Clinical Characteristics of Venous Thromboembolism in COVID-19 Patients Admitted to intensive care unit

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Abstract

Introduction: COVID-19 infection was associated with many morbid conditions, one of which is venous thromboembolism; however, this is varied in incidence and clinical characteristics, with no known definite risk predictors.

Aim: To identify the incidence, clinical characteristics, and risks and outcome of venous thromboembolism in COVID-19 patients.

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 incidence of venous thromboembolism was 30%, where pulmonary embolism (PE) alone was the most frequent type (68.2%), followed by, DVT with PE (15.1%), DVT alone (12.1%), cavernous sinus thrombosis alone CST (3%) and the least frequency was CST with renal artery thrombi (1.5%). Smoking and malignancy were more frequent in VTE group with more statistically significant elevation of D dimer. the pulmonary embolism was lobar in the majority of our patients (69.6%), followed by segmental (17.9%), while the least frequency was for massive pulmonary embolism (12.5%).

Conclusion: VTE is a common event in COVID-19 patients, where smoking and malignancy more frequent, D dimer is significantly elevated, and more morbidity and mortality in those patients.

Introduction

No doubt, that COVID-19 pandemic led to major morbidity and mortality all over the world [1–3]. One of these serious morbid conditions, that is a major cause of death, is the thromboembolic pathogenesis[4–6], which, reported to be associated with it, especially in patients admitted to intensive care unit and those exposed to mechanical ventilations[7]. Till now is not yet known, the true prevalence of venous thromboembolism(VTE) in COVID-19 patients, noting that the few studies to date have shown a frequency ranging from 7–30%, with that range largely explained by variable testing, the severity of patient illness, and comorbidity[8–11]. More over the clinical characteristics was varied from place to place, and even in the same country from time to time [12]. More interesting that these thromboembolic manifestations still occur after the introductions for the protocols using thromboembolic prophylaxis as main line of managements in confirmed COVID-19 patients [13–15]. Do those patients with VTE, have different clinical characteristics from those who have not VTH among the patient with confirmed COVID-19, apart from high level of D-dimer? This study try to answer it regarding our Centre.

Aim of the study

To identify the incidence, clinical characteristics, risks and outcome of venous thromboembolism in COVID-19 patients in our intensive care unit.

Subjects and Methods

this study is a retrospective cohort study comparing the recorded data for two groups of patients with confirmed COVID-19 infection and admitted to the ICU in King Fahd Hospital during 6 months duration from 1 April to 30 September 2020. The first group (66) patients who developed VTE and the second group (220) patients did not develop VTE.

The diagnosis of COVID-19 was confirmed by a positive real-time reverse transcriptase polymerase-chain-reaction test of SARS-CoV-2 on nasal and pharyngeal swab specimens from the patients. The severity of COVID-19 infection according to ACEP2020, divided patient condition into: Mild low risk, Mild at risk, Moderate, Severe and Critical.

Computed tomography pulmonary artery (CTPA) examinations were performed on a 128 slice multi-detector CT scanners (Philips Ingenuity Core128, Philips Medical Systems) by using a standard CTPA protocol done for all patients. Diagnosis of PE was performed by an expert radiologist based on direct visualization of the endoluminal thrombus in the pulmonary arteries. In order to provide a quantitative assessment of the magnitude of the embolism, the pulmonary artery obstruction index (PAOI) was calculated according to the formula proposed by Qanadli et al[16], and classified PE into massive, lobar, segmental and sub segmental. Duppler ultrasound for both lower limbs by Sonoview Full Digital Imaging Ultrasound Scanner: done for all patient for assessing lower limb deep venous thrombosis. CT brain (venous and arterial) phase done for two patients for assessing cavernous sinus thrombosis.

Follow up were done for all the patients to know the prognosis of the disease cured or died (from 17–41) days.

Statistical analysis

Analysis, using SPSS version 21 was performed with respect to 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 Chi square test for the categorical variables. The level of significance was accepted at $p \leq 0.05$.

Results

In **(Table 1)**, the study conducted on (286) COVID 19 confirmed patients, admitted in intensive care unit; divided into two groups: VTE group(66) patients, has male /female38/28, with main age ± SD (47 ± 13), and non VTE group(220) patients, has male /female130/90 with main age ± SD (46 ± 11), although most of the patients were males, no statistical significant differences between the two groups; although the percentage of non smokers, mild smokers, moderate smokers were slightly higher in non-VTE group (11%, 30% and 28% Vs. 10.6%, 28.8%, and 27.7% respectively), with higher percentage for heavy smokers in VTE group (33.4% Vs. 31%), there were no significant differences between the two groups.

Table 2 shows the comorbid conditions in the 2 groups; it shows that hypertension, DM, IHD, CVA, rheumatoid arthritis and SLE, were more prevalent in non-VTE group (78%, 73%, 82%, 6.3%, 6.3%, and 5.4% Vs. 76%, 71%, 79%, 4.5%, 4.5%, and 3% respectively); while only malignancy was more in VTE group (11% Vs. 10%). However, there were no statistical significant differences between the two groups in all the comorbid conditions.

Table 3 shows that there were no significant differences in the two groups regarding the laboratories finding, except for D dimer, which was significantly higher in VTE group. Nevertheless, WBC, eosinophils, ESR, ferritin, urea and creatinine were slightly higher in VTE group; while hemoglobin, lymphocytes, platelets and ALT were slightly higher in non-VTE group.

Table 4 shows that all our patients in the 2 groups were categorized according to ACEP 2020, as severe or critically ill patients, with no statistical differences between the 2 groups; but patients in non VTE group were more managed with oxygen mask and non-invasive ventillations (33.6% and 38.2% Vs. 24.2% and 25.7, respectively) with significantly statistic difference. Meanwhile, the patients in the VTE group more significantly managed with mechanical ventillations (50.1%, Vs. 28.2%) with P value less than 0.001. the table also shows that survivors in non VTE groups were significantly more than non VTE group (69.6% Vs. 54.6%), while the deaths were significantly more in VTE group, compared to deaths in non-VTE group (45.4% Vs. 30.4%) with P value less than 0.001.

Table 5 shows that, pulmonary embolism (PE) alone was the most frequent type (68.2%), followed by, DVT with PE (15.1%), DVT alone (12.1%), cavernous sinus thrombosis alone CST (3%) and the least frequency was CST with renal artery thrombi (1.5%).

Table 6 shows that according to Qanadli et al, the pulmonary embolism was lobar in the majority of our patients (69.6%), followed by segmental (17.9%), while the least frequency was for massive pulmonary embolism (12.5%).

Discussion

this study revised the data for 66 patients with COVID-19 complicated by VTE, and 220 patients with the same infection and in the same place and period but without VTE; we compared the two groups to study the incidence of VTE, and clinical characteristics and risks for developing this complication. Since the repots for pulmonary embolism in post mortems autopsies', many searches reported the co-incidences of VTE with COVID-19 infections, especially pulmonary embolism. However, in spite of many suggested probable mechanisms for these relationships, the true pathogenic mechanisms and incidences are not settled, and have not high evidences due to absence of large prospective studies. In our study, among the total 352 patients who admitted to the ICU, the incidence of VTE was 18.75% (66 patients), where pulmonary embolism alone was the most common (15.7%), which is higher than what reported in previous study (11.6%) in Saudi Arabia[17] ; this may be explained that all our patients are categorized as severely and/or critically ill; it is also higher than some studies[18-20] which, used retrospective data and

reported the incidence of positive patients regardless the severity of their cases and with short follow-up duration. However, it is lower than, retrospective studies in western countries [21,22] used CTA imaging as we did and their incidences ranged from 23%-30% . Nevertheless, our incidence is consistent with Beun et al.[23] who reported that the incidence for positive COVID-19 patients in ICU is 26.6%. The other important finding in our study, that only 19.2% of the pulmonary embolism were accompanied by DVT, while in most of our cases, we did not find source for the pulmonary embolism; this incidence of DVT, is far low from what reported, in autopsies of patients with COVID-19 in German study[24] , where those patient was not clinically suspected to have DVT before death. Although autopsies considered more expressing, for the true incidence for DVT, we cannot rely on this, being the source for pulmonary embolism in COVID patients, as many reports suggest that, the pulmonary embolism in those patients, in fact is a pulmonary thrombosis, which can be explained due to hypercoagulable state in those patients[25] , this is evident by high level of D-dimer, which was significantly high, in our study, compared to patients without VTE. Another evidence in our study for the local pathogenic factors, that about 87.9% had the pulmonary thrombosis at the site of consolidation, where the local inflammatory process is more evident; this also consistent with other searches [26]. Moreover, Thachil J, and Srivastava A., postulated that pulmonary thrombosis in COVID-19 patients has two phenotypes, one of them is pulmonary microthrombosis[27]; these also explained by others as due to viral factors and endothelial dysfunction[28-30] . in our study also, 3 of our patients had CST, where one of them had renal artery thrombosis, however these complications are not common in patients with COVID-19, and although supported by the hypercoagulability state, still local predisposing factors are questionable in those patients; nevertheless, the superior sagittal sinuses were the place of the thrombosis in our cases, which reported to be the most common site in patients with COVID-19 and cerebrovascular thrombosis[31] . regarding renal artery thrombosis, also few studies reported this complication[32-33] , however, our patient had normal renal function at the time of diagnosis, and no comorbid condition except type 2 DM, while some reports suggesting that renal impairment in COVID-19 patients may be attributed to renal artery micro- thrombosis[33-34]. Regarding socio-demographic data and comorbid conditions, there were no statistical differences between those who had VTE and other group without VTE, in our study, so we cannot conclude that there is specific risk predictor for such events; even the initial laboratory findings, except for significant increase in D-dimer, in the thrombotic group. The elevation of D-dimer in COVID-19 patient is documented in many studies with incidences more than 50% and being higher in critical cases [35-36], and in one study concluded that being more than 1 μg/mL is a risk factor for death [37]. Finally, in our study, VTE group had more significant incidence, for mechanical ventilation, and significantly more death rate than non-VTE group; this relationship may be both cause and effect, as patients with VTE specially pulmonary embolism may lead to respiratory failure and need mechanical ventilation, in the same time patients on mechanical ventilations are more prone to venous thrombosis, which explain high mortality rate in COVID-19 managed by Mechanical ventilation[38-39] .

Conclusion

VTE is a common complications in COVID-19 patients, not only the pulmonary embolism, and have to be suspected and early diagnosed, smoking and malignancy may be a probable risk predictors but need more larger studies. However, those patients with VTE significantly have much higher D-dimer, more morbidity and mortality.

Declarations

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

Consent of publications: not applicable

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

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

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Abbreviations

Cavernous Sinus Thrombosis (CST)

Computed tomography pulmonary artery (CTPA)

Pulmonary Artery Obstruction Index (PAOI)

Pulmonary Embolism (PE)

Venous Thromboembolism (VTE)

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Tables

Table (1): personal characteristics and smoking status in the two groups

Variable	VTE Group NO. 66		Non VTE Group No. 220		X2	P value
Age	47 ±13		46 ± 11		0.89	0.154
BMI	29 ± 13		28± 12		0.9	0.12
male	38	58%	130	59%	1.4	0.21
female	28	42%	90	41%	0.19	0.14
Non smoker	7	10.6%	24	11%	1.24	2.14
Mild smoker	19	28.8%	66	30%	2.01	1.25
Moderate smoker	18	27.2%	62	28%	0.35	1.58
Heavy smoker	22	33.4%	68	31%	1.02	0.687

Table (2): comorbid conditions in the two groups

Comorbid condition	VTE Group NO. 66		Non VTE Group No. 220		X2	P value
HTN	50	76%	171	78%	1.51	2.64
DM	47	71%	161	73%	1.61	1.25
IHD	52	79%	180	82%	1.9	1.58
CVA	3	4.5%	14	6.3%	1.5	0.687
Malignancy	7	11%	22	10%	2.4	2.51
Rh. arthritis	3	4.5%	14	6.3%	2.67	2.7
SLE	2	3%	12	5.4%	1.87	1.89

Table (3) some laboratories parameters between the two groups:

p	r	Non VTE group(220)	VTE group(66)	
1.98	1.2	11 ± 4	12.5± 8	WBC
2.54	1.7	14 ± 3	13 ± 2	hemoglobin
1.48	0.9	304 ± 20	203± 21	platelets
2.01	2.0	295 ± 16	320 ± 14	Eosinophil count
1.54	1.7	65 ± 5	50 ± 8	Lymphocyte count
2.54	1.54	51 ± 7	42± 6	Monocyte count
1.87	2.01	12 ± 6	14 ± 4	Urea
2.87	1.36	121 ± 20	125± 23	Creatinine
1.34	1.98	32 ± 6	43 ± 8	AST
2.047	1.45	50 ± 12	45 ± 11	ALT
2.39	2.01	9 ± 2	11± 3	T.BIL
1.98	1.74	0.7± 1	0.9 ±0.8	D.BIL
1.35	0.214	60 ± 9	55 ± 12	T. protein
2.05	0.98	28 ± 6	25 ± 7	Albumin
0.00**	3.21	1 ± 1	3 ± 1	D dimer
1.89	1.25	64 ± 13	75± 14	ESR
2.54	1.6	220± 9	275 ± 12	Ferritin

Table (4): COVID-19 severity, source of oxygen, and outcomes in the two groups

COVID-19 severity	No.	%	No.	%		P value
severe	20	30%	63	28.7%	2.84	2.95
critical	46	69.6%	157	71.3%	2.54	2.74
Source of oxygen therapy						
Oxygen mask	16	24.2%	74	33.6%	-4.5	0.001**
Non-invasive ventilation	17	25.7%	84	38.2%	6.7	0.00**
Mechanical ventilation	33	50.1%	62	28.2%	5.3	0.001**
Outcomes						
survivors	36	54.6%	153	69.6%	11.4	0.001**
Deaths	30	45.4%	67	30.4%	6.6	0.001**

Table (5) the different types and frequencies of VTE

The type	No.	% out of 66	% out of 286
DVT alone	8	12.1	2.8
PE alone	45	68.2	15.7
DVT and PE	10	15.2	3.5
CST alone	2	3	0.7
CST with renal artery thrombi	1	1.5	0.35

Table (6) Degree of PE among VTE group

Degree of PE	No. 56	%
Massive	7	12.5%
Lobar	39	69.6%
Segmental	10	17.9%