

High incidence of common femoral Deep Vein Thrombosis in critically ill Covid-19 patients

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Abstract

Objectives: To estimate the incidence and prevalence of deep venous thrombosis, and to evaluate the discriminative capacity of D-dimer in its diagnosis.

Method: The prospective, observational study was conducted at the critical care unit of a tertiary care hospital in Pakistan from February to September 2021 and comprised consecutively admitted adult critically ill patients who were receiving therapeutic-dose anticoagulation therapy. All patients were screened on day one for deep venous thrombosis by colour doppler and compression ultrasonography. Patients who did not have deep venous thrombosis on the first scan were followed every 72 hours. Data was analysed using SPSS 26.

Results: Of the 142 patients, 99(69.7%) were male and 43(30.3%) were female. The overall mean age was 53.20+/-13.3 years. On the first scan, 25(17.6%) patients had deep venous thrombosis. Of the remaining 117 patients, 78(68.4%) were followed every 72 hours, and 23(29.48%) of them developed deep venous thrombosis. The most common site for DVT was the common femoral vein 46(95.8%) and most deep venous thrombosis cases were unilateral 28(58.33%). D-dimer levels showed no discriminative capacity for diagnosis of deep venous thrombosis ($p=0.79$). There were no significant risk factors for the development of deep venous thrombosis.

Conclusion: There was a high incidence and prevalence of deep venous thrombosis despite therapeutic-dose anticoagulation therapy. The most common affected site was the common femoral vein and most deep venous thrombosis were unilateral. D-dimer levels had no discriminative capacity for the diagnosis of deep venous thrombosis DVT.

Key Words: DVT, Deep vein thrombosis, D-dimer, Ultrasonography, Incidence, Prevalence, DVT site, Anticoagulation, COVID-19, Critical care, IC. (JPMA 73: 533; 2023) DOI: 10.47391/JPMA.6435

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Introduction

High incidence and prevalence of deep vein thrombosis (DVT) have been widely reported in critically ill coronavirus disease-2019 (COVID-19) patients since the start of the pandemic¹⁻⁴. DVT can lead to potentially life-threatening pulmonary emboli and associated high morbidity and mortality^{4,5}. The most reported DVT site is below-knee veins, while proximal venous DVT mostly affects popliteal veins^{2,6-13}. Evidence suggests a high incidence of DVT despite pharmacological thromboprophylaxis⁷. Comparison between prophylactic and therapeutic doses of anticoagulation has shown a beneficial effect of therapeutic anticoagulation in non-intensive care unit (ICU) and ICU populations, but the results are conflicting^{14,15}. However, the incidence and prevalence of DVT in critically ill patients receiving therapeutic-dose anticoagulation has not been reported.

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Several studies have reported an association between D-dimer levels and the presence of DVT with different cut-offs^{16,17}. Besides, detecting a below-knee vein DVT imposes a particular challenge on ICU physicians who usually screen patients for DVT in critical care settings¹⁸.

The current study was planned to estimate the incidence and prevalence of DVT in critically ill COVID-19 patients on therapeutic-dose anticoagulation therapy, and to evaluate the discriminative capacity of D-dimer levels in the diagnosis of DVT.

Patients and Methods

The prospective, observational study was conducted at the critical care unit (CCU) of Sindh Institute of Urology and Transplantation (SIUT), a tertiary care hospital in Karachi, from February to September 2021. After approval from the institutional ethics review board, the sample size was calculated using PASS 11 with confidence level 0.05 and power of study 80%. Incidence of venous thromboembolism was taken as 32%¹⁸. The required sample size was 84. The sample was raised using consecutive sampling technique from among patients of either gender aged 18 years or above who were

hospitalised in the critical care unit (CCU) with the diagnosis of COVID-19 pneumonia and were receiving therapeutic-dose low molecular weight heparin (1mg/kg/day twice daily, 1mg/kg/day once daily in chronic kidney disease [CKD] patients) for at least 48 hours prior to the first screening for asymptomatic lower-limb DVT using colour doppler ultrasonography and complete compression ultrasonography (Toshiba Xairo 200 portable machine) of proximal lower limb veins, from common femoral veins to popliteal veins down to below-knee veins.

Patients were excluded if they had a history of venous thromboembolism or clinical signs of DVT at the time of inclusion in the study, received hormone replacement therapy (HRT), had lower extremity fracture in the preceding 3 months, were paraplegic, hospitalised for >2 weeks prior to the first screening, known case of thrombophilia, and pregnant women.

The screening was done after taking written informed consent from all patients or their surrogate decision-makers. Data was collected on demographics, body mass index (BMI)¹⁹, coexisting conditions, clinical symptoms, risk factors for DVT, D-dimer levels, results of lower limbs doppler, and compression ultrasonography scans. Patients who had DVT on the first screening scan were counted as prevalence out of the total number of patients screened. Those who did not receive any follow-up scans because they either expired or stepped down before 72 hours were also included to estimate overall prevalence. Patients who did not have DVT on the first scan were followed every 72 hours by colour doppler and compression ultrasonography until they developed DVT, expired or stepped down. First screening scans were performed by the radiologist to detect for absence or presence of DVT. Subsequent screening scans were performed by ICU physicians who received training in colour doppler and compression ultrasonography. All positive findings were confirmed by a radiologist.

Data was analysed using SPSS 26. Qualitative variables were expressed as frequencies and percentages. Quantitative variables were reported as mean $\pm$ standard deviation (SD) or median (interquartile range [IQR]), as appropriate. The association between categorical variables was checked using chi-square and Fisher's exact tests. Receiver operating characteristics (ROC) curve was generated to estimate the discriminative capacity of D-dimer levels to diagnose DVT. Univariable and multivariable logistic regression was used to estimate the risk factors for DVT. $P \leq 0.05$ was considered statistically significant.

Results

Of the 158 patients screened, 16(10.12%) were excluded; 8(50%) had anticoagulation therapy stopped due to upper gastrointestinal bleeding, 6(37.5%) were receiving prophylactic-dose anticoagulation therapy, and 2(12.5%) had documented DVT before the start of COVID-19 pneumonia symptoms. Thus, the final sample comprised 142(89.87%) patients, and, among them, 17(12%) patients received intermittent pneumatic compression in addition to anticoagulation.

The sample had 99(69.7%) male and 43(30.3%) female subjects. The overall mean age was 53.20 $\pm$ 13.3 years. The median duration of symptoms before ICU admission was 6 days (IQR: 3-10 days). The median follow-up period was 7 days (IQR: 3-10 days). The median duration of

Table 1: Baseline characteristics of critically ill COVID-19 patients.

Characteristics	Patients (N=142)
Gender, n (%)	
Male	99(69.7)
Female	43(30.3)
Age, y(SD)	53.20(13.3)
BMI, n (%)	
Underweight	18(12.67)
Healthy	45(31.69)
Overweight	22(15.49)
Pre-obese	39(27.46)
Obese	18(12.67)
Coexisting Conditions, n(%)	
Hypertension	81(57.0)
Cardiovascular Disease	12(8.5)
Diabetes mellitus	41(28.9)
Active malignancy	3(2.1)
Acute kidney injury	25(17.7)
Chronic kidney injury	13(9.2)
Chronic kidney injury-on haemodialysis	31(21.8)
Solid-organ transplant recipient	11(7.7)
Solid organ transplant rejection	7(4.9)
Recent Surgery	23(16.2)
Septic shock	42(30.4)
Cardiogenic shock	10(7.2)
Duration of symptoms before	
ICU admission, d(IQR)	6(10.25-3)
Follow up period (IQR)	7(10-3)
Duration of symptoms to development of DVT, d(IQR)	10(14-5)
D dimer levels, ng/ml (IQR)	2.3(6.6-1.0)
DVT screening ultrasonography results (%)	
Patients detected with DVT in ICU	48(33.8)
Prevalence (Frequency of existing cases of DVT)	25(17.6)
Incidence (Frequency of new cases of DVT)	23(29.4)

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Characteristics	Patients (N=142)
DVT site, n (%)	
Common femoral	46(95.8)
Popliteal	1(2.0)
Common femoral and popliteal	1(2.0)
DVT laterality	
Unilateral	28(58.3)
Bilateral	20(41.6)
ICU therapies (%)	
Invasive mechanical ventilation	53(38.4)
Mechanical DVT prophylaxis with intermittent pneumatic compression	17(12.0)

COVID-19: Coronavirus disease-2019, SD: Standard deviation, BMI: Body mass index, ICU: Intensive care unit, IQR: Interquartile range, DVT: Deep vein thrombosis.

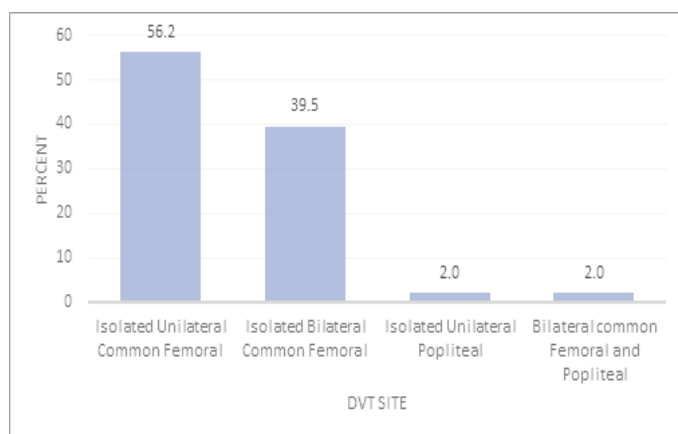


Figure-1: Deep vein thrombosis (DVT) site.

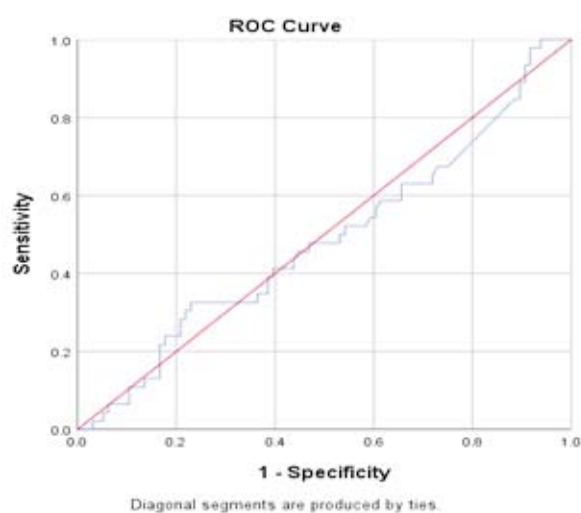


Figure-2: The area under the curve (AUC) for D-dimer in DVT diagnosis. ROC: Receiver operating characteristics, DVT: Deep vein thrombosis.

symptoms till DVT development was 10 days (IQR: 5-14 days) (Table 1).

On the first scan, 25(17.6%) patients had DVT. Of the remaining 117 patients, 78(68.4%) were followed every 72 hours, and 23(29.48%) of them developed DVT. The most common site for DVT was the common femoral vein 46(95.8%) and most DVT cases were unilateral 28(58.33%) (Figure 1).

ROC curve for D-dimer levels did not yield any discriminative capacity for DVT diagnosis, with the area

Table-2: Differential characteristics of patients with and without DVT.

Variable n(%)	DVT (N=48)	NO DVT (N=94)	Chi-square/Fisher Exact p-value
Male	28(28.3)	71(71.7)	0.112
Hypertension	28(34.5)	53(65.4)	0.524
Cardiovascular Disease	3(25.0)	9(75.0)	0.567
Diabetes mellitus	11(25.0)	30(75.0)	0.367
Active malignancy	1(33.3)	2(66.6)	0.972
Acute kidney injury	6(24.0)	19(76.0)	0.379
Chronic kidney injury	15(34.1)	29(65.9)	0.772
Solid organ transplant recipient	3(27.2)	8(72.7)	0.497
Solid organ transplant rejection	1(14.2)	6(85.7)	0.275
Recent Surgery	7(30.4)	16(69.5)	0.826
Septic shock	17(40.4)	25(59.5)	0.192
Cardiogenic shock	3(30.0)	7(70.0)	0.58
Invasive mechanical ventilation	19(35.8)	34(64.1)	0.521
Neuromuscular blocking agents	1(20.0)	4(80.0)	0.477
Mechanical DVT prophylaxis with intermittent			
pneumatic compression	4(23.5)	13(76.4)	0.405
Antiplatelet therapy	2(20.0)	8(80.0)	0.313
Major bleeding requiring blood transfusion	1(16.6)	5(83.3)	0.356
ICU mortality	23(35.3)	42(64.6)	0.512

DVT: Deep vein thrombosis, ICU: Intensive care unit.

under the curve (AUC) for ROC curve being 0.486 ($p=0.79$) (Figure 2).

There was no statistically significant association of DVT with gender, BMI, coexisting conditions, invasive mechanical ventilation, septic shock, mechanical DVT prophylaxis with intermittent pneumatic compression ($p>0.05$). No association was found between ICU mortality and DVT ($p=0.512$). ICU mortality was 23(35.38%) in patients with DVT (Table 2).

There were no statistically significant risk factors for DVT development (Table 3).

Table-3: Univariate and multivariable logistic regression for DVT risk factors.

Variables	Univariate OR (95% CI)	Univariate p value	Multivariate OR (95% CI)	Multivariate p-value
Gender	1.826(0.86-3.85)	0.114	0.510(0.215-1.206)	0.125
Age	0.998(0.972-1.025)	0.892	1.004(0.973-1.036)	0.814
BMI				
underweight	1	1		
Healthy	0.625(0.162-2.413)	0.495	0.509(0.111-2.327)	0.384
Overweight	0.455(0.145-1.422)	0.175	0.404(0.108-1.510)	0.178
Pre-obese	0.368(0.094-1.437)	0.150	0.445(0.101-1.964)	0.285
Obese	0.781(0.252-2.422)	0.669	0.709(0.199-2.525)	0.596
Hypertension	0.792(0.387-1.621)	0.524	1.286(0.497-3.328)	0.604
Diabetes mellitus	1.446(0.648-3.229)	0.368	0.571(0.200-1.633)	0.296
Cardiovascular disease	1.483(0.382-5.758)	0.569	0.606(0.092-3.970)	0.601
Recent surgery	1.114(0.424-2.931)	0.826	0.672(0.223-2.023)	0.480
Septic shock	0.606(0.284-1.291)	0.194	2.170(0.632-7.451)	0.218
Acute kidney injury	1.604(0.593-4.340)	0.352	0.885(0.291-2.693)	0.830
Chronic kidney injury	0.837(0.362-1.935)	0.678	0.633(0.236-1.698)	0.364
Cardiogenic shock	1.140(0.280-4.630)	0.855	0.797(0.113-5.63)	0.820
Intermittent pneumatic compression	1.645(0.505-5.355)	0.409	2.129(0.597-8.648)	0.345
Invasive mechanical ventilation	0.789(0.381-1.631)	0.522	0.887(2.67-2.943)	0.845
Antiplatelet therapy	2.00(0.407-9.819)	0.939	0.319(0.028-3.651)	0.359
Active malignancy	0.957(0.085-10.839)	0.972	1.420(0.101-19.527)	0.801

DVT: Deep vein thrombosis, BMI: Body mass index

Discussion

Pathophysiology of procoagulant state in COVID-19 has been described as “an exacerbated immune-thrombosis”²⁰. Some studies have shown no difference in the incidence of DVT between critically ill COVID-19 and control populations, supporting the possibility of in-situ pulmonary artery thrombosis rather than pulmonary emboli arising from lower extremity DVT^{11,12,21,22}. A piece of supporting evidence for in-situ pulmonary thrombosis is the location of DVT in distal lower limb veins, and distal lower limb venous DVT is associated with a lower risk of pulmonary emboli compared to proximal lower limb DVT^{2,6-8,23,24}. The current study found the common femoral vein as the most common site for DVT (46/48 patients), and in most patients, DVT was isolated and unilateral. High incidence and prevalence of common femoral DVT mandate extensive screening for DVT in COVID-19 patients as it puts them at high risk for developing pulmonary emboli²⁵. This difference may be due to population differences as, to the best of our knowledge, no data is available on the location of DVT in the South Asian population, which mandates further investigation. Furthermore, viruses are known to mutate and evolve. The estimated high incidence of isolated

common femoral DVT can be due to a different viral genotype²⁶. During the current study period, the Delta variant of COVID-19 was prevalent all over the world, including South Asia²⁵. Though the fourth wave in Pakistan was guesstimated to be fuelled by the Delta variant of COVID-19²⁶, the exact spread of the variant was difficult to map as Pakistan could not do a large number of sequencing for coronavirus. As mutation is in the nature of a virus, further research is necessary to investigate the changing viral behaviours.

The current study found a high prevalence (48/142 patients) and incidence (23/78 patients) of DVT despite therapeutic-dose anticoagulation. There were 17 patients who received intermittent pneumatic compression therapy in addition to therapeutic-dose anticoagulation of whom 4 developed DVT (4/17) with no

observed difference in incidence from the anticoagulation-alone group. To the best of our knowledge, the beneficence of intermittent pneumatic compression therapy along with anticoagulation is not reported in COVID-19 patients and requires further investigation.

The current study did not find any association of DVT with coexisting health conditions, such hypertension, type II diabetes and cardiovascular disease. As the study was conducted at SIUT, a good number of our patients had end-stage renal disease (ESRD) (44/142 patients) and most of them were dialysis-dependent (31/44 patients). ESRD is known to increase the risk of DVT²⁷. Unadjusted and adjusted odds ratios in the study, however, showed that ESRD did not cause an increased risk of DVT in critically ill COVID-19 patients. Furthermore, the study showed that solid organ transplant recipients and patients with transplant rejection were not at an increased risk of developing DVT. As septic shock, cardiogenic shock and invasive mechanical ventilation cause decreased mobility, the chances of DVT increase. After adjusting for these variables, the current study found that none of such patients was at a particular risk

for DVT. Using intermittent pneumatic compression therapy has proven to decrease the risk of DVT in hospitalised patients²⁸. The current study adjusted intermittent pneumatic compression therapy use in its population, and it was not found to be a preventive factor in critically ill COVID-19 patients.

The current study did not find any cut-off values for DVT that may help in the diagnosis of DVT with acceptable sensitivity and specificity though several studies have reported different cut-off values for D-dimer levels that may predict the presence or absence of DVT¹⁷. More recent evidence suggests D-dimer to be a prognostic marker than an indicator for DVT²⁹.

Most prospective studies have not reported follow-up periods or average time from onset of symptoms to DVT development to ascertain a critical period for the development of DVT^{2, 4, 8, 9, 15}. During data collection, 4 patients in the current study were detected to have DVT as early as on day 2 of symptoms, while the median time from onset of symptoms to the development of DVT was 10 days. This varies widely from patient to patient. A systematic screening for DVT in all COVID-19 patients starting from day 1 of symptoms is recommended. Patients who do not have DVT on the first scan should be subjected to follow-up scans.

The major strength of the current study is its prospective design and a relatively large sample size.

Major limitations include a limited follow-up period which was mainly due to high in-ICU mortality. Also, CTPA could not be done in patients with suspected pulmonary emboli to avoid complications that may arise during intra-hospital transport due to severe illness requiring invasive monitoring and organ support.

Conclusion

There was a high incidence and prevalence of DVT despite therapeutic-dose anticoagulation. The most common site of DVT was the common femoral vein, and most DVTs were unilateral. There were no associations or risk factors related to the presence of DVT. ICU mortality was not different among patients with or without DVT. D-dimer levels had no discriminative capacity for DVT diagnosis.

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