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Risk of Venous Thromboembolism in Patients with COVID-19

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ABSTRACT

Background: The COVID-19 pandemic has been linked to a hypercoagulable state known as COVID-19-associated coagulopathy (CAC), increasing the risk of "venous thromboembolic events (TEs) such as deep vein thrombosis (DVT) and pulmonary embolism (PE). This study aimed to evaluate the risk factors, laboratory findings, and clinical outcomes of venous thromboembolic events (VTEs) in COVID-19 patients at Suez Canal University Hospital.

Methods: This prospective observational study involved 150 patients, categorized into two groups: Group I (COVID-19 with TEs), and group II (non-COVID-19 with TEs) admitted to Suez Canal University Hospitals in Ismailia, Egypt, from March 2021 to March 2023. **Results:** Group I had significantly higher rates of diabetes (60%), obesity (69.3%), and ICU admission (42.7%) compared to other groups ($p < 0.05$). D-dimer levels > 9.4 μ/mL emerged as the strongest predictor of TEs (AUC = 0.999, sensitivity = 100%, specificity = 97.33%, $p < 0.001$), while fibrinogen demonstrated moderate predictive ability. Among interventions, 53.3% of group I and 56% of group II received anticoagulation. Despite anticoagulation, outcomes for COVID-19-associated TEs were poorer than for non-COVID-19 cases.

Conclusions: Six parameters readily available at the time of admission were identified as risk factors for thromboembolic events, and these may be capable of stratifying the risk of in-hospital thromboembolic events, which are associated with in-hospital mortality, in patients with COVID-19 and CVDRF.

Keywords: COVID-19, thromboembolic events, coagulopathy, D-dimer, anticoagulation, In-hospital mortality, Prediction model.

INTRODUCTION

Previous studies have clearly reported that patients with coronavirus disease-2019 (COVID-19) and cardiovascular disease risk factors (CVDRF) have higher risks of cardiovascular events and mortality than those without CVDRF [1, 2]. Although, one of the leading causes of death in patients with COVID-19 is acute respiratory distress syndrome (ARDS; incidence, 17–41 %) [3]. Pathological autopsy-based studies also suggest multi-organ venous thromboembolism as a potential cause of unexplained death [4].

The pathophysiological background of COVID-19-related of venous thromboembolic events (VTEs) events has not yet been clarified. However, abnormal increases in coagulation capacity due to severe inflammatory reaction and the weakening of anticoagulation and fibrinolysis in patients with COVID-19 may potentially predispose them to a hypercoagulative state and subsequent of venous thromboembolic (VTEs) events [5]. Indeed, a recent report showed that patients with COVID-19 who experienced sudden worsening of symptoms and sudden death frequently showed markedly elevated D-dimer levels [6], which is associated with the severity of venous thromboembolism in patients with COVID-19 [7]. However, a limited number of studies have investigated the risk factors or the relationships between venous thromboembolic (VTEs) events and mortality in patients with COVID-19 and CVDRF, Currently, the administration of routine anticoagulation therapy before risk stratification for embolic events is not recommended [8-10]. Therefore, the aim of this study was to assess the risk factors associated with peripheral thromboembolic events among COVID-19 patients.

PATIENTS AND METHODS

Study Design: This is a prospective observational comparative study that included 150 patients who was divided equally into two groups, group I included patients with confirmed COVID-19 infection within the last six months and thromboembolic complications and group II included patients without COVID-19 infection but presenting with thromboembolic complications. Patients with COVID-19 infection confirmed by PCR within the last six months and patients with thromboembolic complications were confirmed through clinical examination, duplex ultrasound, and CT angiography were included in the study.

Exclusion criteria: Patients who refused to participate, ages under 18 years old, and patients who had pre-existing risk factors for prolonged immobilization (Post-traumatic events, and malignancy).

Patients' assessment:

A) Personal data collection: Name, age, sex, address, occupation, and contact information.

B) Clinical presentation:

- COVID-19 infection symptoms include general fever, fatigue, chills, body aches, headache, respiratory symptoms like cough, dyspnea, sore throat, congestion, anosmia, and gastrointestinal symptoms like loss of taste, nausea, and diarrhea.
- Thromboembolic symptoms including leg swelling, calf tenderness, erythema, warmth, and pain.

C) Risk factor evaluation:

The study evaluated risk factors for thromboembolic complications, identifying key contributors to increased clotting risk. Key factors included hospitalization in the ICU, older age, obesity, hypertension, coronary artery disease, diabetes mellitus, and the use of pro-thrombotic medications like oral contraceptives and hormone replacement therapy [11].

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D) Medical history:

Medical history included previous diagnoses of vasculitis, dyslipidemia, carotid artery disease, diabetes, hypertension, malignancies, and past-thromboembolic events or hospitalization history.

Ethical approval: Approval to conduct this study was obtained by Suez Human Research Ethics Committee of Canal University Hospital, Ismailia, Egypt. Informed written consent was obtained from each participant involved in the research. Confidentiality and personal privacy was respected in all stages of research. The Helsinki Declaration was followed throughout the study's duration.

Statistical analysis

The study used SPSS version 28 for data analysis, presenting quantitative variables as mean ± standard deviation and comparing them using ANOVA and Tukey's post hoc test. Qualitative variables were expressed as frequencies and analyzed using Chi-square or Fisher's exact test. Multivariate logistic regression was used to assess independent risk factors for thromboembolic events. Diagnostic and predictive model analysis involves assessing diagnostic sensitivity, specificity, positive and negative predictive values, and the Receiver Operating Characteristic (ROC) curve to evaluate diagnostic accuracy. AUC > 50% is considered acceptable.

RESULTS

There was a statistically significant difference between both groups regarding age, gender, BMI, cardiovascular risk factors, and ICU admission in group I compared to group II as shown in table (1).

Table (1): Demographic data and cardiovascular disease risk factors of the studied

	Group I (n = 75)	Group II (n = 75)
Age (years)	57.56 ± 12.94	52.6 ± 13.22
Sex	45 (60%)	53 (70.67%)
BMI (Kg/m^2)	29.91 ± 3.08	24.4 ± 2.95
Hypertension	37 (49.33%)	40 (53.33%)
Diabetes mellitus	45 (60%)	34 (45.33%)
Hyperlipidaemia	32 (42.67%)	26 (34.67%)
Smoking	34 (45.33%)	41 (54.67%)
Sick sinus syndrome	1 (1.33%)	2 (2.67%)
Atrio ventricular block	2 (2.67%)	3 (4%)
Coronary artery disease	11 (14.67%)	12 (16%)
Old myocardial infarction	2 (2.67%)	4 (5.33%)
Receiving anti-coagulant	17(22.67%)	18 (24%)
Receiving antiplatelet	14(18.67%)	15 (20%)
ICU admission	32 (42.7%)	6 (8%)
Old age ≥ 65 years	37 (49.3%)	19 (25.3%)
Overweight/obesity (BMI ≥ 30)	52 (69.3%)	44%)

Fever was the most reported symptom in group I (40%), followed by chills (33.33%). Notably, fever was significantly more frequent in group I. Regarding thromboembolic manifestations, deep vein thrombosis (DVT) was diagnosed in 53.33% of group I and 56% of group II as shown in table (2).

Table (2): General symptoms and at time of assessment among the studied groups

	Group I	Group II	P value
Fever	30 (40%)	0 (0%)	<0.001
Fatigue	4 (5.33%)	0 (0%)	0.147
Chills	25 (33.33%)	0 (0%)	<0.001
Body aches	5 (6.67%)	1 (1.33%)	0.094
headache	9 (12%)	5 (6.67%)	0.519
DVT	40 (53.33%)	42 (56%)	< 0.001*

There was a significant increase in D-dimer, fibrinogen, markers of systemic inflammation, such as C-reactive protein (CRP) and ferritin in group I compared to group II ($p < 0.001$). However, there was no statistically significant difference between both groups regarding prothrombin time (PT) ($p < 0.001$) as shown in table (3).

Table 3: Coagulation profile at time of assessment among the studied groups

	Group I (n=75)	Group II (n=75)	P value
Prothrombin time	11.86 ± 0.50	12.1 ± 0.68	< 0.001*
PTT	31.6 ± 4.3	32.3 ± 4.17	< 0.001
INR	0.95 ± 0.08	0.96 ± 0.0.08	< 0.001
Fibrinogen (mg/dL)	398 ± 81.56	331.7 ± 45.56	< 0.001
D-dimer (μ/mL)	25.7 ± 9.67	17.6 ± 6.7	< 0.001

D-dimer levels > 9.4 μ/mL demonstrated the highest predictive value for thromboembolic events, with an AUC of 0.999, 100% sensitivity, and 97.33% specificity ($p < 0.001$), making it the most reliable diagnostic marker. Fibrinogen levels > 323 mg/dL exhibited moderate predictive ability, with an AUC of 0.610, 76% sensitivity, and 41.33% specificity ($p = 0.017$), which suggested a weaker association with thromboembolic complications. In contrast, ferritin levels were not found to be a significant predictor of thromboembolic events ($p = 0.360$), indicating limited diagnostic utility in this context as shown in table (4).

Table (4): Diagnostic accuracy of laboratory parameters for prediction of thromboembolic complications

Parameter	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	P-value
D-dimer (μ/mL)	> 9.4	100.00	97.33	97.4	100.0	0.999	< 0.001*
Ferritin (ng/mL)	≤ 577	28.00	82.67	61.8	53.5	0.543	0.360
Fibrinogen (mg/dL)	> 323	76.00	41.33	56.4	63.3	0.610	0.017*

Regarding clinical response, 88% of group I patients showed improvement, whereas 12% had no response to treatment. In contrast, 93.33% of group II patients demonstrated clinical improvement, with only 6.67% who showed no response ($p < 0.001$), indicating a more favorable prognosis in non-COVID-19 thromboembolic cases as shown in table (5).

Table (5): Response in the studied population

		Group I	Group II	P-value
Improved	120	66 (88%)	70 (93.33%)	<0.001
No improvement	31	9 (12%)	5 (6.67%)	

Among the therapeutic interventions, 53.3% of group I and 56% of group II received anticoagulant therapy for DVT as shown in table (6).

Table (6): Therapeutic Intervention in the Studied Population

		Group I (n = 75)	Group II (n = 75)	P value
DVT	Anticoagulant	40 (53.3%)	42 (56%)	0.74

On multivariate logistic regression analysis, we found that only elevated D-dimer was significant predictor of the incidence of DVT, other variables were insignificant predictors as shown in table (7).

Table (7): Multivariate logistic regression analysis for prediction of the incidence of Deep vein thrombosis

	Coefficient	SE	P	Odds ratio	95% CI
Age (years)	0.006	0.013	0.459	1.045	0.9816 to 1.0315
BMI (Kg/m^2)	-0.029	0.055	0.604	0.972	0.8727 to 1.0823
Temperature (°C)	-0.610	0.393	0.121	0.544	0.2517 to 1.1739
Heart rate (beat/min)	0.015	0.016	0.362	1.015	0.9833 to 1.0471
Respiratory rate (breaths/min)	0.041	0.065	0.524	1.042	0.9177 to 1.1836
SBP (mm Hg)	0.000	0.012	1.000	1.000	0.9764 to 1.0242
DBP (mm Hg)	0.000	0.017	0.981	1.000	0.9670 to 1.0333
No anticoagulant and antiplatelet intake	0.084	0.334	0.752	0.992	0.7984 to 1.6935
Hypertension	-0.296	0.326	0.365	0.744	0.3922 to 1.4104
Diabetes mellitus	0.579	0.334	0.083	1.784	0.9275 to 3.4308
Hyperlipidaemia	0.087	0.331	0.794	1.091	0.5697 to 2.0873
Smoking	0.195	0.329	0.554	1.215	0.6374 to 2.3174
Sick sinus syndrome	0.645	1.263	0.610	1.906	0.1603 to 22.662
Atrio ventricular block	-19.709	9138.16	0.998	0.000	
Coronary artery disease	-0.648	0.523	0.216	0.523	0.1875 to 1.4595
Hb (g/dl)	0.094	0.111	0.396	1.099	0.8841 to 1.3654
WBCs (× 109/L)	0.037	0.071	0.599	1.038	0.9038 to 1.1919
PLT (× 109/L)	-0.005	0.003	0.071	0.995	0.9894 to 1.0004
D-dimer (μ/mL)	0.235	0.178	0.032*	1.386	0.9543 to 1.6346
Ferritin (ng/mL)	-0.001	0.000	0.077	0.996	0.9983 to 1.0001
PT (sec)	-0.025	0.017	0.087	1.008	0.9879 to 1.1324
PTT (sec)	-0.027	0.016	0.093	0.973	0.9430 to 1.0045
INR	0.087	0.098	0.241	1.011	1.0021 to 2.2220
Fibrinogen (mg/dL)	-0.001	0.002	0.781	0.991	0.9952 to 1.0036

DVT: deep venous thrombosis, WBCs: White blood cell count, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International normalized ratio, SE: standard error, CI: confidence interval, *: statistically significant as P value <0.05.

On multivariate logistic regression analysis, we found that only elevated D-dimer, ferritin, and DVT were significant predictors of the in- hospital mortality; other variables were insignificant predictors as shown in table (8).

Table (8): Multivariate logistic regression analysis for prediction of the in-hospital mortality

	Coefficient	SE	P	Odds- ratio	95% CI
Age (years)	-0.001	0.013	0.934	0.999	0.9816 to 1.0315
BMI (Kg/m^2)	-0.010	0.056	0.861	0.990	0.8727 to 1.0823
Temperature (°C)	-0.571	0.404	0.158	0.565	0.2517 to 1.1739
Heart rate (beat/min)	0.004	0.016	0.824	1.004	0.9833 to 1.0471
Respiratory rate (breaths/min)	0.047	0.067	0.486	1.048	0.9177 to 1.1836
SBP (mm Hg)	0.006	0.013	0.636	1.006	0.9764 to 1.0242
DBP (mm Hg)	0.005	0.017	0.770	1.005	0.9670 to 1.0333
Anticoagulant and antiplatelet	-0.354	0.329	0.283	0.702	0.4466 to 1.6005
Hypertension	0.056	0.333	0.867	1.057	0.3922 to 1.4104
Diabetes mellitus	-0.027	0.335	0.937	0.974	0.9275 to 3.4308
Hyperlipidaemia	0.207	0.339	0.541	1.230	0.5697 to 2.0873
Smoking	0.368	0.338	0.275	1.445	0.6374 to 2.3174
Sick sinus syndrome	0.853	1.265	0.500	2.348	0.1603 to 22.6628
Atrio ventricular block	-0.305	1.122	0.786	0.737	
Coronary artery disease	-0.687	0.568	0.226	0.503	0.1875 to 1.4595
Hb (g/dl)	0.121	0.114	0.290	1.128	0.8841 to 1.3654
WBCs (× 109/L)	-0.027	0.072	0.709	0.973	0.9038 to 1.1919
PLT (× 109/L)	-0.002	0.003	0.487	0.998	0.9894 to 1.0004
D-dimer (µ/mL)	0.042	0.015	0.007	1.043	1.0135 to 1.077
Ferritin (ng/mL)	0.036	0.014	0.042*	0.999	0.9125 to 1.2341
PT (sec)	0.073	0.115	0.156	1.008	0.9845 to 1.0754
PTT (sec)	0.000	0.015	0.988	1.000	0.9430 to 1.0045
INR	0.093	0.188	0.620	1.098	1.0721 to 2.2220
Fibrinogen (mg/dL)	-0.003	0.002	0.178	0.996	0.9925 to 1.0014
DVT	3.385	0.425	**0.001**	29.531	12.839 to 67.9206
D-dimer (µ/mL)	0.042	0.015	**0.007***	1.043	1.0135 to 1.0760
Ferritin (ng/mL)	0.036	0.014	**0.042***	0.999	0.9125 to 1.2341
PT (sec)	0.073	0.115	0.156	1.008	0.9845 to 1.0754
PTT (sec)	0.000	0.015	0.988	1.000	0.9430 to 1.0045
INR	0.093	0.188	0.620	1.098	1.0721 to 2.2220
Fibrinogen (mg/dL)	-0.003	0.002	0.178	0.996	0.9925 to 1.0014
DVT	3.385	0.425	**0.001***	29.531	12.839 to 67.9206

WBCs: White blood cell count, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International normalized ratio, DVT: deep venous thrombosis, SE: standard error, CI: confidence interval, *: statistically significant as P value <0.05.

D-dimer can significantly predict the incidence of the thromboembolic complications with AUC of 0.999, P value of < 0.001, at cut off > 9.4 µ/mL, with 100.00% sensitivity, 97.33 % specificity, 97.4% PPV and 100.0% NPV. Fibrinogen can significantly predict the incidence of thromboembolic complications with AUC of 0.610, P value of 0.017, at cut off > 323, with 76.00% sensitivity, 41.33% specificity, 56.4% PPV and 63.3% NPV. On the other hand, ferritin showed insignificant predictor for the incidence of thromboembolic complications (Table 9).

Table (9): Diagnostic accuracy of laboratory parameters for prediction of thromboembolic complications

	Cut- off	**Sensitivity**	**95%CI**	**Specificity**	**95% CI**	**PP V**	**NPV**	**AUC**	**P value**
D-dimer (µ/mL)	> 9.4	100.00	95.2 - 100.0	97.33	90.7 - 99.7	97.4	100.0	0.999	0.001
Ferritin (ng/mL)	≤ 577	28.00	18.2 - 39.6	82.67	72.2 - 90.4	61.8	53.5	0.54	0.360
Fibrinogen (mg/dL)	> 323	76.00	64.7 - 85.1	41.33	30.1 - 53.3	56.4	63.3	0.61	0.017

*p is significant at <0.05.

DISCUSSION

The pathogenesis of COVID-19-associated thromboembolic complications is believed to be multifactorial, involving direct endothelial injury due to viral invasion, a hyperinflammatory state, and hypercoagulability [12]. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor, leading to endothelial dysfunction, which promotes platelet activation, increases von Willebrand factor (vWF), and triggers the coagulation cascade. Additionally, a cytokine storm characterized by elevated interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) exacerbates this hypercoagulable state, leading to an increased incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) [13].

In the present study, it was found that there was a statistically significant difference between both groups regarding age, gender, BMI, cardiovascular risk factors, and ICU admission in group I compared to group II. In the same line, our results agree with **Goldman *et al.*** [13] who reported that the mean BMI was 28.0 ± 5.6 kg/m^2 of COVID-19 group and 7 (44%) of them were females, while that of Non–COVID-19 group was 28.2 ± 5.9 kg/m^2 and 16 (50%) of them were females. the mean age of COVID-19 group was 70 ± 14 years and that of Non–COVID-19 group was 71 ± 15 years. Also, **Cangemi *et al.*** [15] reported that 62% of COVID patients with thrombotic event (group I) were males with mean age of 71.5 ± 13.8 years with 18% of COVID patients had thrombotic event, 57% had Hypertension and 16% were smokers. In the same line, our results agree with **Yachi *et al.*** [16] who revealed that 26 (47.3%) of patients with thrombosis had hypertension, 16 (29.1%) had diabetes mellitus and 6 (10.9%) had heart disease. As well, **Shibahashi *et al.*** [17] demonstrated that 20 (57.1%) of thromboembolic group had hypertension, 17 (48.6%) had diabetes mellitus and 2 (5.7%) had heart diseases.

In the present study, it was found that temperature, heart rate and respiratory rate were significantly different among the studied groups, while, the mean systolic blood pressure (SBP) and the mean diastolic blood pressure (DBP) were close in the 2 groups and showed statistically insignificant difference. **Shibahashi *et al.*** [17] and **Zhang *et al.*** [18] revealed that there were significant differences in temperature, respiratory rate, heart rate, and diastolic blood pressure among groups, but no significant difference in systolic blood pressure.

Our results showed that group I had significantly higher levels of ferritin, ESR and CRP compared to group II. Other parameters (hemoglobin, WBCs, platelets, creatinine, urea, albumin, ALT, AST, potassium & calcium) were insignificantly different among the studied groups. Our results matched with **Shibahashi *et al.*** [17] who reported that there was no statistically significant difference among study groups regarding hemoglobin, platelets, WBCs, AST, potassium and blood urea. Otherwise, they reported that there was statistically significant difference between the studied groups regarding ferritin, albumin, and ALT. Also, **Goldman *et al.*** [14] reported that there was no statistically significant difference between the studied groups regarding platelets and urea. Otherwise, they reported that there was statistically significant difference between the studied groups regarding WBCs. As well, **Kruse *et al.*** [19] reported that ferritin did not differ significantly between patients with COVID and VTE and patients with COVID without VTE. Our results contrast with **Zhang *et al.*** [18] who reported that there was statistically significant difference between the studied groups regarding WBCs and blood urea. Furthermore, **Cheng *et al.*** [20] reported that patients with thrombotic complication had significantly higher levels of ferritin than those without ($P < .01$).

Our current study showed that prothrombin time (PPT) was insignificantly different between group I and group II. Our results are in line with **Goldman *et al.*** [14] who reported that there was no statistically significant difference between COVID patients with thrombosis and non-COVID patients with thrombosis regarding PPT. Our results are in contrast with **Zhang *et al.*** [18] who reported that there was no statistically significant difference between deep vein thrombosis with COVID group compared to non-deep vein thrombosis group with COVID regarding PPT.

Our results showed that INR was insignificantly different between group I and group II. Fibrinogen level significantly elevated in group I compared to group II indicating higher level of inflammation in those with COVID infection especially those with thromboembolic complications. Our results are supported by **Sui *et al.*** [21] who concluded that fibrinogen is commonly elevated in COVID-19 patients than in patients without COVID. On the other hand, our results disagree with **Goldman *et al.*** [13] who reported that there was no statistically significant difference between COVID patients with thrombosis and non-COVID patients with thrombosis regarding INR. Also, **Kruse *et al.*** [19] reported that fibrinogen did not differ significantly between patients with COVID and VTE and patients with COVID without VTE.

We found that D-dimer was significantly elevated in group I compared to group II ($P3 < 0.001$). Our results agree with **Shibahashi *et al.*** [17] who reported that D-dimer was significantly elevated in thromboembolic with COVID group compared to non-thromboembolic group with COVID. Also, our results are supported by **Yachi *et al.*** [16] & **Cangemi *et al.*** [15] who reported that D-dimer was significantly elevated in thrombosis with COVID group compared to non-thrombosis group with COVID (15, 16). Additionally, **Zhang *et al.*** [18] reported that D-dimer was significantly elevated in deep vein thrombosis with COVID group compared to non-deep vein thrombosis group with COVID.

Our results showed that fever and chills were significantly higher in group I compared to group II.

The incidences of general symptoms at time of assessment (fatigue, body aches, and headache) were insignificantly different among the studied groups. Our results are supported by **Zhang *et al.*** [18] who reported that there was no statistically significant difference between the studied groups regarding fatigue and headache. While, they reported that there was no statistically significant difference between the studied groups regarding cough and dyspnea. Also, **Yachi *et al.*** [16] reported that there was no statistically significant difference between the studied groups regarding respiratory disease.

We found that all patients with DVT were managed with oral anticoagulants. In contrary, our results disagree with **Shibahashi *et al.*** [17] who reported that no patients in thromboembolic group with COVID were treated with direct oral anticoagulants and all patients in non-thromboembolic group with COVID were treated with direct oral anticoagulants. Furthermore, **Yachi *et al.*** [16] reported that 13.2% of the studied patients treated with direct oral anticoagulants.

Our results showed that there was insignificant difference between group I and group II regarding incidence of DVT. Our results are supported by **Shibahashi *et al.*** [17] who reported that 2.9% of the studied patients had DVT in thromboembolic with COVID group and no patients had DVT in non-thromboembolic with COVID group. Furthermore, **Topcu *et al.*** [22] concluded that COVID-19 infection is associated with an increased incidence of thromboembolic events. On the other hand, **De Vita *et al.*** [23] reported that DVT significantly higher in non COVID patients with thrombosis compared to COVID with thrombosis.

Our current study showed that Incidence of in-hospital mortality was significantly higher in group I compared group II. Our results are supported by **Shibahashi *et al.*** [17] who reported that in-hospital death was significantly elevated in thromboembolic with COVID group compared to non-thromboembolic group with COVID. Also, **Yachi *et al.*** [16] reported that all-cause mortality was 5.5% and significantly higher in patients with thrombosis (23.6% vs. 5.1%; P < 0.001) than in patients without thrombosis. In the same line, **Zhang *et al.*** [18] who reported that in hospital death was significantly higher in deep vein thrombosis with COVID group compared to non-deep vein thrombosis group with COVID.

On multivariate logistic regression analysis, we found that only D-dimer were significant predictors of the incidence of DVT, other variables were insignificant predictors. Our results are supported by **Zhang *et al.*** [18] who reported that in the multivariate logistic regression model, they found that a higher D-dimer level at admission (D-dimer >1.0 μg/mL; OR, 5.818 [95% CI, 1.422–23.809]; P=0.014) was associated with increased odds of DVT in patients confirmed to have COVID-19. In the same line, our results agreed with **Cho *et al.*** [24] reported that elevated D-dimer was a statistically significant predictor of DVT in multivariable analyses when adjusting for other factors (odds ratio, 6.12; 95% confidence interval, 2.79-13.39; P < .001). Also, **Artifoni *et al.*** [25] reported that D-dimers at baseline were significantly higher in patients with DVT (p < 0.001). Increased D-dimer concentrations of more than 1.0 μg/ml predict the risk of venous thromboembolism. As well, **Middeldorp *et al.*** [26] & **Nopp *et al.*** [27] reported that higher D-dimer risk factors are associated with VTE in univariate regression analyses.

On multivariate logistic regression analysis, we found that only D-dimer, ferritin, and DVT were significant predictors of the in-hospital mortality, other variables were insignificant predictors. Our results are supported by **Bilaloglu *et al.*** [28] reported that regarding multivariate logistic regression analysis, venous thrombosis independently associated with mortality (adjusted hazard ratio, 1.37; 95%CI, 1.02-1.86; P = 0.04). Also, **Bozzani *et al.*** [29] reported that logistic regression analysis revealed that high levels of D-dimer and fibrinogen were statistically significant risk factors for mortality (P < .0001). As well, **Cheng *et al.*** [20] reported that non-survivors had a significantly higher ferritin level compared to the survivors (P < .001). In addition, **Zhang *et al.*** [18] and **Huyut *et al.*** [30] reported that patients with DVT had higher mortality rates than the non-DVT groups (P<0.05). In addition, **Paz Rios *et al.*** [26] & **Middeldorp *et al.*** [31] reported that in multivariate analysis, patients with VTE had a significant association with mortality.

Our results showed that D-dimer can significantly predict the incidence of the thromboembolic complications with AUC of 0.999, P value of <0.001, at cut off >9.4 μ/mL, with 100.00% sensitivity, 97.33 % specificity, 97.4% PPV and 100.0% NPV. Fibrinogen can significantly predict the incidence of thromboembolic complications with AUC of 0.610, P value of 0.017, at cut off >323, with 76.00% sensitivity, 41.33% specificity, 56.4% PPV and 63.3% NPV. Ferritin was an insignificant predictor for the incidence of thromboembolic complications. Our results are supported by **Zhang *et al.*** [18] who reported that D-dimer at area under the curve of 0.708 [95% CI, 0.622–0.784], sensitivity was 88.52% and specificity was 52.86%) to predict DVT. Also, **Garcia-Ortega *et al.*** [32] reported that D-dimer showing a high predictive value of incident pulmonary embolism (PE) (AUC-ROC: 0.86; 95% CI: 0.80 to 0.93). In addition, **Cho *et al.*** [24] reported that an optimal D-dimer cutoff of 6494 ng/mL was determined to differentiate those with and without DVT (sensitivity 80.8%, specificity 68.9%, negative predictive value 88.0%). Similarly, **Artifoni *et al.*** [25] reported that the negative predictive value of a baseline D-dimer level < 1.0 μg/ml was 90% for VTE, PT can significantly predict the incidence of the thromboembolic complications with AUC of 0.954, P value of <0.001, at cut off >13.3 sec, with 94.67% sensitivity, 69.33% specificity, 75.5% PPV and 92.9% NPV. As well, **Kruse *et al.*** [19] reported that D-dimer

concentrations revealed high sensitivity and specificity of thromboembolic risk prediction. Furthermore, **Meng *et al.*** [33] reported that the sensitivity and specificity of predicting cerebral venous sinus thrombosis using only D-dimer were 94.1% and 97.5%, whereas that of D-dimer in combination with fibrinogen were 67.6% and 98.9%.

LIMITATIONS

Our study showed a small sample size and single centre study. Therefore, future studies should use larger sample sizes, randomized controlled trials, longer follow-up periods, and multicentre studies to confirm current results and control for confounding factors.

CONCLUSION

This study highlighted the significant burden of venous thromboembolic complications in COVID-19, 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 venous thromboembolic events exhibited worse clinical outcomes than non-COVID-19 cases, despite anticoagulation therapy. These findings emphasized the need for intensified thromboprophylaxis and individualized treatment strategies to mitigate complications and improve patient survival in severe COVID-19 cases.

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