22
	Range	30 - 75	33 - 75	30 - 75
Sex	Male	45 (60%)	51 (68%)	53 (70.67%)
	Female	30 (40%)	24 (32%)	22 (29.33%)
BMI (Kg/m^2)	Mean ± SD	29.91 ± 3.08	24.1 ± 2.87	24.4 ± 2.95
	Range	18.17 - 29.24	18.59 - 31.22	18.93 - 31.22

Table 1: Demographic Data of the Studied Groups.

Cardiovascular risk factors, such as diabetes mellitus (60% vs. 37.3% in Group II and 45.33% in Group III) and obesity (69.3% in Group I vs. 40% in Group II and 44% in Group III), were more common in patients in Group I. Group I had a considerably higher ICU admission rate (42.7%) than Group II (13.3%) and Group III (8%).

Symptomatology and clinical presentation

COVID-19 patients with thromboembolic events (Group I) exhibited significantly higher rates of systemic symptoms compared to the other groups. Fever was reported in 40% of Group I patients, compared to 10.33% in Group II and none in Group III ($p < 0.001$). Similarly, chills were exclusive to Group I (33.33%, $p < 0.001$), further emphasizing the systemic inflammatory response in this group. Other symptoms such as fatigue, body aches, and headache did not show statistically significant differences between groups.

In terms of thromboembolic symptoms, deep vein thrombosis (DVT) was shown in 53.33% of Group I and 56% of Group III, whereas acute limb ischaemia was seen in 46.67% of Group I and 44% of Group III. In Group II, no thromboembolic incidents were documented. In Table 2, the comparison between Groups I and III was not statistically significant ($p > 0.05$), while the differences between Groups I and II and between Groups II and III were statistically significant ($p < 0.001$).

	Group I (n = 75)	Group II (n = 75)	Group III (n = 75)	P value
Limb ischemia	35 (46.67%)	0 (0%)	33 (44%)	< 0.001* P1 < 0.001* P2 = 0.845 P3 < 0.001*
DVT	40 (53.33%)	0 (0%)	42 (56%)	< 0.001* P1 < 0.001* P2 = 0.74 P3 < 0.001*

Table 2: Limb Ischemia and Deep Venous Thrombosis (DVT) Among Studied Groups.

Laboratory and coagulation profile

Coagulation parameters and inflammatory markers were analyzed to assess their predictive value for thromboembolic events. D-dimer levels were significantly elevated in Group I (25.7 ± 9.67 µ/mL) compared to Group II (6.5 ± 1.76 µ/mL) and Group III (17.6 ± 6.7 µ/mL, $p < 0.001$).

Similarly, fibrinogen levels were highest in Group I (398 ± 81.56 mg/dL), followed by Group II (366.2 ± 77.19 mg/dL) and Group III (331.7 ± 45.56 mg/dL, $p < 0.001$).

Both Group I (CRP: 12.41 ± 10.35 mg/dL, ferritin: 645.1 ± 313.5 ng/mL) and Group II (CRP: 10.25 ± 5.81 mg/dL, ferritin: 541.8 ± 234.6 ng/mL) had significantly higher levels of markers of systemic inflammation than did Group III (CRP: 4.79 ± 2.32 mg/dL, ferritin: 247.4 ± 49.7 ng/mL, $p < 0.001$).

Table 3 indicates that Group II's prothrombin time (PT) was substantially longer (13.4 ± 0.70 sec) than Group I's (11.86 ± 0.50 sec) and Group III's (12.1 ± 0.68 sec, $p < 0.001$).

		Group I (n = 75)	Group II (n = 75)	Group III (n = 75)	P value
Prothrombin time (Sec)	Mean ± SD	11.86 ± 0.50	13.4 ± 0.70	12.1 ± 0.68	< 0.001* P1 < 0.001 P2 = 0.054 P3 < 0.001
	Range	11 - 14.5	12 – 14.5	11 - 14.4	
PTT (Sec)	Mean ± SD	31.6 ± 4.3	36.36 ± 2.74	32.3 ± 4.17	< 0.001 P1 < 0.001 P2 = 0.731 P3 < 0.001
	Range	25 - 40	25 - 42	25 - 40	
INR	Mean ± SD	0.95 ± 0.08	1.06 ± 0.11	0.96 ± 0.0.08	< 0.001 P1 < 0.001 P2 = 0.867 P3 < 0.001
	Range	0.9 - 1.2	1 – 1.5	0.9 – 1.3	
Fibrinogen (mg/dL)	Mean ± SD	398 ± 81.56	366.2 ± 77.19	331.7 ± 45.56	< 0.001 P1 = 0.015 P2 < 0.001 P3 = 0.001
	Range	252 - 549	252 - 496	250 - 399	
D-dimer (µ/mL)	Mean ± SD	25.7 ± 9.67	6.5 ± 1.76	17.6 ± 6.7	< 0.001 P1 < 0.001 P2 < 0.001 P3 < 0.001
	Range	9.5 - 39.8	3.5 - 9.9	7.1 - 29.6	

Table 3: Coagulation Profile at Time of Assessment Among the Studied Groups.

Outcome measures and mortality

All patients diagnosed with DVT in both groups received anticoagulation therapy (100%), reflecting its status as the standard of care. Among patients with viable limb ischemia, anticoagulant and antiplatelet therapies were more frequently administered in Group III (30.3% and 15.2%, respectively) than in Group I (14.3% and 11.4%), though these differences did not reach statistical significance (p = 0.08 and p = 0.68, respectively). No patients in either group underwent thrombolysis, thrombectomy, or angioplasty for viable limb ischemia.

In cases of threatened limb ischemia, both groups showed nearly identical rates of intervention, including anticoagulation, antiplatelet therapy, thrombolysis, thrombectomy, and angioplasty, with no statistically significant differences observed.

Interestingly, Group I had a greater rate of amputation from irreversible limb ischaemia (51.4%) than Group III (39.4%); however, this difference was not statistically significant (p = 0.29). as seen in Table 4 and response is shown in Table 5.

Intervention	Group I (n = 35 limb ischemia/40 DVT)	Group III (n = 33 limb ischemia/42 DVT)	P-value
DVT - Anticoagulant	40 (100%)	42 (100%)	1
Viable Limb Ischemia			
Anticoagulant	5 (14.3%)	10 (30.3%)	0.08
Antiplatelet	4 (11.4%)	5 (15.2%)	0.68
Thrombolysis	0 (0%)	0 (0%)	1
Thrombectomy	0 (0%)	0 (0%)	1
Angioplasty	0 (0%)	0 (0%)	1
Threatened Limb Ischemia			
Anticoagulant	5 (14.3%)	5 (15.2%)	0.92
Antiplatelet	5 (14.3%)	5 (15.2%)	0.92
Thrombolysis	2 (5.7%)	2 (6.1%)	0.95
Thrombectomy	2 (5.7%)	2 (6.1%)	0.95
Angioplasty	5 (14.3%)	4 (12.1%)	0.78
Irreversible Limb Ischemia			
Amputation	18 (51.4%)	13 (39.4%)	0.29

Table 4: Therapeutic Intervention in the Studied Population.

	Group I (n = 75)	Group III (n = 75)	P-value
Improved	66 (88%)	70 (93.33%)	<0.001
No improvement	9 (12%)	5 (6.67%)	

Table 5: Response in the Studied Population.

Discussion

The study's conclusions demonstrate the important role that COVID-19-associated coagulopathy (CAC) plays in the emergence of thromboembolic consequences, especially in patients who are very sick. Our findings show that, in comparison to COVID-19 patients without thromboembolic events (Group II) and non-COVID-19 thromboembolism patients (Group III), COVID-19 patients with thromboembolic events (Group I) had a higher prevalence of

cardiovascular risk factors, such as diabetes mellitus, obesity, and ICU admission. These results are in line with other research showing that endothelial dysfunction and systemic inflammation in COVID-19 raise the risk of venous and arterial thromboembolic events [3,5].

It is thought that the pathophysiology of COVID-19-associated thromboembolic consequences is complex and includes hypercoagulability, a hyperinflammatory state, and direct endothelium damage brought on by viral invasion [4]. Endothelial dysfunction brought on by SARS-CoV-2's binding to the angiotensin-converting enzyme 2 (ACE2) receptor stimulates platelet activation, raises von Willebrand factor (vWF), and starts the coagulation cascade. Furthermore, this hypercoagulable condition is made worse by a cytokine storm that is marked by raised levels of interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), which increases the risk of acute limb ischaemia (ALI), pulmonary embolism (PE), and deep vein thrombosis (DVT) [8].

In our study, DVT was diagnosed in 53.33% of COVID-19 patients with thromboembolic complications, while limb ischemia was observed in 46.67% of Group I patients. These findings align with global reports indicating a higher incidence of thromboembolic events in critically ill COVID-19 patients [9]. Notably, Group II patients (COVID-19 without thromboembolic events) exhibited significantly lower rates of coagulopathy, reinforcing the role of hyperinflammation and endothelial dysfunction in the pathogenesis of CAC.

Predictive value of biomarkers for thromboembolic events

The raised D-dimer values in Group I patients, which were noticeably greater than in Group II and Group III, were a major finding of this study. The strongest predictive value for thromboembolic events was found for D-dimer levels > 9.4 µ/mL (AUC = 0.999, sensitivity = 100%, specificity = 97.33%, $p < 0.001$). This is consistent with earlier research that found D-dimer to be a reliable indicator of thromboembolic complications and death in individuals infected with COVID-19 [10]. fibrinogen levels > 323 mg/dL had a considerable predictive power.

Therapeutic interventions and clinical outcomes

Anticoagulation therapy was the primary treatment strategy, administered to 53.3% of Group I and 56% of Group III patients. However, thrombolysis and thrombectomy were rarely utilized, highlighting the preference for non-invasive management approaches. Amputation was required in 24% of Group I and 17.3% of Group III, emphasizing the severe consequences of thromboembolic complications in COVID-19 patients.

From a clinical response perspective, 88% of Group I patients improved following anticoagulation therapy, while 12% had no improvement. In contrast, 93.33% of non-COVID-19 thromboembolism patients (Group III) exhibited clinical improvement, only 6.67% had no response ($p < 0.001$).

The increased risk of thromboembolic events in COVID-19 patients has been widely documented in the literature. Klok., *et al*. (2020) reported an incidence of 31% for thromboembolic events among ICU-admitted COVID-19 patients, while Mei., *et al*. (2021) observed a thromboembolism rate exceeding 50% in critically ill cases. Our findings are aligned with these reports, [5,11].

Tang., *et al*. (2020) showed that heparin treatment was linked to lower mortality in COVID-19 patients with significantly higher D-dimer levels in a multicenter cohort analysis. This demonstrates the value of anticoagulant medication as a common treatment for CAC [10].

Conclusion

This study highlights the significant burden of COVID-19-associated thromboembolic complications, emphasizing the role of endothelial dysfunction, inflammation, and hypercoagulability. D-dimer > 9.4 µ/mL emerged as the most reliable predictor of thromboembolic events, reinforcing its value in early risk assessment. COVID-19 patients with thromboembolic events exhibited worse clinical outcomes than non-COVID-19 cases, despite anticoagulation therapy. These findings emphasize individualized treatment strategies to mitigate complications and improve patient survival in severe COVID-19 cases.

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