Role of Venous Doppler Ultrasound in Evaluation of the Incidence of Deep Venous Thrombosis (DVT) in Lower Lambs after COVID 19 Infection

Anwaar Ahmed Mubarak[a*], Ahmed Okasha[a], Walid M.Gamal[b], Saeda M. Abd Elwahab[a]

[a]Department of Diagnostic Radiology, Faculty of Medicine, South Valley University , Qena , Egypt

[b]Department of Vascular Surgery, Faculty of Medicine, South Valley University , Qena , Egypt

Abstract

Background: COVID-19-positive patients may present with hypercoagulability and an increased liability to develop deep vein thrombosis (DVT). The preferred imaging technique for detecting the presence of deep vein thrombosis in the lower limb is complete duplex ultrasonography.

Objectives: To estimate the incidence of lower limb deep venous thrombosis (DVT) as a complication of COVID-19 infection among post COVID-19 patients by venous Doppler ultrasound.

Patients and methods: This was a prospective study where fifty patients were followed up for three months after COVID-19 recovery. Lower limb venous Doppler ultrasound was done at Diagnostic and interventional radiology Department after the patients were referred from Vascular Surgery Department.

Results: This prospective study was carried out on 50 patients after COVID-19 recovery. The overall DVT incidence among COVID-19 patients was 6%. After 1 month 96% of cases had no DVT but 4% had DVT (2.0% had right extensive DVT and 2% left femorpopliteal DVT), at 3 month follow up, 94% of cases had no DVT but 6% had DVT (2.0% had right extensive DVT and 4% left femorpopliteal DVT).

Conclusion: The overall DVT incidence among post COVID-19 patients in this study was 6%. Old age and increased D-dimer were significantly associated with COVID-19 severity. Cardiac disorders and obesity were significantly associated with incidence of DVT among COVID-19 patients.

Keywords: COVID 19; Venous Doppler; Ultrasound; DVT; Lower limb.

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Correspondence: drnourahmed1127@gmail.com

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Introduction

COVID 19 that originated in China and subsequently spread all over the world is considered a zoonotic virus and the seventh coronavirus to infect humans and produce a respiratory illness with symptoms that are similar to the common cold **(Bassetti et al., 2020).**

COVID-19 severity can be classified as follows: mild type: radiological examination reveals no abnormalities and just minor symptoms; moderate: fever, cough and other symptoms with CT chest shows pneumonia; severe type: one of the following exists: respiratory distress, arterial oxygen partial pressure/FiO2 of less than 300 mm Hg, or an oxygen saturation on room air at rest of less than 93%. Critical type: at least one of the following needs to be present: an intensive care unit (ICU) is required in cases of respiratory failure, shock, or other organ dysfunction **(Feng et al., 2020).**

In severely ill-COVID-19 patients, thromboembolism and prothrombotic coagulation abnormalities are becoming common complications, and they may lead to morbidity and death **(Suh et al., 2021).**

Doppler ultrasonography makes use of sound waves to see blood flow inside the vessels. Regular ultrasonography employs sound waves to provide pictures of structures inside our body, but it is unable to show blood flow **(Kasban et al., 2015).** The main imaging procedure for suspected DVT is venous compression ultrasonography **(Karande et al., 2016).**

The aim was to estimate the incidence of lower limb deep venous thrombosis (DVT) as a complication of COVID-19 infection among post COVID-19 patients by venous Doppler ultrasound.

Patients and methods

Type of the study: prospective analysis

Study Setting: Diagnostic and Interventional Radiology Department at Qena University Hospital, South Valley University.

Study subjects: Inclusion criteria:-The study included fifty cases after COVID-19 recovery, with diagnosis of COVID-19 infection confirmed by nasopharyngeal swabs and reverse transcription polymerase chain reaction (RT-PCR) or chest computed tomography (CT).

Exclusion criteria:-Pre-existing indication for anticoagulation (e.g., pulmonary embolism or deep vein thrombosis), prolonged recumbency, severely ill patients, also patients with a known history of DVT were excluded.

Methodology*:* The present study was approved by the Ethics Committee, Faculty of Medicine, South Valley University, Qena, Egypt (Ethical approval code is SVU-MED-RAD028-1-22-2-327).

All patients were subjected to the following:

History and Clinical Examination: Complete history taking, which include:- Personal history, present illness, relevant risk factors for lower extremity peripheral venous disease, presence of comorbidity, drug history.

Full Clinical Examination with focus on manifestations of DVT as limb pain, swelling, hotness and discolored skin.

Investigations

-Laboratory:-

•Latex agglutination slide test was performed for qualitative and semiquantitative determination of C-reactive protein in non-diluted serum.

•Erythrocyte sedimentation rate (ESR) was done.

•D-dimer level was measured by immune turbidimetry assay with the coagulational laboratory auto analyzer (ACL 2000; Instrumentation Laboratory, Milan, Italy). D-dimer level was graded in accordance with the level of estimation. Graded as normal level, when < 200 ngm/ml, slight elevation was 200-500 ngm/ml, moderate elevation was 500-1000 ngm/ml and severely elevation was 1000-2000 ngm/ml.

•Serum ferritin.

• Complete blood picture (CBC):- platelet, lymphocyte, hemoglobin, eosinophil, basophil and neutrophil count.

•Nasopharyngeal, and oropharyngeal swabs were collected for COVID-19 (PCR) test.

-Imaging:-X-ray Chest, HRCT Chest: The two most commonly identified pulmonary findings are GGOs and reticular opacities, typically with bilateral, multifocal pattern in a peripheral, sub-pleural, and posterior distribution.

CORADS classification : CORADS 1: normal or non-infectious abnormalities, CORADS2 abnormalities consistent with infections other than COVID19 , CORADS3 unclear whether COVID 19 is present , CORADS4 abnormalities suspicious for COVID19 , CORADS 5 typical COVID 19, CORADS 6 PCR + **(Salehi, S. et al , 2020)**

Venous duplex Ultrasound protocol

The examination was performed after COVID -19 recovery then was repeated for three months. The equipment used was logic S8 (Probe frequency

range-Linear: 9 MHz, Curvilinear: 6-1 MHz), logiq P9 machine (Probe frequency range-Linear: 12-6 MHz, Curvilinear: 5-1 MHz), Logiq P7 (Probe frequency range-Linear: 9 MHz, Curvilinear: 6-1 MHz), SIEMENS machine (Probe frequency range-Linear: 12-4 MHz, Curvilinear: 5-2 MHz). For the femoral and popliteal venous segments as well as the calf veins, linear array transducers were employed. The IVC and iliac veins were assessed using convex transducers.

Technique: Patients were evaluated either seated or when the leg was slightly externally rotated in reverse Trendelenburg position at an angle of around 15 or 20 degrees.

The probe was first placed in the groin region. In both the longitudinal and transverse views, the common femoral and femoral veins were examined. During its ascent to the saphenofemoral junction, the great saphenous vein was visualized. With each recognized venous segment, light compression was used. The spacing between each maneuver was 2 cm. Power Doppler and colour Doppler analysis were performed on each segment.

P-value <0.05 was considered significant. P-value <0.001 was considered as highly significant. P-value >0.05 was considered insignificant.

Results

There was statistically significant difference between the 3 studied groups of corona patients (mild, moderate, severe) regarding age where the mean was 42.6± 3.0, 41.7± 3.8 and 57.3±12.4 respectively (P 0.000**), but there were no significant differences regarding BMI, sex nor smoking.**(Table.1)** .

For the popliteal vein, the probe was positioned behind the knee. Then tibioperoneal trunk, posterior tibial, peroneal and anterior tibial veins were examined .The soleal and gastrocnemius veins were examined near their confluence with the popliteal vein.

The vein was evaluated for the following: Absence or decreased vein compressibility, thrombus inside the vein, static echoes in entire color fill in full expansion of vein, absence of flow on spectral Doppler, lack of flow augmentation, and loss of spontaneous and respiratory phasicity.

Statistical analysis

Version 22.0 of the Statistical Program for Social Science (SPSS) was used to analyze the data. Frequency and percentage were used to express qualitative data, whilst mean and standard deviation (SD) were used to express quantitative data.

Chi-square (X^2) test of significance was performed to compare proportions between two qualitative parameters.

Table1. Demographic data of the studied groups

Variables		Mild n=13	Moderate n=13	Severe n=24	P value
Age		42.6± 3.0	41.7± 3.8	57.3± 12.4	0.000**
BMI		29.0± .83	31.2± 5.1	31.5 ±5.5	0.3
Sex	**Female**	6 (46.2%)	4(30.8%)	14(58.3%)	0.27
	Male	7 (53.8%)	9(69.2%)	10(41.7%)	
Smoking	**Yes**	3 (23.1%)	3 (23.1%)	5 (20.8%)	0.98
	No	10 (76.9%)	10 (76.9%)	19 (79.2%)	

There was statistical significant difference between the 3 groups regarding symptoms where all patients with DVT had limb swelling, limb pain, discolored skin and warm sensation. But those without DVT, 4.3% of them had limb pain and swelling mostly of systemic causes and no one of them had discolored skin or warm sensation. **(Table.2)**

Table 2. Comparison of symptoms between the study groups

Variables		No DVT N=47	right extensive DVT N= 1	left femoropopliteal DVT N= 2	P value
limb pain	yes	2(4.3%)	1(100%)	2(100.0%)	0.000**
	no	45(95.7%)	0	0	

limb swelling	yes	2(4.3%)	1(100%)	2(100.0%)	0.000**
	no	45(95.7%)	0	0	
discolored skin	yes	0	1(100%)	2(100.0%)	0.000**
	no	47(100.0%)	0	0	
warm sensation	yes	0	1(100%)	2(100.0%)	0.000**
	no	47(100.0%)	0	0	

Cardiac disease and obesity were contributing risk factors for developing DVT where 66.6% of patients with DVT (right extensive DVT and left femoropopliteal DVT) had cardiac disease and obesity with statistical significant difference **(Table.3)**

Table 3. Comparison of comorbid diseases between the study groups

Variables		No DVT N=47	right extensive DVT N= 1	left femoropopliteal DVT N= 2	P value
Hypertension	Yes	10(21.3%)	1(100%)	2(100.0%)	0.12
	No	37(78.7%)	0	0	
Diabetes mellitus	Yes	13(27.7%)	1(100%)	0	0.18
	No	34(72.3%)	0	2 (100.0%)	
Bronchial Asthma	Yes	6(12.8%)	0	0	0.8
	No	41(87.2%)	1(100%)	2 (100.0%)	
COPD	Yes	3(6.4%)	0	0	0.9
	No	44(93.6%)	1(100%)	2 (100.0%)	
Cardiac disorders	Yes	5(10.6%)	1(100%)	1(50.0%)	0.01*
	No	42(89.4%)	0	1(50.0%)	
Obesity	Yes	3(6.4%)	1(100%)	1(50.0%)	0.01*
	No	44(93.6%)	0	1(50.0%)	

As regards to D-dimer, ferritin and INR, there were significant differences between the 3 studied groups of corona patients, but there was no significant difference regarding WBCs. **(Table. 4).**

Table 4. Comparison of lab investigations between the studied groups

Variables	Mild n=13	Moderate n=13	Severe n=24	P value
D-dimer	0.39± .13821	0.9462 ± .5910	1.39 ±1.02	0.002**
Ferritin	217.8 ±165.4	329 .6± 125.2	435.7 ±231.4	0.007**
WBCs	7.9± 3.7	7.3 ±3.5	6.8 ± 6.3	0.8
INR	1.14 ±. 15	1.06± .112	1.18± .143	0.04**

There was significant difference between the 3 studied groups regarding CT picture where 87.5% of severe cases, 61.5% of moderate cases, 46.2% of mild cases had bilateral GGO. 50.0% of severe cases, 30.8% of moderate and 7.7% of mild cases had Crazy-paving appearance. There was significant difference regarding CO-RAD classification. **(Table.5)**

Table 5. Comparison of the CT picture and CO- RAD classification between the studied groups

Variables		Mild n=13	Moderate n=13	Severe n=24	P value
Normal	Yes	6(46.2%)	3(23.1%)	1(4.2%)	0.009*
	No	7(53.8%)	10(76.9%)	23(95.8%)	
Bilateral GGO	Yes	6(46.2%)	8(61.5%)	21(87.5%)	0.02*
	No	7(53.8%)	5(38.5%)	3(12.5%)	
Crazy-paving appearance	Yes	1(7.7%)	4(30.8%)	12(50.0%)	0.03*
	No	12(92.3%)	9(69.2%)	12(50.0%)	
CO-RAD classification		2.76 ±1.7	3.69± 1.3	4.6 ±0 .48	0.000**

After 1 month 96% of cases had no DVT but 4% had DVT (2.0% had right extensive DVT and 2% left femorpopliteal DVT). After 3 month 94% of cases had no DVT but 6% had DVT (2.0% had right extensive DVT and 4% left femorpopliteal DVT. **(Table.6, Fig. 1, Fig.2).**

Table 6. Incidence of DVT After 1and 3 months

Variables		frequency	Percent
After 1 month	normal study	48	96.0%
	right extensive DVT	1	2.0%
	left femorpopliteal DVT	1	2.0%
After 3 month	normal study	47	94.0%
	right extensive DVT	1	2.0%
	left femorpopliteal DVT	2	4.0%

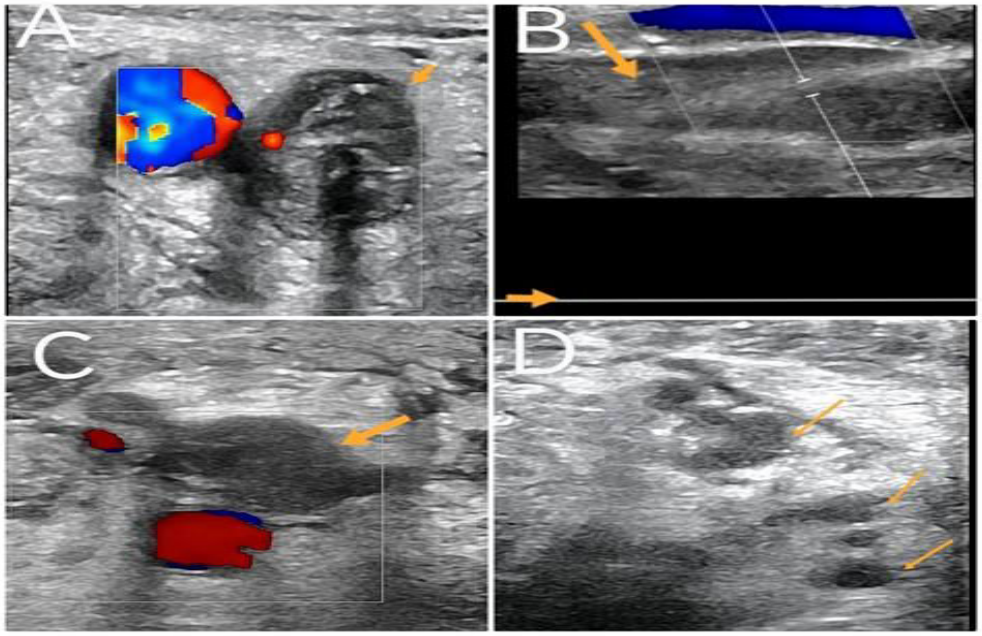

Fig.1. A 45 year-old female patient, presented with severe right lower limb pain, swelling, hotness from 4 weeks. Venous Doppler ultrasound for both lower limbs showed right subacute DVT with no DVT at left limb. **(A)** Right common femoral vein was seen distended with intramural heterogeneous thrombus. No color flow within. **(B)**Right femoral vein was seen distended with heterogeneous thrombus inside, no flow within the vein by pulsed wave Doppler. **(C)**Right popliteal vein was seen distended by thrombus with no detected color flow. **(D)**Thrombosed right calf veins was detected by B mode.

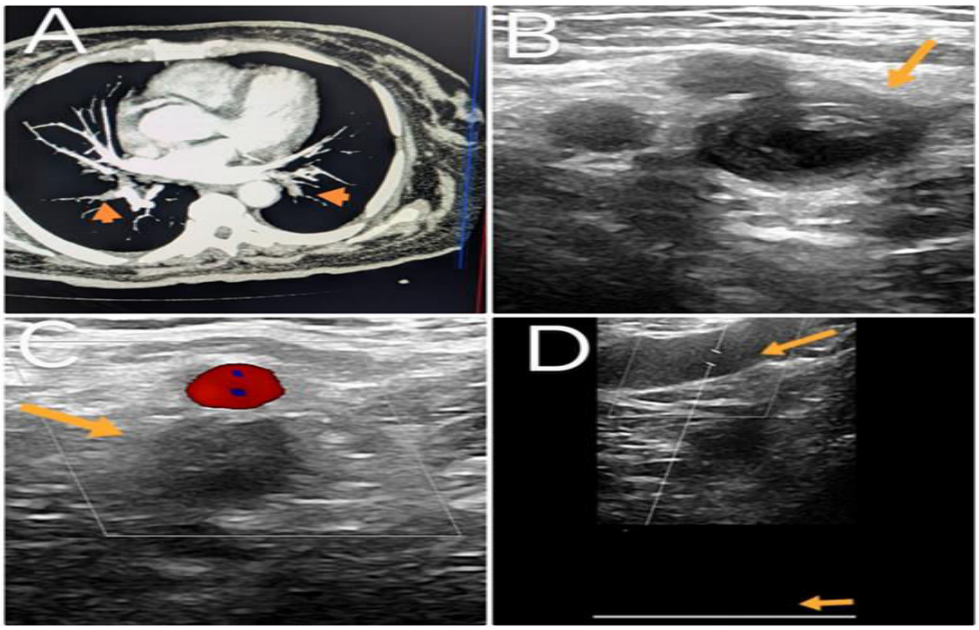

Fig.2. A 55 year-old female patient, presented with dyspnea, chest pain from one day, with history of severe left lower limb pain and swelling from one week. CT pulmonary angiography was done revealed acute pulmonary embolism .Venous Doppler ultrasound for both lower limbs revealed acute DVT at left lower limb with no DVT at right side. **(A)** Axial CT pulmonary angiography showed multiple filling defects at lower segmental branches of both pulmonary arteries. **(B)** Left common femoral vein was seen distended with intramural hypoechoic thrombus. **(C)**Left femoral vein was seen distended over heterogeneous thrombus with no flow within by color mode. **(D)** Left popliteal vein was seen distended with intramural hypoechoic thrombus with no flow within by duplex Doppler interrogation.

Discussion

In December 2019, patients with pneumonia of unknown origin were found in Wuhan, Hubei, China, **(Huang et al., 2020).** Later, samples of the lower respiratory tract taken from these patients revealed the presence of a novel coronavirus (SARS-CoV-2) **(Zhou et al., 2020).**

According to **Wang et al. (2020),** COVID-19 has a wide spectrum of clinical manifestations, from asymptomatic and moderate upper respiratory tract symptoms to severe illness up to multiorgan failure and death. Furthermore, it is challenging to tell the clinical course or recognize patients at risk disease progression. **(Zhou et al., 2020).**

The clinical and demographic characteristics of COVID-19 patients throughout the world have been shown to vary significantly **(Lippi et al., 2020).** COVID-19 pneumonia is more likely to affect those with co-morbid conditions. Additionally, among COVID- 19 patients with various disease severity, blood biomarkers significantly vary. **(Guan et al., 2020).** The pathogenesis of the disease could be explained by the interaction between the S protein and ACE2. It has been suggested that the high level of systemic inflammation linked to COVID-19 might hasten the onset of subclinical conditions or result in de novo systemic damage **(Zheng et al., 2020).** Furthermore, COVID-19-positive patients may present with hypercoagulability and an increased risk of deep vein thrombosis (DVT) **(Ranucci et al., 2020).**

The three groups of corona patients (mild, moderate, severe) involved in our study had mean ages of 42.6± 3.0, 41.7± 3.8, and 57.3±12.4 respectively. When compared to mild or moderate patients, severe patients were noticeably older.

In the same line, **Ghweil et al. (2020)** included 30 patients with severe/critical COVID-19 (of average age 62.6 ± 10.1) and 36 patients with mild to moderate infection (of average age 55.5 ± 10.1). Significantly severe infection was found in older patients than mild to moderate infection.

Regarding BMI, the mean BMI between the 3 studied groups of corona patients (mild, moderate, severe) was 29.0± .83, 31.2± 5.1, 31.5 ±5.5 with no significant differences between studied groups.

According to **Yang et al. (2020)** and **Soeroto et al. (2020)** meta-analysis, patients with severe COVID-19 had higher BMIs than those with non-severe COVID-19. But **Cai et al. (2020)** study of 298 COVID-19 patients at the Third People's

Hospital in Shenzhen, China, reported that there was no difference between the non-severe (n=240) and severe (n=58) patients, whose BMI values were 22.9 kg/m2 and 25.5 kg/m^2, respectively. The studies were therefore quite different from one another.

The overall DVT incidence among post COVID-19 patients in our study was 6%. After one month, 4% of cases had DVT and 96% had no DVT whereas at three month follow up, 6% of cases had DVT and 94% had no DVT).

A study of 163 COVID-19 patients with a median follow-up of 30 days after hospital discharge was conducted by **Patell et al. (2020).** Patients on anticoagulant therapy were excluded. A total of 2.5% (95% CI 0.8 to 7.6) of thrombotic events occurred during the follow-up period, with VTE alone occurring in 0.6% (95% CI 0.1-4.6) and haemorrhage occurring in 3.7% (95% CI 1.4-9.8) of cases. This is almost identical to our findings, as the incidence of DVT one month after COVID-19 recovery was 4%.

In a meta-analysis of 27 studies with 3342 COVID-19 patients included, **Suh et al. (2021)** reported the incidence of DVT at the study-level in patients with the disease. The combined incidence rates of DVT and PE were 14.8% (95% CI: 8.5, 24.5; I^2 = 0.94) and 16.5% (95% CI: 11.6, 22.9; I^2 = 0.93), respectively.

Babic et al. (2021) included 118 cases with a non-severe COVID-19 infection. With a median age of 48 years and an interquartile range of 30-85 years, DVT was found in 50 (42.4%) patients. 40 patients (80%) had symptoms of DVT, and 38 patients (76%) (χ^2 = 51.71, p < 0.001) had Class I calf vein thrombosis. The following were the most significant risk factors for DVT: elevated C-reactive protein (p = 0.000), fibrinogen (p = 0.000), low lymphocytic count (p = 0.002), obesity (p = 0.017), and neutrophil count (p = 0.042).

According to **Klok et al. (2021),** who reported on 184 COVID-19 patients receiving ICU care, there were 65 patients with PE, 3 patients with further venous thrombosis, and 7 patients with arterial thrombosis, for a crude cumulative thrombosis rate of 57% (95% CI 47-67%).

DVT was observed in 46.1% of cases in a study that included 143 COVID-19 patients who underwent lower limb ultrasonography. 43 (65.2%) had a distal DVT, whereas the other 23 (34.8%) had a proximal DVT **(Zhang et al., 2020).**

This variability in studies could be due to differences in the ethnical distribution of patients, age, inclusion criteria, sample size, sampling procedures, and methods of detecting of DVT or period of study.

Such variation in research may be caused by variations in the ethnical distribution of patients, age, inclusion criteria, sample size, sampling techniques, DVT detection methods, or time period of the study.

Regarding comorbidities, it was noticed that cardiac disorders and obesity were significantly associated with incidence of DVT among participants of our study.

This is in line with the findings of **Wang et al. (2020),** who conducted a retrospective cohort analysis with 609 COVID-19 patients who were classified according to obesity classes. In comparison to patients without obesity, those who were obese had considerably greater risk-adjusted probabilities of developing venous thromboembolism.

According to our data, a prospective multicenter research conducted in 5 hospitals with 373 patients who had pneumonia related to the Covid-19 virus found that cardiovascular disorders were significantly related to thrombotic events **(Violi et al., 2021).**

The findings of the current study demonstrated a significant association between high blood ferritin levels and COVID-19 severity. When compared to mild or moderate patients, severe patients' ferritin levels were significantly (p-value 0.001) higher.

According to **Ghweil et al. (2020),** patients with severe or critical COVID-19 had mean ferritin values that were significantly higher than those with mild to moderate infection, all with a p-value less than 0.05. Additionally, **Taha et al. (2021)** found that patients with severe COVID-19 and those who died from the infection had noticeably higher ferritin levels. With an odds ratio of 11.08, ferritin above 350 ng/mL was a reliable predictor of COVID-19 severity. 269 (49.1%) of 548 patients, that were reported by **Li et al., (2020),** had severe disease when they were admitted. The authors found a significant association between severe COVID-19 upon admission and high serum ferritin levels.

Based on the findings of the current study, individuals with severe COVID-19 infections had significantly higher blood D-dimer levels than patients with mild or moderate infections. When compared to mild or moderate individuals, we discovered statistically significant (p-value< 0.001) higher D-Dimer levels in severe patients.

These results concur with those of **Zhou et al. (2020),** who discovered that D-dimer greater than 1 µg/mL is related to COVID-19 mortality.

According to the findings of our study, patients with mild to moderate COVID-19 showed a significantly higher incidence of bilateral peripheral GGO, but those with severe or critical infection had crazy-paving appearances on their CT chest. One CORAD 5 and the other CORAD 3 were identified on the CT chest of two DVT patients. The severity of the COVID-19 infection was also significantly predicted by CT chest results.

Twenty one COVID-19 cases were reported by **Pan et al. (2021)**. They came to the conclusion that crazy-paving appearance may be thought of as one of the markers that could be used to assess the course of the disease after seeing the quick expansion of ground glass opacities into crazy-paving appearance on disease progression, with its removal in the absorption stage.

Findings obtained in the present study were in the same line with **Ghweil et al. (2020),** who found that 30 patients (100%) with severe COVID-19 showed crazy-paving pattern (in terms of reticular and/or interlobular septal thickening with or without GGO) and that 12 cases (33.3%) of mild to moderate infection had normal CT chest and 24 patients (66.6%) had focal or multifocal GGO with patchy consolidations that distributed peripherally, affecting mostly the posterior part or lower lung lobes.

Limitations of the study: The major limitations of our study were small sample size, single center-based enrolment and lack of long term follow up of the patients.

Conclusion

The overall DVT incidence among post COVID-19 patients in this study was 6%. Old age and increased D-dimer were significantly associated with COVID-19 severity. Cardiac disorders and obesity were significantly associated with incidence of DVT among COVID-19 patients.

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