Incidence of Deep Venous Thrombosis in Recently Diagnosed Mild and Moderate Cases Of COVID-19 Patients

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KEYWORDS

Coronavirus disease 2019, venous thromboembolism, deep vein thrombosis

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is an infectious viral respiratory disease that is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and may lead to venous thromboembolism (VTE) due to vascular endothelium dysfunction, hyper-inflammatory immune response and hypercoagulability.

Objectives: The aim of our study is to detect the incidence of lower limbs DVT on early presentation of mild and moderate COVID-19 cases and the practicability of Duplex ultrasound screening for DVT in these cases.

Methods: We performed a prospective cohort study that included one-hundred-eighty mild and moderate COVID-19 patients by non- random sampling of patients who have been presented at our authorized hospitals. Study cases underwent clinical assessment for signs of DVT including calculation of the two level DVT Wells score. Regardless the symptoms and Wells score; all included patients were subjected to bilateral lower limb venous duplex examination from external iliac to tibial veins. D-dimer levels have been recorded. Another confirmatory Duplex study was performed within one week from the first duplex to safely exclude DVT in the patients who had first normal venous duplex.

Results: Our study included 121 male patients and 59 female patients. The mean age of the study population was 25.475±6.030. The diagnosis of DVT depending on bilateral lower limbs venous duplex study in our study was confirmed in seventeen patients denoting an incidence of 9.4%; nine patients were diagnosed as distal DVT representing 52.94% of the DVT cases while proximal DVT was present in eight patients. The DVT was unilateral in all of the seventeen cases. The level of D-dimer in our study population (measured in ng/ml) ranged from 185 – 1347 with a mean of 497.85 ± 209.82. In the DVT cases group The D-dimer levels ranged from 788-1347 ng/ml with a mean of 1027.24 ± 136.71 (P-value < 0.001).

Conclusion: The incidence of lower limb DVT in mild and moderate COVID-19 patients included in our study was 9.4% concluding that COVID-19 can be considered as a risk factor for DVT even in non-critically ill COVID-19 patients. Lower limb venous duplex study might be considered in COVID-19 patients depending on Wells score and D-dimer level as a predictive model for DVT in those patients. Confirmed COVID-19 diagnosis could be included in VTE prediction score risk assessment systems.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the cause of the infectious Coronavirus disease 2019 (COVID-19), that has resulted in a major hazard to global health **(1).**

The outbreak was first revealed in Wuhan city in China, in December 2019. On January 30, 2020, it was deemed a public health emergency of international significance, and on March 11, 2020, it was officially identified as a pandemic **(2).**

Venous thromboembolic disease was reported as one of the major complications that may occur in COVID-19 patients **(3).** COVID-19 may lead to VTE due to dysfunction of vascular endothelium, hyper-inflammatory immune response and hypercoagulability **(4).**

Data reported from the initial autopsies shows that non-suspected pulmonary embolism or DVT could account for 58% of deaths and for 33% was the main cause of death **(5).**

However, the main cause of clinical deterioration and death among hospitalized patients is not clearly proved whether to be due to venous thromboembolic events or due to complications induced by the severe pneumonia and inflammatory responses. Therefore, it is believed that efforts should also focus on the non-critically ill mild and moderate cases of COVID-19 patients to help in the

prevention of the thromboembolic complications.

The objective of our study is to detect the incidence of DVT on early presentation of mild and moderate COVID-19 cases and the practicability of Duplex ultrasound screening for DVT in these cases.

2. Methodology

According to the approved standards to the ethical committee of Ain Shams University we performed our prospective cohort study that has been conducted at Ain Shams University hospitals and Ahmed Maher teaching hospital.

The study included 180 COVID-19 patients by non- random sampling of patients who have been presented at our authorized hospitals during the period from November 2021 to the end of March 2023.

The following criteria were applied on the patients:

Inclusion Criteria:

Mild and moderate COVID-19 patients who have been recently diagnosed (within 48 hours) by PCR or highly suspected according to chest CT (CO-RADS 4 or higher) and patients who accepted to be included in the study.

Exclusion Criteria:

Patients with history of recurrent DVT, patients who have already been on therapeutic anticoagulation, patients younger than 16 years old, patients with history of malignancy, severe and critically ill COVID-19 patients and patients who refused to provide informed consent.

Suspected COVID-19 patients underwent clinical examination and laboratory testing including blood cell count, C-reactive protein (CRP) and serum ferritin as a part of COVID-19 diagnostic work up, D-dimer levels have been recorded and discussed in study results. The diagnosis of COVID-19 has been confirmed using polymerase chain reaction (PCR) testing of nasopharyngeal specimens or by chest CT (using Siemens SOMATOM definition AS system) according to COVID-19 reporting and data system (CO-RADS) classification.

Table (1): Summary of CO-RADS Classifications and the Matching Level of Suspicion for lung Involvement in COVID-19 cases [(6)].

CO-RADS Category	Level of Suspicion for Pulmonary Involvement of COVID-19	Summary
0	Not interpretable	Scan technically insufficient for assigning a score
1	Very low	Normal or noninfectious
2	Low	Typical for other infection but not COVID-19
3	Equivocal/unsure	Features compatible with COVID-19 but also other diseases
4	High	Suspicious for COVID-19
5	Very high	Typical for COVID-19
6	Proven	RT-PCR positive for SARS-CoV-2

Note.—CO-RADS = COVID-19 Reporting and Data System, COVID-19 = coronavirus disease 2019, RT-PCR = reverse transcription-polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Case severity assessment was done according to the Egyptian ministry of health and population COVID-19 management protocol, according to the protocol mild COVID-19 cases were considered when the patients suffered at presentation from mild COVID-19 symptoms (including fever, loss of taste or smell and respiratory symptoms with normal SpO2) and normal CT imaging. Positive chest CT findings while SpO2 not less than 92% on room air categorized the study patient as moderate case. Demographic, clinical, and laboratory results have been recorded and assessing activities of daily living in study patients was done according to Barthel index.

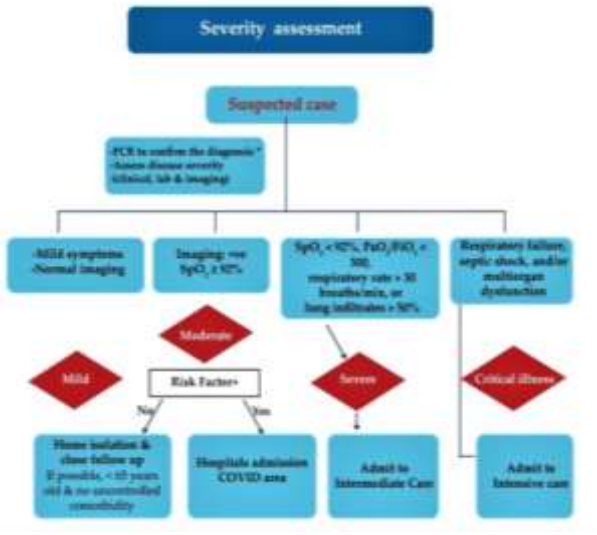

Fig. (1): The Egyptian ministry of health and population COVID-19 protocol (September 2021).

Table (2): Barthel index activity [7].

Barthel Index Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc. or requires modified diet 10 = independent	
BATHING 0 = dependent 5 = independent (or in shower)	
GROOMING 0 = needs help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	
DRESSING 0 = dependent 5 = needs help, but can to about half unaided 10 = independent (including, buttons, zips, laces, etc.	
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	

Included patients underwent clinical assessment for signs of DVT and the two level DVT Wells score has been calculated. Regardless the symptoms and Wells score; all study included patients underwent bilateral lower limb venous duplex examination from external iliac to tibial veins.

Table (3): Two level DVT Wells score [8].

Clinical Feature	Points
Active cancer (on treatment, treated in the last 6 months or palliative)	1
Paralysis, paresis or plaster immobilisation of the lower limb	1
Bedridden for 3 days or more, or major surgery in the past 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf Swelling 3 cm larger than the symptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previous DVT	1
Alternative diagnosis is at least as likely as DVT	-2
Clinical probability simplified score	Points
DVT likely	2 points or more
DVT unlikely	1 point or less

Using the Mindray DC-N2 ultrasound system, the lower limb deep veins were examined using compression with the Mindray 75L38EA (5-10 MHz) linear transducer on B mode at 2-cm intervals.

Color Doppler flow was used to detect luminal filling defects, and Doppler tracings to detect spontaneous flow and phasicity.

The diagnosis of DVT has been established according to the presence of at least two from the following ultrasound criteria: Loss of normal vein compressibility, intraluminal venous thrombus visualization, loss of spontaneous phasic venous flow, the absence of venous flow augmentation and an increase in the diameter of the examined vein ***(9)*.**

In order to safely rule out DVT, patients who had a normal initial were subjected to a second confirmatory duplex study within seven days of the first duplex scan.

3. Results and Discussion

This study was conducted on one-hundred-eighty mild and moderate cases of COVID-19 patients fulfilling the previously mentioned inclusion criteria.

According the COVID-19 severity and the final venous duplex result the study populations have been projected to two separate comparisons ; the first between mild COVID-19 cases (Group A) and the moderate COVID-19 cases (Group B), the second between the DVT cases (Group I) and non-DVT cases (Group II).

The study results included mean patients age, sex, comorbidities including type 2 diabetes mellitus, hypertension and smoking history D-dimer levels, site and laterality of DVT, Wells score and Barthel index and for study groups' cases.

The primary end-point was the incident diagnosis of lower limb DVT depending on lower limb venous duplex study.

The study population included 121 male patients and 59 female patients representing 67.2 % and 32.8% of the whole study population respectively.

The age of the studied population ranged from 18-77 years with a mean of 25.475±6.030.

The study revealed that 25% of the patients were known as type 2 diabetes mellitus patients, 32.8% were hypertensive and 47.8% were smokers (Table 4).

Table (4): Comorbidities of the study population

Co-morbidities		**Total no.=180**
Type 2 diabetes	Diabetic	45 (25%)
Hypertension	Hypertensive	59 (32.8%)
Smoking	Smoker	86 (47.8%)

The application of the Egyptian ministry of health and population COVID-19 management protocol on our study patients to assess COVID-19 severity revealed that 83 patients were mild COVID-19 cases (Group A) and 97 were moderate cases (Group B), representing 46.1 % and 53.9% of the whole study cases respectively.

Activities assessment of daily living in study patients according to Barthel index revealed that Barthel score ranged from 85-100 with a mean of 98.72 ± 3.67.

Clinical examination and recording of Wells pretest probability of DVT score for the study population revealed that Wells score ranged from 0-4 with a median of 1 and interquartile range (IQR) 0-1.

According to the two level DVT Wells score: DVT was likely in 8 patients representing 4.4 % of all cases and unlikely in 172 patients representing 95.6% of the study population.

The level of D-dimer in our study population (measured in ng/ml) ranged from 185 – 1347 with a mean of 497.85 ± 209.82.

The diagnosis of DVT depending on bilateral lower limbs venous duplex study in our study was confirmed in 17 patients denoting an incidence of 9.4%, 9 patients were diagnosed as distal DVT representing 52.94% of the DVT cases (Group I) and 8 patients diagnosed as proximal DVT representing 47.06% of Group I. The DVT was unilateral in all the 17 cases.

The whole study cases were divided according to COVID-19 severity into Group (A) including 83 mild COVID-19 cases and Group (B) including 97 moderate cases.

62 male patients were included in Group (A) representing 74.7% of the group cases and 21 females representing 25.3% of group (A) cases.

Group (B) included 59 males representing 60.8% of the group cases.

In group (A) the age ranged from 18-70 with a mean of 34.99 ± 11.9 while in group (B) cases ranged from 19-77 with a mean of 49.34 ± 13.02 (P-value < 0.001)

Venous duplex study in mild COVID-19 cases (group A) resulted in 4 DVT patients representing 4.8% of group (A) cases, 3 out of these cases were distal DVT and one proximal DVT. Group (B) included 13 DVT patients representing 13.4% of group B cases, 6 out of these DVT patients were distal DVT and 7 were proximal DVT (Table 5).

Table (5): venous duplex results in groups A & B

	COVID-19 severity		**Test-value**	**P-value**	**Sig.**
	Mild (Group A)	**Moderate (Group B)**			
	No.=83	**No.=97**			
DVT	4 (4.8%)	13 (13.4%)	3.852*	0.050	S

venous Duplex	Normal	79 (95.2%)	84 (86.6%)	4.592*	0.101	NS
	Unilateral distal DVT	3 (3.6%)	6 (6.2%)			
	Unilateral proximal DVT	1 (1.2%)	7 (7.2%)			

*: Chi-square test

The D-dimer levels (ng/ml) ranged from 185-1012 in group (A) and from 200-1347 in group (B), with a mean of 436.13 ± 158.69 in group (A) and 550.66 ± 233.38 in group (B) (P-value <0.001) (table 6 & Figure 2).

Table (6): D-dimer levels in groups A & B

		COVID-19 severity		**Test-value**	**P-value**	**Sig.**
		Mild (Group A)	**Moderate (Group B)**			
		No.=83	**No.=97**			
D-dimer (ng/ml)	Mean±SD	436.13 ± 158.69	550.66 ± 233.38	-3.784•	<0.001	HS
	Range	185 – 1012	200 – 1347			

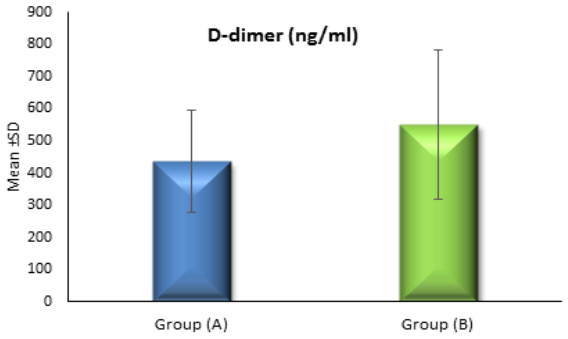

Fig. (2): Relation of COVID-19 severity with D-dimer levels

The whole study cases were subjected to another comparison depending on the diagnosis of DVT, where group (I) includes DVT cases and group (II) includes non-DVT cases.

Twelve male patients were included in Group (I) representing 70.6% of the group cases.

109 males and 54 females made comprised Group (II), accounting for 66.9% and 33.1% of the cases in Group (II), respectively.

In Group (I) the age ranged from 29-65 with a mean of 49.09 ± 9.92 while in group (II) cases ranged from 18-77 with a mean of 42.06 ± 14.65 (P-value 0.056).

Group (I) included 4 mild COVID-19 cases and 13 moderate cases representing 23.5% and 76.5% of the group cases respectively. 79 mild COVID-19 cases and 84 moderate cases were included in group (II) representing 48.5% and 51.5% of group (II) respectively (Table 7).

Wells pretest probability of DVT score ranged from 0-4 in group (I) with a median of 1 and interquartile range (IQR) 1-3, denoting that DVT is likely in 8 patients and unlikely in 9 patients representing 47.1% and 52.9% of group (I) cases.

Wells score ranged from 0-1 in group (II) denoting unlikely DVT probability in all group (II) cases. (Figures 3,4, Table 8).

(7): COVID-19 severity in groups I & II

		Non-DVT (Group II)	DVT (Group I)	Test-value	P-value	Sig.
		No.=163	No.=17			
COVID-19 severity	Mild	79 (48.5%)	4 (23.5%)	3.852*	0.050	S
	Moderate	84 (51.5%)	13 (76.5%)			

*: Chi-square test

Table (8): Wells score in groups (I & II)

		Non-DVT (Group II)	DVT (Group I)	Test-value	P-value	Sig.
		No.=163	No.=17			
Wells score	Median(IQR)	0 (0 - 1)	1 (1 - 3)	-5.349‡	<0.001	HS
	Range	0 – 1	0 – 4			
Wells score	Unlikely	163 (100%)	9 (52.9%)	80.274*	<0.001	HS
	Likely	0 (0%)	8 (47.1%)			

*: Chi-square test; ‡: Mann-Whitney test

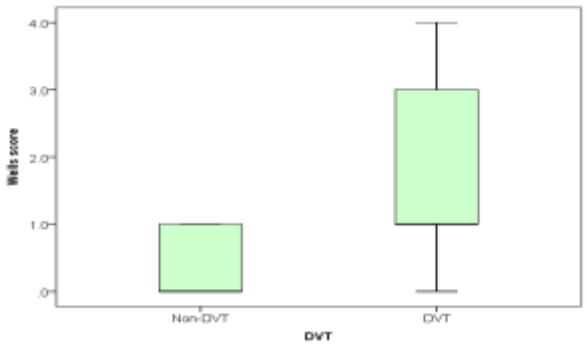

Fig. (3): Wells score in DVT (I) and Non-DVT groups (II)

The D-dimer levels (ng/ml) ranged from 788-1347 in group (I) and from 185-780 in group (II), with a mean of 1027.24 ± 136.71 in group (I) and 442.64 ± 119.67 in group (II) (P-value <0.001) (Table 9 & Figure 4).

Table (9): D-dimer levels in Groups (I) & (II)

		Non-DVT (Group II)	DVT (Group I)	Test-value	P-value	Sig.
		No.=163	No.=17			
D-dimer (ng/ml)	Mean±SD	442.64 ± 119.67	1027.24 ± 136.71	-18.909•	<0.001	HS
	Range	185 – 780	788 – 1347			

•: Independent t-test

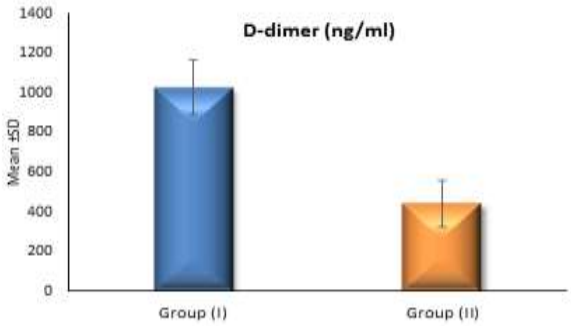

Fig. (4): D-dimer levels in Groups (I) & (II)

DISCUSSION

Our study is a prospective cohort study that was conducted on one-hundred-eighty mild and moderate cases of COVID-19, The diagnosis of DVT depending on bilateral lower limbs venous duplex study was confirmed in 17 patients denoting an incidence of 9.4%, 9 patients were diagnosed as distal DVT representing 52.94% of the DVT cases and 8 patients diagnosed as proximal DVT representing 47.06% of the DVT cases. The DVT was unilateral in all the 17 cases; Wells pretest probability revealed that DVT was likely in 8 patients and unlikely in 9 (denoting a sensitivity of 47.05 %).Our study revealed that the D-dimer levels ranged from 788-1347 ng/ml in the DVT group with a median of 1027.24 ± 136.71, and ranged from 185-780 in the Non-DVT group (a median of 442.64 ± 119.67).

Several studies focused on detecting DVT in non-critically ill COVID-19 patients as VTE is considered a major preventable complication of COVID-19.

Table (10): Prospective studies that focused on detecting DVT in non-critically ill COVID-19 patients.

Researcher	**Study year**	**Patients (n.)**	**Incidence of DVT**	**Site of DVT**	**Symptomatic DVT (out of DVT cases)**
Our study	2022-2023	180	9.4%	52.94% distal DVT	47.1%
Pieralli F.	2021	227	13.7%	54.7% distal DVT	6%
Demelo-Rodriguez	2020	156	14.7%	95.6% distal DVT	The study was limited to asymptomatic cases
Santoliquido A.	2020	84	11.9%	80% distal DVT	20%
Jimenez-guiu X.	2020	57	10.5%	83.3% distal DVT	16.6%

Jimenez-Guiu et al. introduced a prospective cohort study that was performed on Non-ICU COVID-19 patients revealing that 6 patients confirmed to have lower limb DVT out of 57 examined patients denoting an incidence of 10.5%.They used Wells score as a clinical pretest probability of DVT, according to which DVT was unlikely for 98.2% of the patients and likely for 1.8% of patients. Five out of the six patients with DVT had an unlikely Wells score and one had a likely Wells score. The DVT was asymptomatic in five patients, only one patient who complained from painful calf region

and had a leg swelling in the previous day of presentation. According to their study results five patients were diagnosed to have distal DVT representing 83.3% of the DVT cases, and one patient diagnosed as proximal DVT (16.7%) (9).

Angelo Santoliquido et al. performed a systematic screening to diagnose DVT by lower limb venous duplex in successive non-ICU hospitalized COVID-19 patients, regardless the presence of DVT signs or symptoms. DVT was confirmed in 10 patients, representing an incidence of 11.9%. Distal DVT was present in 8 patients, with an incidence rate of 9.5%. Proximal DVT was confirmed in two patients denoting an incidence of 2.4%, regarding the laterality; DVT was bilateral in four cases and unilateral in six cases. Symptomatic DVT was present only in 2 out of the 10 patients with DVT. A D-dimer level higher than 1500 ng/ml was present in 80% of the DVT patients in their study (10).

Their results are consistent with those of Demelo-Rodriguez et al, who reported an incidence of DVT of 14.7% among 156 non-ICU hospitalized COVID-19 patients.

Out of 23 DVT patients; one case was proximal DVT and bilateral DVT was found in seven patients. According to Demelo-Rodriguez et al D-dimer levels more than 1570ng/ml were associated with higher incidence of asymptomatic DVT (11).

Pieralli et al. performed a prospective multicenter study including 227 non-ICU COVID-19 patients, a surveillance protocol with lower limb venous duplex revealed an overall DVT incidence of 13.7%(6.2% proximal DVT and 7.5% distal DVT) and 94% of the DVT cases were asymptomatic only 6 % complained from leg swelling and painful calf. D-dimer levels revealed a median of 2349 ng/mL in the DVT cases (12).

Many studies also included ICU admitted COVID-19 patients in addition to other severity categories of the disease. Researchers from all over the world focused on studying the incidence of VTE in COVID-19 patients; Kampouri et al. published a retrospective study in Switzerland including 491 that revealed VTE incidence of 9.3%, Tasplin et al. introduced another retrospective study on 168 COVID-19 patients and the incidence of VTE was 6.5% (13, 14).

Larger sample size was included in the retrospective study that was performed by Spyropoulos et al. including 9407 patients, their results revealed VTE incidence of 2.9% (15).

Higher VTE incidence was detected by Freund et al. that performed a retrospective study including 974 COVID-19 patients with VTE incidence of 15% among them (16).

Cui et al. published a retrospective study including 81 severe COVID-19 patients whom had been admitted to ICU, their results revealed that the incidence of VTE was 25% among that study group (17).

A multicenter study in Netherlands included 184 severe COVID-19 patients, the overall incidence of VTE in their study group was 27% (18).

A study performed by Middeldorp et al. revealed that the incidences of VTE among ICU admitted COVID-19 patients and ward admitted patients were 28% and 3.3% respectively (19).

Being suspected as a major cause of mortality in COVID-19 patients; VTE in COVID-19 patients was a topic that had been discussed by several meta-analytic studies. Longchamp et al. performed a systematic review and meta-analysis depending on data from 33 studies including a number of 4009 patients. Their meta-analysis that included hospitalized COVID-19 in both medical wards and/or intensive care units revealed that the overall incidence of proximal lower limb DVT was 3% and regarding pulmonary embolism the incidence was 8%. In critically ill COVID-19 patients whom had been admitted to ICU the incidence of proximal DVT was 8% and 17% that is much higher compared to general wards admitted COVID-19 patients who had a VTE incidence of 2% (20).

Longchamp et al suspected that the higher incidence of VTE in ICU admitted COVID-19 patients compared to other ICU patients may be due to specific factors in these patients such as prolonged

immobility and the frequent use of muscle relaxant in COVID-19 patients with acute respiratory distress syndrome (ARDS). That is in addition to COVID-19 associated coagulopathy pathological mechanisms including; vascular endothelial cell dysfunction, hyper-inflammatory immune response and hypercoagulability (21).

Nopp et al. have published a large meta-analysis that included 66 studies with a total number of 28,193 patients. They estimated an overall VTE incidence of 14.1% in hospitalized COVID-19 patients but they did not differentiate between distal and proximal DVT in their results (22).

Other meta-analytic works revealed higher VTE incidence among COVID-19 hospitalized patients. Porfidia et al. meta-analysis study revealed an overall VTE incidence of 26% including upper limb DVT (23).

Suh et al. introduced a meta-analysis study to detect the incidence of DVT and pulmonary embolism in COVID-19 patients; they included twenty-seven studies with a total number of 3342 patients. According to their results the overall incidence of DVT was 14.8% and the incidence of pulmonary embolism was 16.5%. Regarding the ICU patients; the incidence of DVT was 21.2% and the incidence of pulmonary embolism was 24.7% that was higher compared to non-ICU patients as the incidence of DVT and pulmonary embolism in those patients was 7.4% and 10.5% respectively. DVT was diagnosed in 42.4% of pulmonary embolism patients (24).

4. Conclusion and future scope

The incidence of lower limb DVT in mild and moderate COVID-19 patients included in our study was 9.4% concluding that COVID-19 can be considered as a risk factor for DVT even in non-critically ill COVID-19 patients.

Duplex study of lower limb venous system could be considered in COVID-19 patients depending on Wells score and D-dimer level as a predictive model for DVT in those patients.

Confirmed COVID-19 diagnosis might be included in VTE prediction score risk assessment systems.

Considering our study limitations, we focused only DVT in lower limbs without including upper limbs or other deep venous system thrombosis, confirmation of COVID-19 diagnosis was depending on chest CT according to COVID-19 reporting and data system (CO-RADS) classification in some cases without performing PCR, Larger sample size might have been recommended to determine conclusions drawn from this study.

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