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Clinical Characteristics of Venous Thromboembolism in COVID-19 Patients Admitted to the Intensive Care Unit

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Abstract

Background: COVID-19 infection has been linked to several morbid illnesses, one of which is venous thromboembolism; yet, the incidence and clinical characteristics of this disorder vary, and there are no recognized definitive risk predictors.

Aim of Study: The goal of this study was to find out how common venous thromboembolism is in COVID-19 patients, as well as the clinical characteristics, risks, and outcomes.

Patients and Methods: A retrospective cohort study comparing the recorded data for two groups of patients with confirmed COVID-19 infection and admitted to the ICU in 6 months duration.

Results: The most common type of venous thromboembolism was a pulmonary embolism (PE), which accounted for 68.2 percent of cases, followed by DVT with PE (15.1 percent), DVT alone (12.1 percent), cavernous sinus thrombosis alone CST (3 percent), and CST with renal artery thrombi (1.5 percent). Smoking and cancer were more common in the VTE group, as was a statistically significant increase in D dimer. The most common type of pulmonary embolism in our patients was lobar (69.6%), followed by segmental (17.9%), and finally massive pulmonary embolism (12.5 percent).

Conclusion: VTE is a prevalent issue in COVID-19 individuals, who had higher rates of smoking and malignancy, and considerably increased D dimer, with higher rates of morbidity and mortality.

Key Words: *COVID-19 – Pulmonary embolism – Venous thromboembolism.*

Introduction

THE global COVID-19 pandemic undoubtedly caused enormous morbidity and mortality **[1-3]**. One of these serious morbid illnesses that is a major cause of death is thromboembolic pathogenesis **[4-6]**, which has been connected to it, particularly in patients hospitalized to critical care units and those who are exposed to mechanical ventilation **[7]**. The exact prevalence of venous thromboembolism (VTE) in COVID-19 patients is unknown at this time, with the few studies done to date revealing a frequency ranging from 7% to 30%, with the variation largely explained by variable testing, the severity of the patient's illness, and comorbidities **[8-11]**.

Furthermore, clinical findings differed from one region to the next, and even from time to time within the same country **[12]**. Even more surprising is the persistence of thromboembolic symptoms after thromboembolic prophylaxis has been established as the first line of treatment in confirmed COVID-19 patients **[13-15]**. Except for a high D-dimer level, do individuals with VTE have different clinical characteristics than those who do not have VTE among confirmed COVID-19 cases?

The study's purpose was to find out how frequently venous thromboembolism occurred in our COVID-19 intensive care unit, as well as its clinical features, risks, and outcomes.

Patients and Methods

Ethical approval:

This cohort study was done for one year with the Regional Ethics Committee at the King Fahad

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Abbreviations:

CST : Cavernous Sinus Thrombosis.
CTPA : Computed tomography pulmonary artery.
PAOI : Pulmonary Artery Obstruction Index.
PE : Pulmonary Embolism.
VTE : Venous Thromboembolism.

ICU Hospital in Al Madina, Saudi Arabia, between August 1, 2020, and September 30, 2021, and complied with the Helsinki Declaration's criteria. Before participating in this study, all individuals had to sign a written consent form.

Data collection:

All of the patients were interviewed, and a senior pulmonologist examined their lungs thoroughly. A total of 286 patients (168 men and 118 women) between the ages of 36 and 73 were enrolled in this study, with an average age of 46±13 years. Patients who agreed to participate in the trial and had medically proven Covid-19 infections were included, but patients with alternative sources of lung infections were excluded.

The patients were split into two groups: Those who developed VTE (66 patients) and those who didn't (220 patients).

Confirmation of COVID-19 infection:

The diagnosis of COVID-19 was established by a positive real-time reverse transcriptase polymerase-chain-reaction test for SARS-CoV-2 on patients' nasal and pharyngeal swab specimens. COVID-19 infection is classified into five severity levels by ACEP2020: Mild low risk, mild at risk, moderate, severe, and critical.

Diagnosis of pulmonary embolism:

Computed tomography pulmonary artery (CT-PA) is a type of CT imaging that uses a standard technique on a 128 slice multi-detector CT scanner (Philips Ingenuity Core 128, Philips Medical Systems) to identify pulmonary embolism (PE). PE was diagnosed by a skilled radiologist after direct observation of an endoluminal thrombus in the pulmonary arteries. To establish a quantitative assessment of the embolism's size, the pulmonary artery obstruction index (PAOI) was calculated using the method established by Qanadli et al., **[16]** , and PE was divided into four categories: Large, lobar, segmental, and subsegmental.

Full Digital ultrasonography scanner Imaging with Sonoview was performed to assess deep venous thrombosis in the lower extremities, all patients undergo duplex ultrasonography of both lower limbs. All of the patients were followed-up to see if their symptoms had improved or not (from 17-41) days.

Antiphospholipid antibodies were tested in patients who had already had thrombosis, as well as a full rheumatological examination to check whether there was any associated disease.

Further evaluation of patients who have cerebral manifestations:

For all individuals who developed focal neurological manifestations, After a neurologist took a neurological history and assessed the patient, a CT brain (venous and arterial) phase was used to evaluate any anomalies and rule out the possibility of cavernous sinus thrombosis.

Statistical analysis: Analysis, using SPSS version 21 was performed concerning the main study aim. Descriptive characteristics for participants are expressed as means and standard deviation (SD) for continuous variables, number, and percent for categorical variables. We used the independent sample test to show the significant difference between the continuous variable and the Chi-square test for the categorical variables. The level of significance was accepted at p0.05.

Results

The study included 286 COVID-19 confirmed patients admitted to the critical care unit, who were separated into two groups: VTE patients (66), 38 (57.6%) of whom were male, with a mean age ± SD (47±13), and non-VTE patients (220), 130 (59.1%) of whom were male, with a mean age ± SD (46±11), although most of the patients were males, no statistically significant differences between the two groups; Although the percentage of non-smokers, mild smokers, and moderate smokers were slightly higher in the non-VTE group (11 percent, 30 percent, and 28 percent Vs. 10.6 percent, 28.8 percent, and 27.7 percent respectively), with a higher percentage of heavy smokers in the VTE group (33.4 percent vs. 31 percent), there were no statistically significant differences between the two groups.

Table (1) shows That hypertension, diabetes, IHD, CVA, rheumatoid arthritis, and SLE were more prevalent in the non-VTE group (78 percent, 73 percent, 82 percent, 6.3 percent, 6.3 percent, and 5.4 percent vs. 76 percent, 71 percent, 79 percent, 4.5 percent, 4.5 percent, and 3 percent, respectively), while only malignancy was more prevalent in the VTE group (11 percent vs. 10 percent), however, there were no statistically significant differences between the two groups.

Except for D dimer, which was considerably greater in the VTE group, there were no significant differences in the laboratory findings between the two groups, as shown in Table (2). Nonetheless, the VTE group had slightly greater WBC, eosi-

nophils, ESR, ferritin, urea, and creatinine, whereas the non-VTE group had slightly higher hemoglobin, lymphocytes, platelets, and ALT.

Table (1): Demographic data and risk factors.

Categorical variables N (%) Non-Categorical variables mean ± SD	VTE Group	Non-VTE Group	*p*-value
Number	66 (100%)	220 (100%)	
Age*	47±13	46±11	0.154
BMI*	29±13	28±12	0.12
Male	38 (58%)	130 (59%)	0.21
Female	28 (42%)	90 (41 %)	0.14
Smoking:			
Non	7 (10.6%)	24 (11 %)	2.14
Mild	19 (28.8%)	66 (30%)	1.25
Moderate	18 (27.2%)	62 (28%)	1.58
Heavy	22 (33.4%)	68 (31%)	0.69
Hypertension	50 (76%)	171 (78%)	2.64
Diabetes Mellitus	47 (71 %)	161 (73%)	1.25
Ischemic heart Disease	52 (79%)	180 (82%)	1.58
CVA	3 (4.5%)	14 (6.3%)	0.687
Malignancy	7 (11%)	22 (10%)	2.51
Rheumatoid arthritis	3 (4.5%)	14 (6.3%)	2.7
Systemic Lupus Erythrematosos	2 (3%)	12 (5.4%)	1.89

N = Number. % = Percentage. SD = Standard deviation.
VTE = Venous thromboembolism. * = Values are mean ± SD.
**p-Value = Statistically significant relation when p less than 0.05.

Table (2): Comparing the laboratories parameters between the two groups.

	VTE group (Mean ± SD)	Non-VTE group (Mean ± SD)	*p*-value
WBC	12.5±8	11 ±4	1.98
hemoglobin	13±2	14±3	2.54
platelets	203±21	304±20	1.48
Eosinophil count	320±14	295±16	2.01
Lymphocyte count	50±8	65±5	1.54
Monocyte count	42±6	51±7	2.54
Urea	14±4	12±6	1.87
Creatinine	125±23	121±20	2.87
AST	43±8	32±6	1.34
ALT	45±11	50±12	2.047
T.BIL	11 ±3	9±2	2.39
D.BIL	0.9±0.8	0.7± 1	1.98
T. protein	55±12	60±9	1.35
Albumin	25±7	28±6	2.05
D dimer	3±1	1±1	0.00*
ESR	75±14	64±13	1.89
Ferritin	275±12	220± 9	2.54

VTE = Venous thromboembolism, SD = Standard deviation.
Values are expressed in mean ± SD.
* p-value = Statistically significant relation when p is less than 0.05.

Table (3) reveals that all of our patients in the two groups were classified as severe or critically ill patients according to ACEP 2020, with no statistical differences between the two groups; however, patients in the non-VTE group were more likely to be treated with oxygen masks and non-invasive ventilation (33.6 percent and 38.2 percent vs. 24.2 percent and 25.7, respectively), with a statistically significant difference. Meanwhile, with a p-value less than 0.001, the patients in the VTE group were more significantly controlled with mechanical ventilation (50.1 percent vs. 28.2 percent). The table also reveals that non-VTE group survivors were considerably higher than VTE group survivors (69.6 percent vs. 54.6 percent), whereas VTE group fatalities were significantly higher than non-VTE group deaths (45.4 percent vs. 30.4 percent) with a p-value less than 0.001.

Table (3): COVID-19 severity and outcome, and oxygen source.

	VTE group N (%)	Non-VTE group N (%)	*p*-value
Severity:			
Mild low risk	0 (0%)	0 (0%)	–
Mild at risk	0 (0%)	0 (0%)	–
Moderate	0 (0%)	0 (0%)	
Severe	20 (30%)	63 (28.7%)	2.95
Critical	46 (69.6%)	157 (71.3%)	2.74
Outcomes:			
Survivors	36 (54.6%)	153 (69.6%)	0.001*
Deaths	30 (45.4%)	67 (30.4%)	0.001*
Oxygen therapy:			
Oxygen mask	16 (24.2%)	74 (33.6%)	0.001*
Non-invasive ventilation	17 (25.7%)	84 (38.2%)	0.001*
Mechanical ventilation	33 (50.1%)	62 (28.2%)	0.001*

VTE = Venous thromboembolism.
Values are expressed in number and percentage.
* p-Value = Statistically significant relation when p less than 0.05.

Table (4) demonstrates that pulmonary embolism (PE) was the most common type of thromboembolism in our patients (68.2%), followed by DVT with PE (15.1%), DVT alone (12.1%), cavernous sinus thrombosis (CST) alone (3%), and CST with renal artery thrombi (1.5 percent). Lobar pulmonary embolism was the most common kind of pulmonary embolism in our patients (69.6%), followed by segmental (17.9%), and lastly massive pulmonary embolism (12.5 percent).

Table (5) shows that 13.6 percent of the VTE group tested positive for Antiphospholipid Antibodies. Serositis was seen in 6.1 percent of the patients, skin lesions in 4.5 percent, arthritis in 3%, and neurological symptoms in another 3%.

Table (4): The frequencies and percentage of venous thromboembolism.

	VTE group N (%)	All patients N (%)
PE according to the severity:		
Massive	7 (12.5%)	7 (2.4%)
Segmental	10 (17.9%)	7 (2.4%)
Lobar	39 (69.6%)	39 (13.6%)
PE:		
Alone	45 (68.2%)	45 (15.7%)
With DVT	10 (15.2%)	10 (3.5%)
Total	55 (83.3%)	55 (19.2%)
DVT:		
Alone	8 (12.1%)	8 (2.8%)
With PE	10 (15.2%)	10 (3.5%)
CST:		
Alone	2 (3%)	2 (0.7%)
With renal artery thrombosis	1 (1.5%)	1 (0.35%)

VTE = Venous thromboembolism.
Values are expressed in number and percentage.
PE = Pulmonary embolism.
DVT = Deep venous thrombosis.
CST = Cavernous sinus thrombosis.

Table (5): Antiphospholipid antibodies among VTE group and their clinical correlation

	Antiphospholipid Antibodies	
	Positive N (%)	Negative N (%)
Skin lesions	3 (4.5%)	27 (40.9%)
Arthritis	2 (3%)	40 (60.6%)
Serositis	4 (6.1%)	41 (62.1%)
Neurological symptoms	2 (3%)	0 (0%)
Total	9 (13.6%)	57 (86.4%)

VTE = Venous thromboembolism.
Values are expressed in number and percentage.

Discussion

We investigated the prevalence, clinical features, and risks for developing VTE in 286 people with confirmed COVID-19, 66 of whom had VTE while the other 220 did not. Several searches have found a link between VTE and COVID-19 infections, particularly pulmonary embolism, but the evidence for pulmonary embolism is only found in post-mortem autopsies. Despite the numerous suggested causes for these links, probable mechanisms for these relationships, the true pathogenic mechanisms, and incidences are not settled, and the high proof is absent due to a lack of large prospective studies.

Regarding socio-demographic data and comorbid conditions, there were no statistical differences between those who had VTE and those who did not, so we cannot conclude that there is a specific risk predictor for such events; even the initial laboratory findings, except for a significant increase in D-dimer in the thrombotic group, were not statistically significant. Many investigations have demonstrated D-dimer elevation in COVID-19 patients, with occurrences exceeding 50% and being greater in critical situations (35-36), and one study found that having more than 1 g/mL is a risk factor for death **[37]**.

In our study, 18.75% (66 patients) of the patients had VTE, with pulmonary embolism being the most common (15.7%), which is higher than an earlier study in Saudi Arabia (11.6%) **[17]** and some studies **[18-20]** that used retrospective data and reported the incidence of positive patients regardless of the severity of their cases and with short follow-up periods. The fact that all of our patients are classified as severely or critically ill could account for these discrepancies. However, it is lower than, retrospective studies in western countries **[21,22]** that revealed incidences of 23 percent to 30 percent using CTA imaging, and with Beun et al. with those of Beun et al., who discovered a 26.6 percent prevalence of positive COVID-19 patients in the ICU **[23]**.

Another important finding in our study was that only 19.2% of pulmonary embolisms were accompanied by DVT, even though we did not find a source for the pulmonary embolism in the majority of cases; this DVT incidence is far lower than that reported in autopsies of COVID-19 patients in a German study **[24]**, where those patients were not clinically suspected of having DVT before death. Although autopsies are considered more revealing for the true incidence of DVT, we cannot rely on this as the source of pulmonary embolism in COVID patients, as many reports suggest that the pulmonary embolism in those patients is actually a pulmonary thrombosis, which can be explained by their hypercoagulable state **[25]**, as evidenced by the high D-dimer level, which was significantly higher in our study when compared to patients without VTE.

This study also highlighted the importance of local pathogenic factors, with 87.9% of persons with pulmonary thrombosis having it around the site of consolidation, where the local inflammatory process is more evident; this is similar to prior findings **[26]**. In addition, Thachil J. and Srivastava A. suggested that COVID-19 patients have two types of pulmonary thrombosis, one of which is pulmonary micro thrombosis **[27]**, while others have connected viral factors to endothelial dysfunction **[28-30]**.

Three patients in our study had CST, and one of them had renal artery thrombosis. These complications are uncommon in COVID-19 patients, and despite their hypercoagulability, local predisposing factors in those patients are unclear; in our cases, thrombosis occurred in the superior sagittal sinuses, which has been reported to be the most common site in COVID-19 patients with cerebrovascular thrombosis **[31]** . Only a few studies have reported renal artery thrombosis; however, despite some reports suggesting that renal impairment in COVID-19 patients could be due to renal artery micro thrombosis **[32-33]** , our patient had a normal renal function at the time of diagnosis and no comorbid conditions other than type 2 diabetes.

Finally, in our study, patients with VTE had a higher incidence of mechanical ventilation and a higher death rate than non-VTE patients; this relationship could be both cause and effect, as patients with VTE, particularly pulmonary embolism, can cause respiratory failure and require mechanical ventilation; at the same time, patients on mechanical ventilation are more prone to venous thrombosis, which explains the high mortality rate in COVID-19 managed by mechanical ventilation **[38,39]** .

Conclusion: VTE, not just pulmonary embolism, is a common consequence in COVID-19 patients, and it must be identified and diagnosed early. Smoking and malignancy may be risk predictors, but further research is needed. Patients with VTE, on the other hand, had a considerably higher D-dimer, as well as more morbidity and mortality.

Declarations:

Ethical considerations: This paper is approved by the ethical committee in King Fahd Hospital.

Consent of publications: Not applicable.

Availability of data: All the data are recorded in the hospital database and not permitted to be shared.

Conflict of interest: We have no conflict of interest to be declared.

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الخصائص السريرية للأنضمام الخثارى الوريدى فى مرضى كوفيد-١٩ المقبولين فى وحدة العناية المركزة

مقدمة: تم ربط كوفيد-١٩ بعدد من الأمراض منها الجلطات الدموية والوريدية ومع ذلك يختلف معدل حدوث هذا الاضطراب والخصائص السريرية ولا توجد تنبؤات محددة للمخاطر معترف بها.

الهدف من الدراسة: كان الهدف من هذه الدراسة هو معرفى مدى شيوع الجلطات الدموية الوريدية فى مرضى كوفيد-١٩ بالإضافة إلى الخصائص السريرية والمخاطر والنتائج.

الطرق: دراسة جماعية بأثر رجعى تقارن البيانات المسجلة لمجموعتين من المرضى والمجموعة الأولى تعانى من إصابة مؤكدة بالكوفيد-١٩ ومن ثم تم قبولها فى وحدة العناية المركزة خلال ستة أشهر والمجموعة الثانية غير مؤكدة.

النتائج: كان النوع الأكثر شيوعاً من التجلط الخثارى الوريدى هو التجلط الرئوى والذى يمثل ٦٨ مريضاً ويليه تجلط أوردة الساق وكان التدخين والسرطان أكثر شيوعاً فى المرضى المصابة بالتخثرات.

الخلاصة: التخثرات والجلطات هى مشكلة منتشرة بين الأفراد المصابة بكوفيد-١٩ مع ارتفاع معدل المرضى والوفيات.