ORIGINAL ARTICLE

Incidence and Risk Factors Associated with Thromboembolic Events among Patients with COVID-19 Inpatients: A Retrospective Study

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Abstract

Aims and objectives: Despite thromboprophylaxis, some severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients develop thrombotic complications with poor prognosis. Our goal is to comprehensively assess the incidence, risk factors, and clinical outcomes associated with thromboembolic events (TE) among adult patients presenting with coronavirus disease-2019 (COVID-19).

Materials and methods: The study was conducted as an observational and retrospective study across COVID-19 patients ($n = 207$) in a tertiary care hospital in the Middle East and North Africa (MENA) region. Electronic health records were collected from the COVID-19 Database from April 2020 to December 2020 which included clinical history and TE.

Results: Fifty-six (27.05%) out of 207 patients (age: 54.42 ± 15.01 years) developed TE despite the anticoagulant therapy. The incidence of venous thromboembolism (VTE) was significantly higher for patients aged >50 years compared to <50 years (73.21% vs 26.79%, $p < 0.05$). There were no differences in the incidence of VTE between genders ($p = 0.561$). 165 patients (79.71%) received anticoagulant therapy, yet 48 (29%) developed TE. The most commonly used anticoagulant was low-molecular-weight heparin (LMWH, 47.34%). In spite of efficient treatment and medical management, the majority of patients with TE (45 out of 56 patients, 80.35%) experienced mortality. The comorbidities that significantly increase the risk of TE include hypertension (HTN) and ischemic heart disease (IHD). The laboratory parameters that were associated with an increased risk of VTE include ferritin, lactate dehydrogenase (LDH), and creatinine.

Conclusion: The COVID-19 patients develop thrombotic complications. Future studies should clarify the underlying mechanisms of TE and optimize the antithrombotic regimens in COVID-19 patients.

Keywords: Coronavirus disease-2019, Severe acute respiratory syndrome coronavirus 2, Thromboembolic events, Thrombotic events, Vascular thromboembolism.

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Highlights

- Over a quarter of coronavirus disease-2019 (COVID-19) patients developed thromboembolic events (TEs) despite adequate anticoagulant therapy.
- Factors associated with increased risk of TEs include hypertension (HTN) and ischemic heart disease (IHD); as well as laboratory parameters such as elevated ferritin, lactate dehydrogenase (LDH), and creatinine.
- About four-fifths of COVID-19 patients who developed TEs died.

Introduction

The COVID-19 is an infectious disease that currently has been declared a global pandemic. A significant issue, particularly in moderate to severe cases of COVID-19, is the prevalence of "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coagulopathy".[1] Also, SARS-CoV-2 coagulopathy has been associated with a higher risk of morbidity and mortality in COVID-19 patients.[2] The majority of TEs documented in COVID-19 patients is venous thromboembolism (VTE). The inpatient rates of VTE vary widely between 1.7 and 46%, with significant mortality presumptive to be secondary to VTE.[3] On the contrary, autopsy studies indicated 71.4% of COVID-19 patients who died exhibited disseminated intravascular coagulation (DIC) compared to 0.6% in survivors.[3]

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Although VTE occurs in less than 5% of patients admitted for infectious respiratory diseases, the incidence is as high as 20% in COVID-19 patients even with adequate thromboprophylaxis.[4,5] According to a meta-analysis,[6] the pooled incidence rates of pulmonary embolism (PE) and deep vein thrombosis (DVT) in patients with COVID-19 were 16.5 and 14.8%, respectively, while the incidences for both exceeded 20% in patients admitted to the intensive care unit (ICU).[6] In fact, postmortem studies have reflected classical macrovessel disease and pulmonary microthrombi suggested fatal PE in VTE-related mortality in COVID-19 patients.

Recent reviews have highlighted important procoagulant mechanisms that are upregulated in COVID-19.[7,8] Similarly, many non-specific inflammatory biomarkers are elevated in hospitalized COVID-19 patients, including C-reactive protein (CRP) and erythrocyte sedimentation rates, as well as several procoagulant factors such as von Willebrand factor and factor VIII.[9,10] Likewise, many proinflammatory cytokines are elevated, including tumor necrosis factor-alpha (TNF-α) and interleukin 2R (IL-2R), IL-6, IL-8, and IL-10.58, 59 TNF-α, and IL-6, in particular, are elevated to a degree that differs from bacterial sepsis or influenza.[11,12] The thromboembolic effects of many of these cytokines have been documented, alone or in combination.[13]

Significant predictors of VTE in COVID-19 patients include D-dimer, sepsis-induced coagulopathy scores, lymphocyte count, and prothrombin time (PT). However, such predictors are based on smaller cohorts.[3] Moreover, there is inconclusive evidence regarding higher rates of thrombosis and its associated mortality in COVID-19 patients. The extant literature suggests that full-dose anticoagulation therapy reduces VTE and mortality in COVID-19 patients, some authors have found no benefit with prophylactic or therapeutic doses of anticoagulants in the referred patients. Rather, the rate of mortality due to VTE from preemptive therapy since admission was 2.3 times higher.[3] This finding raises the dilemma over the beneficial role of anticoagulants. Also, the current literature indicates inconclusive evidence regarding the predictors and outcomes of VTE in COVID-19 patients.[3–6] Therefore, this study aimed to comprehensively assess the prevalence, and risk factors associated with vascular TEs among patients with COVID-19.

Materials and Methods

Study Design

The primary study was an observational, single-centered and retrospective study among 207 adults clinically confirmed COVID-19 patients admitted to a tertiary care hospital in Middle East and North Africa (MENA) region from April 2020 to December 2020.

Inclusion and Exclusion Criteria

The inclusion criteria were adults aged ≥18 years, admitted to the hospital with laboratory-confirmed COVID-19 infection based on a positive result on real-time reverse transcriptase polymerase chain reaction (RT-PCR) testing for SARS-CoV-2. Exclusion criteria were negative RT-PCR results for COVID-19, patients dying within 24 hours of admission, pregnant women, patients aged less than 17 years, and those discharged against medical advice.

Data Collection

Baseline parameters such as age, sex, body mass index (BMI), use of anticoagulants, ICU admission, presence of other comorbidities, hemoglobin A1C (HbA1c), and various laboratory parameters were collected for all the patients. All the investigations were performed at the time of admission. All patients were followed up until hospital discharge, death, or until December 2020, whichever came first. The various TEs that were considered in our study were VTE (covering PE) and DVT,[13,14] arterial thrombosis,[15] abdominal and thoracic aortic thrombosis with symptoms like unilateral distal limb ischemia, bilateral distal limb ischemia, bilateral lower extremity weakness, bilateral lower extremity loss of sensation, and acute periumbilical abdominal pain.[16] We analyzed electronic health records to obtain information on recent exposures, signs, and symptoms. Each patient was screened for thrombosis under the local COVID-19 patient management protocol.[17] In this study, PE was not routinely screened; however, computed tomography pulmonary angiogram (CTPA) was performed on patients who had a clinical suspicion. Furthermore, B-mode compression ultrasound (CUS) imaging was also performed for every patient who had a clinical suspicion of VTE and it included an assessment of the superficial and deep venous systems and arterial systems. The anticoagulants employed in the study were as follows: Subcutaneous heparin, heparin infusion, warfarin, novel anticoagulants, fondaparinux, and low-molecular-weight heparin.

Treatment Protocols

The Saudi Ministry of Health (MoH) Protocol for Patients Suspected of/Confirmed with COVID-19 guidelines were followed for treating the patients admitted to hospital (https://www.moh.gov.sa/en/Ministry/MediaCenter/Publications/Documents/MOH-therapeutic-protocol-for-COVID-19.pdf). According to the treatment protocol, oxygen therapy was titrated to target SpO_2 above 92% using oxygen delivery devices such as low-flow devices {nasal prongs, simple face mask, high-flow devices [venturi mask, high-flow nasal cannula (HFNC)], non-invasive ventilation (NIV)} and invasive mechanical ventilation. Standard medical care including systemic corticosteroids, tocilizumab, remdesivir, and anticoagulation were administered as per the management protocol. Supportive care for critically ill patients in the form of advanced hemodynamic monitoring, hemodynamic support, enteral nutrition, glycemic control, and stress ulcer prophylaxis was used in all eligible patients. Antibiotics and antifungals were administered according to local antibiogram and institutional pneumonia management guidelines/pathways. Renal replacement therapy and other supportive interventions were administered based on the clinical condition of the patients.

Data Analysis

The data analysis involved the analysis of descriptive and inferential statistics. The descriptive statistics include mean (M) ± standard deviation (SD), frequencies, percentages, and interquartile range (IQR). The inferential statistics include Chi-square/Fisher's exact test for categorical variables, while the comparison of mean was done using two independent sample *t*-tests for normally distributed variables and using Mann–Whitney's *U* test. The unadjusted and adjusted odds ratios (ORs) were calculated using binary logistic regression and 95% confidence intervals (CIs) were calculated using the stepwise method. All statistical analysis for the present study was conducted with a Statistical Package for the Social Sciences (SPSS) software for Windows, version 28 (IBM Corporation, Armonk, New York, USA).

Ethical Considerations

The study was conducted after obtaining appropriate approval from the Institutional Review Board (IRB). Despite the study being conducted retrospectively, the confidentiality of each patient was protected both during and after the completion of the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Table 1: Comparison of various parameters among patients with and without TEs

Parameters	*Thrombotic events (n = 56)*	*No thrombotic events (n = 151)*	*p-value*
Demographic details (*n*/%)			
Age in years (M/SD)	58.41 ± 13.59	52.81 ± 15.30	0.01
17–35	2 (3)	20 (13.2)	0.009
35–50	13 (23)	38 (25)	0.512
>50	41 (73.2)	81 (53.2)	0.002
Gender			
Male	41 (73.2)	98 (64)	0.561
Female	15 (26.8)	53 (36)	
Anticoagulant used	48 (29.1)	117 (70.9)	0.191
Required ICU admission	50 (42.7)	67 (57.3)	<0.001
BMI			
Normal weight	17 (30.35)	54 (35.76)	0.214
Comorbidities (*n*/%)			
Diabetic	51 (91)	35 (23)	0.002
HTN	32 (57)	29 (19.2)	0.001
IHD	10 (17.8)	12 (7)	0.003
HF	4 (7)	9 (5)	0.04
Chronic lung disease	–	2 (1.3)	0.001
Chronic obstructive pulmonary disease (COPD)	–	2 (1.3)	0.001
Bronchial asthma	2 (3)	5 (3)	0.001
Chronic liver disease	1 (2)	–	0.01
CKD	7 (13.7)	10 (6.6)	0.045
Outcome (death)	45 (80.35)	26 (17.2)	0.001
Laboratory investigations			
HbA1c (M/SD)	8.2 ± 3.2	8.8 ± 3.3	0.250
Hemoglobin (M/SD)	11.5 ± 3.2	12.7 ± 2.1	0.020
WBC (M/IQR)	8.75 (6.6, 11.5)	6.4 (4.4, 8.8)	0.001
Lymphocyte (M/IQR)	1.2 (0.9, 1.7)	1.3 (0.8, 1.8)	0.558
Neutrophil (M/IQR)	6.4 (4.5, 9.4)	4.6 (2.4, 6.8)	0.001
Platelets (M/IQR)	253 (161, 342)	225 (164.5, 311.5)	0.582
Activated partial thromboplastin time (aPTT) (M/IQR)	32 (20.8, 35.1)	31.7 (29, 34.2)	0.315
PT (M/IQR)	12.5 (11.2, 15.5)	12.3 (11.3, 13.3)	0.340
AST (M/IQR)	55 (33.5, 93)	38 (24, 68)	0.012
Bilirubin (M/IQR)	8 (6, 13.8)	8 (5, 11.3)	0.392
Ferritin (M/IQR)	736.18 (313.71, 1544.46)	340.28 (142.30, 768.07)	0.015
Creatinine (M/IQR)	120.0 (88.0, 260.0)	98.0 (72.50, 142.50)	0.019
Fibrinogen (M/IQR)	950.0 (848.0, 952.0)	620.0 (331.80,946.50)	0.091
CRP (M/IQR)	107.75 (34.47, 197.00)	56.0 (9.93, 147.50)	0.017
D-dimer (M/IQR)	0.90 (0.35, 1.88)	0.66 (0.37, 1.20)	0.226
LDH (M/IQR)	279 (138, 411)	268 (88, 7753)	1.000

Results

Following confirmation of COVID-19 diagnosis, 56 (27.05%) of the 207 admitted patients developed TEs. The demographic, clinical history, and laboratory parameters in patients with and without TE are presented in Table 1. Overall, 117 (56.52%) of the admitted patients had severe or critical COVID-19 disease requiring ICU admission. Also, 50 (42.70%) of patients with severe or critical COVID-19 disease requiring ICU admission had TE while 67 (57.3) had no TE ($p < 0.001$).

Table 1 depicted that there were no differences between males and females in terms of TEs ($p = 0.561$). The mean age-group of the study participants was 54.42 ± 15.01. However, the mean age of patients who experienced TE was significantly more

Table 2: Odds ratio for TE risk

Variables	*OR (95% CI)*	*p-value*
Age	1.02 (1.01, 1.05)	0.020
Male gender	1.23 (0.62, 2.44)	0.561
Current smoker	1.56 (0.37, 6.55)	0.540
Diabetes mellitus	1.73 (0.90, 3.33)	0.099
HTN	2.61 (1.35, 5.05)	0.004
IHD	2.33 (1.07, 5.10)	0.034
HF	1.43 (0.51, 4.02)	0.496
Dyspnea	2.88 (1.37, 6.04)	0.005
Altered consciousness	3.53 (1.16, 10.72)	0.026
PCO_2 on arterial blood gas (ABG)	1.06 (1.01–1.11)	0.023
Required ICU admission	10.45 (4.2, 25.84)	<0.001
Outcome (death)	19.67 (8.99, 43.03)	<0.001
WBC	1.10 (1.03, 1.18)	0.007
Hemoglobin at admission (mg/dL)	0.84 (0.70, 0.99)	0.049
Neutrophil at admission	1.01 (0.98, 1.04)	0.726
Lymphocyte at admission	1.04 (0.86, 1.26)	0.670
AST at admission (mg/dL)	1.00 (0.99, 1.01)	0.289
Platelet at admission	1.00 (0.99, 1.00)	0.461
aPPT at admission	1.00 (0.95, 1.06)	0.960
PT at admission	1.09 (0.95, 1.27)	0.213
Fibrinogen at admission	1.01 (0.99, 1.01)	0.163
Creatinine at admission	1.002 (1.000, 1.003)	0.036
Lactate at admission (mg/dL)	0.96 (0.86, 1.07)	0.455
LDH at admission	1.003 (1.001, 1.006)	0.004
CRP at admission	1.006 (1.000, 1.012)	0.052
D-dimer at admission	1.002 (0.98, 1.02)	0.778

than those who did not experience TE. Table 1 further depicted that the incidences of TE were significantly higher in individuals more than 50 years, suggesting age is a significant predictor of VTE. The analysis of laboratory values showed that the levels of white blood cells (WBC), neutrophil, aspartate transaminase (AST), ferritin, creatinine, and CRP levels were significantly elevated in patients experiencing TE compared to their counterparts who did not experience TE. However, the Hb levels were significantly lower in the former compared to the latter. With regard to comorbidities, the study reflected that the incidences of TE were significantly higher in patients suffering from diabetes, hypertension (HTN), IHD, and chronic kidney disease (CKD). Similarly, Table 1 showed that mortality was significantly higher in those with TE compared to those without TE (80% vs 17.2%, $p = 0.001$). However, to explore the risk of comorbidities and demographics, ORs were analyzed for the respective variables of TE predisposition (Table 2).

The analysis of the ORs indicated that HTN, IHD, dyspnea, altered consciousness, ICU admission, Hb levels at admission, creatinine levels at admission, and lactate dehydrogenase (LDH) were significantly associated with a higher risk of VTE. The receiver operating characteristic (ROC) analysis was similarly done to estimate the laboratory parameters that could be associated with a higher or lower risk of VTE (Table 3).

Table 3: The ROC curve analysis for laboratory parameters

Parameters at admission	*Area under the curve*	*95% CI*	*p-value*
WBC	0.692	(0.609–0.775)	<0.001
Neutrophil	0.668	(0.582–0.754)	0.001
Fibrinogen	0.752	(0.538–0.966)	0.538
Creatinine	0.635	(0.532–0.738)	0.019
CRP	0.665	(0.545–0.785)	0.017
D-dimer	0.583	(0.449–0.718)	0.226
LDH	0.717	(0.600–0.834)	0.001
Ferritin	0.665	(0.550–0.780)	0.015

Table 3 shows the ROC curve analysis for various laboratory parameters. All the results were found to be statistically significant ($p < 0.05$) except for the levels of fibrinogen and D-dimer.

Considering the high risk of VTE, the study estimated the extent of TE prophylaxis received by the patients. The various types of anticoagulants used to treat the patients. The most commonly used drug was low molecular weight heparin (LMWH, 47.34%), followed by heparin SC (23.67%), heparin infusion (17.36%), novel anticoagulants (NOAC, 0.48%), warfarin (0.48%), and others (9.18%). We further analyzed the differences in laboratory parameters based on the initiation of anticoagulant therapy (Table 4).

Table 4 shows a comparison between patients (paired analysis) with and without TE before and after the initiation of anticoagulant therapy. The analysis showed that anticoagulant therapy exhibited comparable biochemical parameters between those who experienced VTE and those who did not. However, those with TE had significantly higher levels of lactic acid even after thromboprophylaxis.

Discussion

This study showed that there was a high prevalence of clinically relevant TE in COVID-19 patients who were admitted to the hospital for moderate and severe/critical illness. Despite prophylactic or therapeutic anticoagulants, these complications occurred. The underlying mechanism of TE remains unclear. In the presence of severe hypoxemia, capillaries in the lungs may undergo vasoconstriction, reducing blood flow and causing occlusion of the arteries.[18] In addition, hypoxia induces the activation of hypoxia-inducible factors (HIFs). The hypoxic state induces the activation of hypoxia inducible factor 2α (HIF2α) subunits and decreases hydroxylation, thus inducing or inhibiting many genes, including tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1). The evidence suggests that obesity-related inflammation and endothelial dysfunction impact severity of COVID-19.[19] This finding suggests that obesity either confounds or interacts with VTE risk factors.

An ideal balance exists between the host coagulation pathway and the fibrinolytic pathway that controls fibrin deposition and maintains the viability of the lung epithelium. The binding of urokinase plasminogen activator (uPA) to urokinase plasminogen activator receptor (uPAR) greatly facilitates fibrinolysis on epithelial surface cells, clearing the lung of abnormal fibrin deposits.[20] When this fibrinolytic function is impaired during lung inflammation, the

Table 4: Changes in biochemical parameters before and after administration of anticoagulant in those experienced TE compared to those who did not

Lab parameters (M/IQR)	*Patients with TE*			*Patients without TE*		
	Before	*After*	*p-value*	*Before*	*After*	*p-value*
WBC	8.75 (6.64, 11.46)	11.14 (7.14, 15.05)	0.049	6.36 (4.42, 8.82)	9.82 (7.14, 13.28)	0.025
Neutrophil	6.43 (4.58, 9.37)	8.54 (5.79, 14.17)	0.031	64.65 (2.40, 6.75)	70.37 (5.54, 11.77)	0.011
Fibrinogen	950.0 (848.0, 952.0)	846.00 (511.25, 954.25)	0.655	620.00 (331.8, 946.5)	945.00 (620.0, 984.0)	0.035
Creatinine	120.00 (88.00, 260.00)	128.00 (83.50, 388.00)	0.446	98.00 (72.50, 142.50)	130.50 (87.00, 525.00)	0.002
CRP	107.75 (34.47, 197.00)	186.50 (131.00, 237.75)	0.001	56.00 (9.93, 147.50)	189.00 (95.73, 215.50)	0.004
D-dimer	0.90 (0.35, 1.88)	1.74 (1.01, 5.80)	0.036	0.66 (0.37, 1.20)	1.78 (0.79, 3.90)	0.01
Ferritin	736.20 (313.70, 1544.5)	1151.15 (530.50, 2755.29)	0.008	340.28 (142.3, 768.07)	1384.35 (541.77, 2836.55)	0.004
LDH	0.05 (0.02, 0.46)	0.11 (0.02, 1.20)	<0.001	0.02 (0.02, 0.29)	0.06 (0.01, 1.15)	0.679

alveolar spaces accumulate abnormal amounts of fibrin that lead to an increase in the procoagulant activity.[20]

In our study, the majority of COVID-19 patients reporting VTE were males, but there were no differences between males and females in terms of TEs. The most susceptible patients were those aged above 50 years. Our findings are consistent with findings of a previous study which found that patients with COVID-19 who were older and had higher CRP and D-dimer levels had an increased risk of DVT.[21] Although the VTE and PE risks are higher in COVID-19 patients, such risks are often overestimated.[22] However, The VTE incidence in our study was 27% is well aligned with previous studies that showed that VTE incidence was 21% in hospitalized COVID-19 patients and rising to 31% in the subpopulation that admitted to ICU. We found that mortality was higher in VTE patients compared to those who did not experience TE (80% vs 17.2%). In a pooled analysis, mortality rates were 74% higher among adult patients with VTEs compared with those without VTEs (23% vs 13%, respectively). The mortality rates reported in this study were higher than reported by previous studies because we incorporated different cases of TE and not just VTE.

In the present study, 39.1% of obese patients developed VTE. Obesity is associated with a dysfunctional endothelium as a result of an alteration caused by several mechanisms, including low-grade inflammation, generated by either the perivascular adipose tissue (PVAT) or the vasculature itself.[23] Because a dysfunctional endothelium is now widely recognized as a risk factor for cardiovascular events in high-risk patients, this alteration may contribute to increased cardiovascular risk.[23]

The most common comorbidity that we found to be present among patients with VTE was HTN followed by diabetes mellitus (DM), IHD, chronic kidney disease (CKD), heart failure (HF), bronchial asthma, and chronic liver disease. This is in line with a previous study where the most common comorbidity was HTN, followed by DM, and IHD.[24] The majority of thrombotic events found in our study were among the patients admitted to the ICU ($p < 0.01$). These findings are in line with a previous study in which a cumulative incidence of arterial or venous thrombosis of 31% was found to be present in COVID-19 patients who had been admitted to ICU.[25] Another study found VTE in 35 out of 74 patients admitted to the ICU despite being on thrombosis prophylaxis.[20] A probable explanation could be that patients with severe COVID-19 pneumonia can trigger a state of sepsis that in turn can release inflammatory cytokines such as IL-6, IL-8, and TNF-α, among others, that lead to hypercoagulability.[25] A study by Yin et al. found higher mortality rates and platelet counts in consecutive patients with severe COVID-19 as compared to non-COVID patients.[24] Another alternative hypothesis suggests that the virus causes direct alveolar inflammation, leading to hemostasis activation and vascular thrombosis in the lungs.[25]

It was found that hospitalized COVID-19 patients, who previously used anticoagulants, were associated with a lower risk of hospital mortality.[26] Thus, anticoagulant therapy is an important intervention for ensuring improved prognosis in COVID-19 patients. However, some studies have suggested that the dose of anticoagulants could mediate VTE risk rather than the type of anticoagulant therapy.[3]

Haybar et al. in their study concluded that thromboprophylaxis should be administered from hospitalization until 7–14 days after discharge, especially for patients with high-risk factors such as a previous history of VTE, active cancer, or BMI above 30.[27] According to a meta-analysis, if VTE is identified in COVID-19 patients, therapy with parenteral anticoagulants should be initiated, and once stabilized, patients can be transitioned to oral anticoagulant therapy, which could include either a direct oral anticoagulant (DOAC) or vitamin K antagonist depending on patient-specific variables.[28]

Several drugs such as heparinoids (heparins or pentasaccharides), vitamin K antagonists, and direct anticoagulants are used in the prophylaxis and treatment of VTE. Besides their anticoagulant properties, heparinoids are also known to have an additional anti-inflammatory potential that may affect the clinical evolution of people with COVID-19.[29] In our study, the most commonly used anticoagulant was LMWH (47.34%) in both groups (TE and non-TE). Similarly, in a previous study of 449 patients with severe COVID-19, the most commonly used form of heparin was LMWH which was used for 7 days or more.[3] The 28-days mortality between heparinized and non-heparinized patients did not show any difference. Middeldorp et al. reported that about 20% of the included COVID-19 patients had VTE in spite of routine thromboprophylaxis with LMWH.[5] However, it remains to be established whether these results may be translated to Caucasian populations, which seldom develop DIC.[30] However, we did not compare prophylactic and higher doses of LMWH for preventing thrombotic events in patients with COVID-19, thus the optimal dose is unknown and is a matter of active debate as reported by previous studies.[31]

The D-dimer represents the activation of coagulation and fibrinolysis pathways and is therefore one of the tests used to detect thrombosis in patients.[32] Measuring the level of D-dimer and other coagulation parameters from the early stage of the

disease can also be useful in controlling and managing COVID-19 disease. Reported evidence of coagulopathy in COVID-19 patients showed an increased level of D-dimer, LDH, mild to no changes in PT and partial thromboplastin time (PTT), and increased levels of antiphospholipid antibodies.[33,34] In our study, except for fibrinogen and CRP, all the other coagulation parameters showed a statistically significant difference in the VTE group before and after using anticoagulants ($p < 0.05$). Previously, early-phase COVID-19 infections have been shown to cause leukopenia, lymphocytopenia, elevated CRP, increased D-dimer, prolonged PT, and increased fibrinogen levels.[3,35]

Zhou et al. reported that ICU patients had higher median (IQR) D-dimer levels than non-ICU patients did [2400 ng/mL (600–14400) vs 500 (300–800), respectively], and the mortality rate was 18 times higher with D-dimer concentration above 1000 ng/mL upon admission.[9] In the same way, the increase in the levels of ferritin was reported by many other studies in COVID-19 as being the consequence of the cytokine storm.[11,36,37] The presence of elevated ferritin levels has been linked to thrombosis associated with COVID-19 as opposed to thrombosis without COVID-19.[38] Nevertheless, the International Society on Thrombosis and Haemostasis (ISTH) does not recommend screening for VTE based solely on elevated D-dimer levels and maintains that VTE should be diagnosed based on clinical suspicion.[39] The present study did not estimate the risk of VTE as a function of mechanical ventilation, which could have helped to assess the effect size of other risk factors in comparison to VTE. This is because one study showed that days on MV significantly increased the risk of VTE in COVID-19 patients. The power of the study was more than 80%.

There are numerous ways in which the COVID-19 pandemic can negatively influence the development of thrombotic and TEs.[40] COVID-19 has an important implication as it is strongly associated with the development of cytokine storm and thereby exacerbating the systemic inflammatory response and management of patients with severe disease.[41,42] The usefulness of anticoagulants and treatment strategies to overcome coagulation needs to be revisited in the context of COVID-19. Future research is warranted to understand the mechanism operating behind such adverse events and possibly to prevent any untoward events. To clarify the underlying mechanisms of VTE in COVID-19 and to determine the optimal antithrombotic regimens, it is important to conduct longitudinal studies and clinical trials.

Limitations

There were certain limitations to our study. First, the sample size was relatively small in this single-centered observational study. Second, patients who had neither symptoms nor signs of VTE were not routinely and objectively investigated, therefore it was hard to exclude the possibility of asymptomatic events. Finally, the present study did not explore the incidence of TE based on the dose of anticoagulants used and the associated mortality risks.

Conclusion

The prevalence of thrombotic complications in COVID-19 patients is high and contributes significantly to mortality and morbidity. Our study findings indicate that despite anticoagulants, a large number of COVID-19 patients develop serious thrombotic complications. Future studies should explore the dose, duration, and type of anticoagulants with respect to TE incidence and associated clinical outcomes. To clarify the underlying mechanisms of TE in COVID-19 and to determine the optimal antithrombotic regimens, it is important to conduct longitudinal studies and clinical trials.

Ethical Approval

The study was conducted after obtaining appropriate permission from the Institutional Review Board (IRB).

Availability of Data and Materials

All data will be provided upon request.

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