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Incidence of Venous Thromboembolism in Hospitalized Patients with COVID-19

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ABSTRACT

Background: COVID-19 triggers widespread blood clotting. Studies show high D-dimer concentrations (not less than 0.5 milligrams per liter) in nearly half of cases, with frequent mild platelet drops and clotting time increases.

Aim: To assess the occurrence of venous thromboembolism (VTE) and its correlation with illness degree and death among hospitalized cases with confirmed coronavirus disease 2019 (covid-19) infection.

Patient and methods: History taking, CT of the chest and laboratory examination involving renal and hepatic function tests, complete blood count, C-reactive protein (CRP), serum ferritin, and D-dimer have been performed.

Results: A total of 123 hospitalized COVID-19 cases have been enrolled, the mean age of the examined group was 59±15.3 years; 59.3% of cases were males, while 40.7% were females; the majority were non-smokers (65%), while 23.6% were smokers; 64.2% of patients had moderate disease, while only 13% had critical disease; the majority of patients survived (90.2%); and 7.3% of the participants developed venous thromboembolism.

Conclusion: VTE was observed in 7.3% of COVID-19 patients and has been correlated with increased disease degree, inflammation, longer hospitalization, and higher mortality. Early detection and preventive strategies are essential to improve outcomes.

Keywords: COVID-19 ;Venous thromboembolism (VTE); Disease severity; Mortality.

INTRODUCTION

Coronavirus disease 2019, referred to as COVID-19, is due to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and may result in systemic coagulation activation [(1)].

Researchers state elevated D-dimer concentrations (0.5 milligrams per liter or greater) in forty-six percent to sixty-three percent of cases, as well as other signs of coagulation activation involving mild thrombocytopenia and a moderately prolonged prothrombin time [(2,3)].

Emerging proof demonstrates that severe COVID-19 is frequently complicated by coagulopathy, which has prothrombotic impacts that elevate the possibility of venous thromboembolism and death [(4)].

The pathophysiological mechanisms associated with SARS-CoV-2, which leads to Coronavirus disease 2019, might predispose infected individuals to venous and arterial thromboembolic events (hereafter collectively referred to as TE) [(5)].

Factors related to severe COVID-19 include smoking, diabetes mellitus, magnificence, chronic kidney disease (CKD), obesity, pregnancy, chronic obstructive pulmonary disease (COPD), cardiac disease, & transplants. Clinical features such as dyspnea and laboratory findings including leukocytosis, thrombocytopenia, raised procalcitonin, lymphopenia, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), D-dimer, CRP, and diminished concentrations of albumin have been correlated with elevated mortality and severity [(4,5)].

In this study, we assessed the occurrence of VTE and its association with illness severity and death among hospitalized cases having COVID-19 infection.

PATIENTS AND METHODS

Study Design

This prospective observational research has been performed in the period from December 2021 to June 2022 in Bruida central hospital, Alqasim, Saudi Arabia and Al-Hussein University Hospital, Cairo, Egypt.

Inclusion and Exclusion Criteria

Inclusion criteria involved adult cases aged eighteen years or older who have been admitted to the hospital with confirmed Coronavirus disease 2019 infection, confirmed through reverse transcription polymerase chain reaction (RT-PCR) examination.

Exclusion criteria were a case with a documented history of venous thromboembolism prior to COVID-19 infection.

METHODS

All patients were subjected to clinical evaluation, which included history taking with emphasis on comorbid conditions, physical examination involving oxygen saturation and vital signs, assessment of coronavirus disease 2019 illness degree classified as moderate, severe, or critical.

Previous history of venous thromboembolism, COVID-19 vaccination status and administration of thrombo-prophylaxis during hospitalization were also documented. Baseline laboratory investigations at admission (Renal and hepatic function tests, complete blood count, D-dimer, C-reactive protein, and serum ferritin) have been carried out. Patients were closely

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monitored during their hospital stay for the occurrence of venous thromboembolism that confirmed by appropriate radiological imaging (e.g., CT pulmonary angiography, venous Doppler ultrasound) and for clinical outcomes, including mortality.

Outcome Measures: The 1ry outcome is to detect the occurrence of VTE between hospitalized coronavirus disease 2019 cases and the death rate during hospitalization. Secondary outcomes involved associations between laboratory parameters, comorbidities, disease severity, and patient survival, in addition to evaluating the impact of thromboembolic events on length of hospital stay and overall clinical course.

Ethical Considerations

The present research investigation received formal approval from The Academic and Ethical Committee of Buraidah Central Hospital, under the assigned protocol number MS-51–2021. Prior to participation, written informed consent was meticulously obtained from each individual case included in the study. Furthermore, the entirety of the study protocol rigorously adhered to the ethical principles outlined in the Declaration of Helsinki, which stands as the authoritative ethical standard established by the World Medical Association for all research endeavors involving human subjects.

Statistical Analysis

Continuous parameters have been represented as mean values with standard deviations (SD), whereas categorical parameters have been expressed as percentages and frequencies. Comparisons between groups (such as survivors versus non-survivors, patients with venous thromboembolism versus those without venous thromboembolism, and patients across different severity categories) have been carried out utilizing the chi-square test for categorical parameters and independent t-tests or one-way analysis of variance (ANOVA) for continuous parameters. Statistical significance has been set at a p-value of below 0.05, with Bonferroni correction utilized in cases of multiple comparisons. All statistical analyses have been carried out applying SAS software version 9.4 (SAS Institute, Cary, NC, united states of America.

RESULTS

Table (1): Distribution of patient characteristics in the studied group.

		Study group Number=123
Age (years) Mean ±SD		59±15.3
Sex	Male	73(59.3%)
	Female	50(40.7%)
Smoking status	Smokers	29(23.6%)
	non-smokers	80(65%)
	Ex smokers	14(11.4%)
Severity of the disease	Moderate	79(64.2%)
	severe	28(22.8%)
	critical	16(13%)
Mortality rate	survivor	111(90.2%)
	non-survivor	12(9.8%)
Developed venous thromboembolism		9(7.3%)

SD: standard deviation.

This table show that, mean age of the studied group was 59±15.3 years, 59.3% of patients were males while, 40.7% were females, the majority were non-smokers 65% while, 23.6% were smokers, 64.2% of patients had moderate disease, while only 13% had critical disease, the majority of patients survived 90.2% and 7.3% of the participants developed venous thromboembolism.

Table (2): Factors associated with severity levels of COVID-19 among patients

		Moderate Number=79	Severe Number=28	Critical Number=16	P value
Age (years) Mean ±SD		55.67±15.73	62.21±12.3	64.25±8.04	**0.025**
Sex	male	46(58.2%)	16(57.1%)	11(68.75%)	0.71
	female	33(41.8%)	12(42.9%)	5(31.25%)	
Smoking		20 (25.3%)	12 (42.9%)	11 (68.75%)	**0.002**
Mean ±SD					
Hemoglobin (gram/deciliter)		11.8±1.92	11.1±2.03	10.4±2.3	**0.02**
TLC (× 10^3 /cm^3)		4.6±0.4	5.43±1.12	16.37±3.7	**0.009**
Platelets (×10^3 /cm^3)		231.25±9.4	239.17±16.3	213.4±19.6	0.69
ALT (U/L)		39.35±6.13	37.6±3.2	93.9±11.4	**0.046**
AST (U/L)		35.56±6.2	31.48±2.39	85.2±14.4	**0.039**
Urea (mg/dl)		37.54±2.3	55.6±9.15	75.3±4.25	**<0.001**
Creatinine (mg/dl)		0.97±0.47	1.41±1.28	1.64±0.63	**0.001**
Ferritin (ng/ml)		519.3±42.21	796±64.4	1105.1±64.2	**<0.001**
CRP (mg/dl)		58.49±4.16	91.6±6.7	156.4±8.19	**<0.001**
D-dimer (mg/L)		0.67±0.18	0.91±0.2	2.88±0.64	**<0.001**
Oxygen saturation (%)		91.7±1.94	88.2±3.12	79.26±6.35	**<0.001**
Systemic hypertension		26 (32.9%)	16(57.1%)	9(56.25%)	**0.036**
Diabetes mellitus		17(21.5%)	13(46.4%)	6(37.5%)	**0.033**
Cardiac diseases		6(7.6%)	7(25%)	4(25%)	**0.027**
Malignancy		2(2.5%)	1(3.6%)	2(12.5%)	0.18
Autoimmune diseases		0(0%)	0(0%)	2(12.5%)	**0.001**
Thyroid disease		1(1.27%)	1(3.6%)	1(6.25%)	0.45
Pulmonary disease		6(7.6%)	7(25%)	3(18.75%)	**0.048**
Renal disease		0(0%)	1(3.6%)	1(6.25%)	0.12
Neurological disease		0(0%)	2(7.1%)	0(0%)	**0.031**
Old VTE		1(1.27%)	1(3.6%)	1(6.25%)	0.45
Hepatic disease		1(1.27%)	0(0%)	2(12.5%)	**0.018**
COVID vaccination		14(17.7%)	4(14.3%)	1(6.25%)	0.5
Thrombo-prophylaxis		65(82.3%)	26(92.9%)	14(87.5%)	0.38
VTE		0(0%)	2(7.1%)	7(43.75%)	**<0.001**
Length of stay (days) Mean ±SD		5.21±1.3	10.1±2.4	14.5±2.6	**<0.001**
Mortality		1(1.27%)	2(7.1%)	9(56.25%)	**<0.001**

SD: standard deviation; p-value under 0.001 is highly significant, P value below 0.05 is statistically significant, P value above 0.05: Not significant, TLC: Total Leukocyte Count; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; CRP: C-Reactive Protein; VTE: Venous Thromboembolism.

This table shows that there was statistically significant difference among the studied groups regarding age and smoking. Also, there was statistically significant difference among the studied groups regarding hemoglobin, TLC, ALT, AST, urea, creatinine, ferritin, CRP, D-dimer and oxygen saturation. Also, there was a statistically significant difference among the studied groups regarding systemic hypertension, diabetes mellitus, cardiac diseases, autoimmune diseases, pulmonary disease, neurological disease, hepatic disease and VTE.

Table (3): Comparison of patient characteristics, laboratory data, comorbidities, and outcomes between the studied groups:

		Survivor Number=111	Non-Survivor Number =12	P value
Age (years) Mean ±SD		59.45±13.96	68.25±12.04	**0.03**
Gender	male	64 (57.7%)	9 (75%)	0.24
	female	47 (42.3%)	3 (25%)	
Smoking		35 (31.5%)	7 (58.3%)	**0.015**
Hemoglobin (g/dl)		11.98±1.84	10.86±1.69	**0.04**
TLC (× 10^3 /cm^3)		7.32±1.89	25.62±3.64	**<0.001**
Platelets (×10^3 /cm^3)		243.59±4.75	191.69±15.23	0.08
ALT (U/L)		44.23±6.56	129.17±22.35	**<0.001**
AST (U/L)		43.77±6.93	119.22±25.69	**<0.001**
Urea (mg/dl)		41.79±5.78	97.69±4.53	**<0.001**
Creatinine (mg/dl)		1.08±0.79	1.93±0.26	**0.004**
Ferritin (ng/ml)		635.22±39.16	1,259.65±31.85	**<0.001**
CRP (mg/dl)		77.65±5.24	166.62±13.65	**<0.001**
D-dimer (mg/L)		0.79±0.05	4.1±0.62	**<0.001**
Oxygen saturation (%)		91.43±4.11	82.49±11.59	**<0.001**
Systemic hypertension		45 (40.5%)	6 (50%)	0.52
Diabetes mellitus		31 (27.9%)	5 (41.6%)	0.32
Cardiac diseases		14 (12.6%)	3 (25%)	0.24
Malignancy		4 (3.6%)	1 (8.3%)	0.43
Autoimmune diseases		1 (0.9%)	1 (8.3%)	0.053
Thyroid disease		3 (2.7%)	0 (0%)	0.56
Pulmonary disease		13 (11.7%)	3 (25%)	0.19
Renal disease		0 (0%)	2 (16.6%)	**<0.001**
Neurological disease		2 (1.8%)	0 (0%)	0.63
Old VTE		1 (0.9%)	2 (16.6%)	**<0.001**
Hepatic disease		1 (0.9%)	2 (16.6%)	**<0.001**
COVID vaccination		19 (17.1%)	0 (0%)	0.12
Thrombo-prophylaxis		95 (85.6%)	10 (83.3%)	0.83
VTE		2 (1.80%)	7 (58.3%)	**<0.001**
Length of stay (days)		10.01±7.56	17.56±8.85	**0.001**
Severity	moderate	79 (71.2%)	0 (0%)	**0.001**
	severe	26 (23.4%)	2 (16.7%)	
	critical	6 (5.4%)	10 (83.3%)	

This table showed that:

1- There was no statistically significant difference between the survivors and non survivors regarding sex while, there was statistically significant difference regarding age and smoking.

2- There was a statistically significant difference between the studied groups regarding hemoglobin, TLC, ALT, AST, urea, creatinine, ferritin, CRP, D-dimer and oxygen saturation.

3- There was statistically significant difference between the studied groups regarding renal disease, old VTE, hepatic disease and VTE.

4- There was a statistically significant difference between the studied groups regarding length of stay (days) and severity.

Table (4): Distribution of demographics and comparison of laboratory data, comorbidities, disease severity, and clinical outcomes among cases with and without VTE:

		VTE Number =9	Non-VTE Number =114	P value
Age (years), Mean± SD		59.2±11.8	58.10±14.2	0.82
Smoking		4 (44.4%)	39 (34.2%)	0.53
Gender	**Male**	7(86.7%)	66 (57.9)	0.24
	Female	2(13.3%)	48 (42.1%)	
Hemoglobin (g/dl)		11.10±1.34	12.9±1.90	**0.006**
TLC (× 10^3 /cm^3)		22.91±5.74	14.33±3.91	0.098
Platelets (×10^3 /cm^3)		241.3±11.2	235.81±8.5	0.07
ALT (U/L)		75±5.1	46.51±4.1	**46.51**
AST (U/L)		66.7±2.1	41.22±7.21	**0.045**
Urea (mg/dl)		74.13±7.13	45.15±3.90	**0.01**
Creatinine (mg/dl)		1.77±0.15	1.19±0.14	**0.04**
Ferritin (ng/ml)		1138.93±48.11	632.37±51.51	**0.001**
CRP (mg/dl)		170.2±11.12	74.82±9.31	**<0.001**
D-dimer (mg/L)		3.78±0.69	0.94±0.26	**<0.001**
Oxygen saturation		83.11±9.81	93.05±5.7	**<0.001**
Systemic hypertension		5(55.6%)	46(40.4%)	0.37
Diabetes mellitus		3(33.3%)	33(28.9%)	0.78
Cardiac diseases		1(11.1%)	16(14%)	0.8
Malignancy		1(11.1%)	4(3.5%)	0.27
Autoimmune diseases		0(0%)	1(0.88%)	0.77
Thyroid disease		0(0%)	3(2.6%)	0.62
Pulmonary disease		2(22.2%)	14(12.3%)	0.39
Renal disease		0(0%)	2(1.75%)	0.69
Neurological disease		0(0%)	2(1.75%)	0.69
Old VTE		2(22.2%)	1(0.88%)	**<0.001**
Hepatic disease		1(11.1%)	2(1.75%)	0.08
COVID vaccination		1(11.1%)	18(15.8%)	0.7
Thrombo-prophylaxis		8 (88.9%)	97(85.1%)	0.76
Severity	moderate	0(0%)	79(69.3%)	**<0.001**
	Severe	2(22.2%)	26(22.8%)	
	Critical	7(77.7%)	9(7.9%)	
Severity				
Moderate		0(0%)	79(69.3%)	**<0.001**
Severe		2(22.2%)	26(22.8%)	
Critical		7(77.7%)	9(7.9%)	
Length of stay (days)		16.9±6.92	10.12±6.41	**0.002**
Mortality		7 (73.3%)	5(3.9%)	**<0.001**

This table shows that:
There was no statistically significant difference between the studied groups regarding age, smoking and sex.
There was statistically significant difference between the studied groups regarding hemoglobin, ALT, AST, urea, creatinine, ferritin, CRP, D-dimer and oxygen saturation.
There was a statistically significant difference between the studied groups regarding old VTE and severity.
There was a statistically significant difference among the studied groups regarding length of stay and mortality.

DISCUSSION

123 PCR proven covid-19 cases have been involved in this research. The mean age of the examined group was 59±15.3 years, 73 cases (59.3%) were men, while 50 cases (40.7%) were women, the majority were non-smokers (65%), while 23.6% were smokers, 79 patients (64.2%) had moderate disease, 28 (22.8%) were sever and only 16 patients (13%) had critical disease; the majority of patients survived (90.2%); and 7.3% of the participants developed venous thromboembolism.

In line with **Giannis *et al.*** [7] determined the prevalence of venous thromboembolism and death among coronavirus disease 2019 cases who have been introduced to a large healthcare system for the first time, most of cases (43.2%) were aged from 18 to 59 years, 64.4% of patients were males while 35.6% were females, 13.7% were active/former smokers, 11.6% had been admitted to the ICU, and 7.5% of the participants developed venous thromboembolism. As well, **Sethi *et al.*** [8] found correlation of death and thrombosis in coronavirus disease 2019 and reported that the mean age of the studied group was 62.3 ± 13.3 years; 68.2% of patients were males, while 31.8% were females; on the other hand, 21.2% of patients had moderate disease, while 66.7% had critical disease.

In this research, older age correlates with greater illness severity and elevated rates of death.

Similarly, **Ali *et al.*** [9] evaluated the different factors affecting severity and mortality in addition to the occurrence of VTE in coronavirus disease 2019 cases and reported a statistically significant difference has been found among the examined groups as regards age and smoking, whereas a statistically insignificant difference has been observed among the studied groups according to sex. As well, **Narin Çopur *et al.*** [10] recognized the risk factors correlated with the severity of illness and death in coronavirus disease 2019 cases, stated that a statistically significant difference has been found among the examined groups as regards age and sex.

Our study revealed that laboratory examinations involving low hemoglobin concentration, high total leucocytic count, elevated hepatic enzymes, high creatinine level, elevated inflammatory markers (CRP, serum ferritin), and high level of D-dimer were significantly raised in critically diseased cases and non-survivors.

Comparable outcomes have been documented by **Ali *et al.*** [9] who stated that a statistically significant variance has been observed among the severe and critical cases regarding hemoglobin, TLC, ALT, AST, urea, creatinine, ferritin, CRP, D-dimer, and oxygen saturation. Also noted that a statistically significant variance has been observed among survivors and non-survivors according to hemoglobin, TLC, ALT, AST, urea, creatinine, ferritin, CRP, D-dimer, and oxygen saturation. whereas there was a statistically insignificant variance between the examined groups according to platelets.

Also, **Narin Çopur *et al.*** [10] stated that a statistically significant variance has been observed between the examined groups with regard to WBC, AST, ferritin, CRP, and D-dimer. Moreover, **Assal *et al.*** [11] aimed to investigate the indicators of degree of illness and death in coronavirus disease 2019, stated that a statistically significant variance has been observed between the examined groups as regards TLC, ALT, AST, ferritin, urea, CRP, and D-dimer, while a statistically insignificant variance has been found among the studied groups with regard to platelets and hemoglobin. Regarding the presence of comorbidities, diabetes mellitus, systemic hypertension, autoimmune diseases, heart diseases, pulmonary disease, neurological disease, hepatic disease, and VTE patients developed severe disease, but renal, hepatic, and old VTE patients were related to high death rates. A statistically significant difference has been observed among survivors and non-survivors regarding the presence of these comorbid conditions. So, mortality increased in hepatic, renal, and old VTE patients.

Similarly, **Ali *et al.*** [9] stated that there was a statistically insignificant difference between the disease severity and mortality regarding malignancy, thyroid disease, renal disease, old VTE, COVID vaccination, and thromboprophylaxis, whereas a statistically significant variance has been observed among the disease severity and mortality regarding systemic hypertension, diabetes mellitus, cardiac diseases, autoimmune diseases, pulmonary disease, neurological disease, hepatic disease, and VTE. As well, **Narin Çopur *et al.*** [10] stated that a statistically significant difference has been observed among the examined groups as regards respiratory illness, chronic renal illness, coronary artery disease, diabetes mellitus, and hypertension. Also, **Assal *et al.*** [11] concluded that a statistically significant difference has been found among the examined groups regarding hypertension, diabetes mellitus, and renal disease, while there was a statistically insignificant variance between the examined groups with malignancy.

But our outcomes disagree with **Arunan *et al.*** [12] who stated that a statistically significant variance has been observed among survivors and non-survivors according to diabetes mellitus and hypertension.

This study illustrated that a greatly statistically significant difference has been found among the severity of disease regarding the length of stay and mortality ($p < 0.001$). Similarly, **Ali *et al.*** [9] found that there was a greatly statistically significant difference among the examined groups regarding length of stay and mortality ($p < 0.001$). As well, **Assal *et al.*** [11] stated that a statistically significant variance has been found among survivors and non-survivors according to severity.

The frequency of VTE in this research was 7.3%. **Assal *et al.*** [11] reported highly comparable outcomes.

Oxygen saturation, AST, ALT, hemoglobin, CRP, D-dimer, serum ferritin, and history of old venous thromboembolism varied significantly among non-VTE and VTE groups. But no significant association between the development of VTE in COVID-19 cases regarding age, smoking, or sex. **Ali *et al.*** [9] and **Mackiewicz-Milewska *et al.*** [13] documented comparable findings; however, our findings disagree with those of **Li *et al.*** [14], who indicated a greater prevalence of comorbidities, smoking, and male sex within the VTE group.

Our finding indicates that coronavirus disease 2019 cases with venous thromboembolism events had a greater mean length of stay; these results are in line with **Ali *et al.*** [9] who concluded that a statistically significant distinction has been found among the examined groups regarding length of stay and mortality ($p < 0.001$).

Also, results are in accordance with **Agarwal *et al.*** [15] who performed a systematic review to recognize predictors of venous thromboembolism in coronavirus disease 2019 and stated that coronavirus disease 2019 cases with venous thromboembolism events had a greater mean length of stay of about four days in comparison with cases without venous thromboembolism (raw variance in mean: 3.9, *p*-value equal to 0.038).

A significant finding in this study was that VTE events were more common in critical cases and were associated with higher mortality (77.7% of venous thromboembolism cases were critical COVID-19 patients, & 77.7% of VTE cases were non-survivors). A result consistent with **Ali *et al.*** [9] recorded that a statistically significant distinction has been found among VTE and non-VTE groups regarding severity of illness and death.

Critically diseased cases with COVID-19 have an increased possibility of VTE which can be explained by the following points the patient is bedridden in the ICU, same risk factors associated with sever disease, and VTE such as increasing the age, obesity and hemostatic changes related to COVID-19, e.g., lower platelet count, greater D-dimer level and prolongation of prothrombin time [16]. Furthermore, severe COVID-19 may result in sepsis, which can subsequently cause disseminated intravascular coagulation. Sepsis is related to the production of inflammatory cytokines, involving interleukin 8 and 6 & tumor necrosis factor-α, which result in coagulation activation and the onset of venous thromboembolism [17].

CONCLUSION

VTE was observed in 7.3% of COVID-19 patients and has been correlated with increased disease degree, inflammation, longer hospitalization, and higher mortality. Early detection and preventive strategies are essential to improve outcomes**.** VTE was observed in 7.3% of COVID-19 patients and has been correlated with increased disease degree, inflammation, longer hospitalization, and higher mortality. Early detection and preventive strategies are essential to improve outcomes**.**

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