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Characteristics of Deep Vein Thrombosis on Ultrasound in Mechanically Ventilated SARS-Cov-2 Patients

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Abstract **Original Research Article**

Aim: To evaluate the prevalence of asymptomatic DVT and its characteristics on venous doppler and grey scale ultrasound in lower limbs in mechanically ventilated SARS-Cov-2 Patients with high levels of D-dimer. ***Methods:*** This cross-sectional observational study was carried out in the Department of Radiodiagnosis Sri Aurobindo Medical College and P.G. Institute, Indore over the period of one year. Doppler ultrasound (DU) was performed on critically ill SARS-COV-2 patients (n =45) with severe respiratory failure, with the diagnosis of severe pneumonia and high levels of D-dimer by bedside US examination was performed with a high-frequency linear transducer on GE-logiq E machine. DU protocol includes grayscale, colour and spectral Doppler evaluation. The examination included the deep venous system of the thigh, calf, and saphenous veins. ***Result:*** Out of Forty-five patients [age, mean age 47.1 years; female/male ratio, 0.66; DVT was diagnosed in 24 patients (53.3%), 6 (25%) in proximal venous territory femoral vein, 4 (16.66%) in popliteal veins and 14 (58.33%) in distal venous territory beneath popliteal vein. CFV diameter was increased to a mean of 13.2 mm (10.8-14.6) (normal range, 9.1-12) and PBFV reduced to a mean of 10.8 cm/s (8.1-14.5) (normal range, 21.3-49.2) on doppler in positive DVT patients. ***Conclusion:*** We propose that DU allows the detection of DVT in asymptomatic mechanically ventilated SARS-Cov-2 Patients with elevated D-dimer patients. Low resistant venous return evidenced by larger than normal CFV diameters and lower than normal PBFVs may have facilitated proximal DVT occurrence.

Keywords: SARS- Cov-2, Doppler ultrasound, Common Femoral Vein, Deep venous thrombosis, Vein diameter, Peak blood flow velocity.

INTRODUCTION

Similar to the severe acute respiratory distress syndrome, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) produces a severe respiratory illness that is associated high rate of intensive care unit (ICU) admissions and a high fatality rate [1]. The SARS-CoV-2 infection has been associated with a high rate of thrombotic events, such as deep vein thrombosis (DVT) and acute pulmonary embolism (APE) in patients admitted to the intensive care unit (ICU) [2].

Blood hypercoagulability has been attributed to the imbalance between procoagulant factors and natural coagulation inhibitors, as supported by the extremely high fibrinogen, D-Dimer, factor VIII, and von Willebrand factor in SARS-COV-2 patients [3, 4]. Blood hypercoagulability together with the endotheliopathy and immobility resulting from sedation and invasive mechanical ventilation in the ICU, are creating optimal conditions for the occurrence of venous thrombosis [5, 6]. Furthermore, D-dimer levels are recognized as an independent predictor for survival and thromboembolic events in SARS-COV-2 [7].

Detailed descriptive aspects of DVT and rheological conditions in the lower limb venous system that may have facilitated DVT have been poorly studied. However, these characteristics are useful for estimating the risk of thrombus migration and may thus influence patient management.

The purpose of our study was to evaluate the prevalence of asymptomatic DVT to describe DVT characteristics and investigate rheological conditions of

the lower limb veins in mechanically Ventilated SARS-Cov-2 Patients and high levels of D-dimer by bedside Doppler ultrasound (DU).

METHODOLOGY

This cross-sectional observational study was conducted in Sri Aurobindo Medical College & Post Graduate institute, Indore from 1st April 2021 to 30th March 2022 which admits critically ill SARS-Cov-2 patients from central India- Madhya Pradesh. The study protocol was approved by the Ethics Committee, SAIMS, Indore.

In this study venous Doppler of 45 patients (≥18 years old) was performed on confirmed SARS-COV-2 patients admitted to the ICU, who developed acute severe respiratory failure, requiring invasive mechanical ventilation and with elevated D-dimer levels > 0.5 µg/ml (normal range < 0.5 µg/ml). US examination was performed with a high-frequency linear transducer (6-12 MHz) on the GE-logiq machine. DU protocol includes grayscale, colour and spectral Doppler evaluation. The examination included the deep venous system of the thigh, calf, and saphenous veins. DVT was diagnosed in cases of increased vein diameter, presence of echogenic material, non-compressibility of the veins and absence of colour and spectral Doppler signal (Fig 1). The common femoral vein diameters and PBFVs were recorded (Fig 2).

Patients were excluded if they were under full-dose anticoagulant therapy or if they developed symptomatic DVT. Several patients showed alterations in coagulation parameters, so the International Society of Thrombosis and Haemostasis (ISTH) score, a scoring system for disseminated intravascular coagulation (DIC), was calculated.

Computed tomography pulmonary angiography (CTPA) could not be performed due to the risk of unstable patient transfer to radiology, so DU was carried out at the patient's bedside to screen venous thromboembolic disease.

Regarding descriptive statistical analysis, categorical data were expressed as frequencies, proportions and percentages and continuous data were expressed as mean ± standard deviation (SD).

RESULTS

Initially, forty-eight successive mechanically ventilated SARS-COV-2 patients were included in the study. Three patients were not included because one was diagnosed with pulmonary embolism before ICU admission and the other two developed symptomatic DVT. Thus, the study comprised patients, 27 males (60%) and 18 females (40%). The mean patient age was 47.1 years ± 13.2 (SD) (Table-1).

Table 1: Gender Distribution

Gender	**No. of Patients**	**% of Total**
Female	18	40.0 %
Male	27	60.0 %

Deep Vein Thrombosis

All patients had an ultrasound examination performed after 72 hours of tracheal intubation. DVT was diagnosed in 24 cases (53.3%) (Figure 1). Six (25%) were in the proximal venous territory femoral vein, four (16.66%) in popliteal veins and fourteen (58.33%) in distal venous territory beneath the popliteal vein. DVTs were bilateral in three patients (12.5%) (Table 2).

Table 2: Distribution of patients with DVT according to its Location in lower limb

Site	**No. of Patients (n=24)**	**% Total**
Proximal in Femoral V	6	25%
Popliteal V	4	16.66%
Distal Beneath Popliteal V	14	58.33%

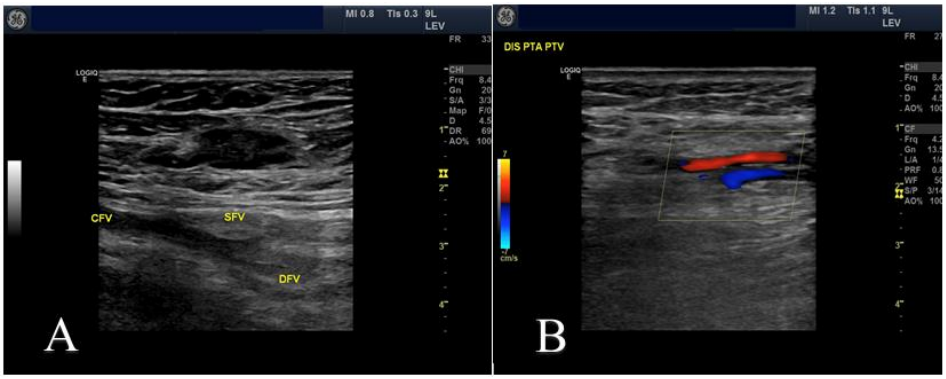

Figure 1: A: Gray scale longitudinal scan showing echogenic thrombus in the right SFV with the loss of compressibility. B: Gray scale and Colour Doppler mode scan showing echogenic thrombus in the distal PTV

The mean D-Dimer of Patients with DVT had higher was 30.8 µg/ml (SD of 20.08) to patients without DVT 6.33 µg/ml (SD of 3.22) which showed a positive significance of the association of higher D-dimer in patients with DVT with a p-value of <.001 (Mann-Whitney U Test) (Table 3).

Table 3: Distribution according level of D-dimer in patients with absent and present DVT (Mann-Whitney U Test)

	DVT	No. of Patients (45)	Mean (SD)	p-value
D-Dimer (µg/ml)	Absent	21	6.33 (3.22)	<.001
	Present	24	30.80 (20.08)	

Several patients showed alterations in coagulation parameters, so the International Society of Thrombosis and Haemostasis (ISTH) score, a scoring system for disseminated intravascular coagulation (DIC), was calculated. All the patients presented ISTH scores <5, suggesting non-overt or low-grade DIC however ISTH scores of 3 and 4 showed a positive association in patients with DVT with p-value <.001 (Chi-Square Test) (Table 4).

Table 4: Distribution of cases in accordance to ISTH Scoring in patients with absent and present DVT (Chi Square Test)

DVT		ISTH Score					χ^2 Tests
		1	**2**	**3**	**4**	**Total**	
Present	No. of patients	3	9	9	3	24	
	Percentage	12.5 %	37.5 %	37.5 %	12.5 %	100.0 %	
Absent	No. of patients	12	9	0	0	21	**Value- 17.3**
	Percentage	57.1 %	42.9 %	0.0 %	0.0 %	100.0 %	
Total	No. of patients	15	18	9	3	45	**Df-3**
	Percentage	33.3 %	40.0 %	20.0 %	6.7 %	100.0 %	
p-value							<.001

Femoral Vein Diameter and PBFV in DVT patients

The vein diameter in patients with DVT was determined at the mean value of 13.2 mm (10.8-14.6) in common femoral veins (Figure 2). Of note, normal values found in a study which included non-intubated healthy subjects were 9.1-12.5 mm in right and 9.4-11.4 mm in the left, respectively [8]. Mean PBFV in DVT was 10.8 cm/s (8.1-14.5) in the common femoral vein, with normal values being 21.3-49.2 in right and 21.1-52.8 cm/s in the left, respectively (Table 5) [8].

Table 5: CFV Diameter and PBFV in patients with absent and present DVT (Independent T test)

	No of Patients	Mean (SD)	p-value
CFV Diameter	Present (24)	13.2 (1.06)	
	Absent (21)	10.5 (1.05)	<.001
PBFV	Present (24)	10.8 (1.64)	
	Absent (21)	13.4 (2.02)	<.001

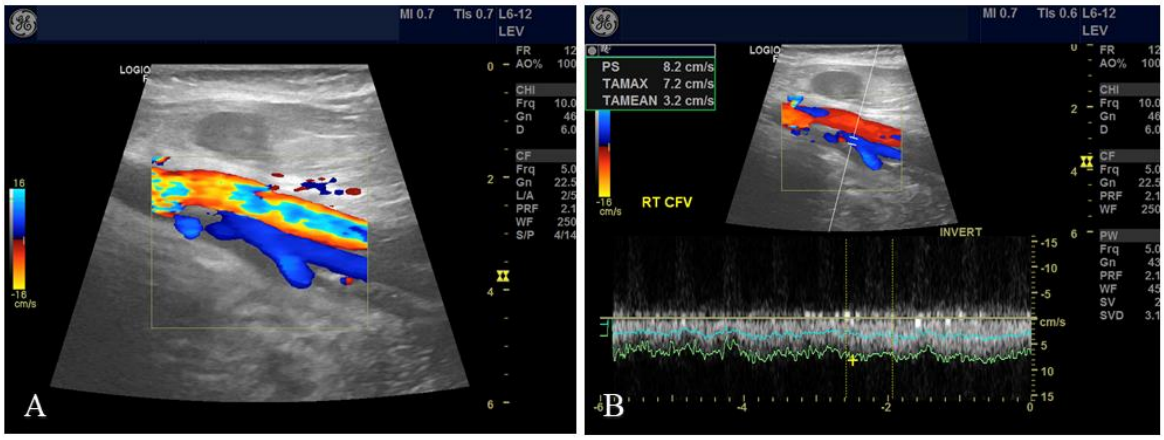

Figure 2 (A): Grayscale and Color Doppler modes scan showing partial thrombus in the right common femoral vein with increased diameter. (B) Colour Doppler modes scan showing reduced PSV of 8.2cm/sec

DISCUSSION

SARS-COV-2 has been associated with a higher risk of thrombotic events like DVT and APE [9-11]. Some studies propose that thromboembolic events could be secondary to a systemic procoagulant response (excessive inflammation, hypoxia, platelet activation and endothelial dysfunction) to SARS-COV-2 infection [12, 13]. The evidence to date supports the concept that the thrombotic manifestations of severe SARS-COV-2 are due to the ability of SARS-CoV-2 to invade endothelial cells via ACE-2 (angiotensin-converting enzyme 2), i.e on the endothelial cell surface.

Diagnosis of DVT and its localization are important issues for multiple reasons. Firstly, diagnosing DVT is important, as it results in anticoagulant treatment to ensure the prevention of thrombosis extension and facilitate spontaneous physiological thrombolysis. Without effective anticoagulation, DVT may extend and give rise to life-threatening pulmonary embolism, given the local rheological conditions and hypercoagulability in critically ill SARS-COV-2 patients [3, 6, 14-16]. Moreover, the pulmonary microcirculatory thrombosis that may occur as a consequence of COVID-19, participates in the increased pulmonary arterial resistance and right ventricular pressures, and may consequently decrease velocities of venous return to the heart and contribute to peripheral venous stasis [17, 18]. Based on post-mortem studies, approximately 10% of COVID-19-attributed fatalities have been estimated to be caused by pulmonary embolism [18]. A recent study also found an increased frequency of distal DVT in up to 85% of the SARS-COV-2 ICU patients [(10)]. Multiple studies reported a high incidence of DVT in critically ill SARS-COV-2 patients.

Despite our study has limitations a small sample size, the results suggest a higher incidence of asymptomatic DVT in critically ill SARS-COV-2 patients than reported by other studies in non-SARS-COV-2 critically ill patients where the incidence was around 10% [19, 20].

In our study, we found an increased incidence of asymptomatic DVT (53.3%), (elevated D-Dimer and severe respiratory failure). The most important finding in our study is that 25% of the patients presented proximal thrombosis in the common femoral vein, which can be easily dislodged and generate pulmonary embolism. The second most important finding is that the common femoral veins have a larger diameter and lower PBFVs than values found in normal subjects [13].

Distribution of characteristics of deep vein thrombosis on ultrasound in mechanically Ventilated SARS-Cov-2 Patients

	Mean	**SD**	**Test (p-value)**
Age (years)	47.1	13.20	Insignificant
D-Dimer (µg/ml)	6.33	3.22	Mann-Whitney U Test (p-value <.001)
CFV Diameter (mm)	13.2	1.06	Independent T test (p-value <.001)
PBFV (cm/sec)	10.8	1.64	Independent T test (p-value <.001)

We observed larger common femoral vein diameters and decreased PBFVs, compared to the normal values reported in the literature [8]. These two major factors facilitate thrombosis due to venous stasis in comparison to normal subjects. Larger vein diameters decrease blood flow velocity if blood output remains unchanged. Moreover, according to the non-Newtonian fluid nature of the blood, a lower blood flow velocity increases viscosity and the risk of erythrocyte aggregate generation [21]. In addition, blood flow velocity in a vessel is highest in the centre and decreases towards the vessel walls [22]. In mechanically ventilated patients with larger venous diameters, this property may even lead to lower velocities in the immediate vicinity of the endothelium compared to physiological conditions, resulting in increased venous stasis. This enhances the predisposition to thrombosis [22]. Although we only measured PBFVs in the common femoral veins, we strongly believe that our observations illustrate modifications in the overall lower limb venous network with likely decreased velocities compared to normal subjects [8, 23].

Due to the observed high DVT prevalence, increased anticoagulant prophylaxis has been used in our ICU patients, resulting in a significant decrease in proximal (femoral or popliteal) DVT prevalence as previously shown [24]. In consideration of this, we recommend using bedside ultrasound to identify DVT, particularly in ICU patients who cannot be moved to do CTPA.

CONCLUSION

In critically SARS-COV-2 ill mechanically ventilated patients with severe respiratory failure and elevated D-dimer, the incidence of asymptomatic DVT is high. Increasing vein diameter and decreasing PBFVs are two potential local factors that predispose patients to thrombotic complications.

The decision to thoroughly anticoagulant these patients may be impacted by the fact that doppler ultrasound makes it possible to detect DVT in asymptomatic individuals.

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