

## Deep Vein Thrombosis : An Unusual Presentation in COVID- 19 Patients-Our Experience and Comparison with Non COVID-19 Deep Vein Thrombosis Cases

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### ABSTRACT

**Introduction:** Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was found in Wuhan China which caused the acute respiratory illness and became the pandemic as declared by World Health Organization on March 11, 2020. Viral inclusion bodies have been identified in endothelial cells in a variety of organs. Deep Vein Thrombosis(DVT) is one atypical presentation which is thought to be triggered by endothelial dysfunction and exacerbated by hypoxia in patients with COVID-19.

**Methods:** It was a single center retrospective study in Kathmandu University Dhulikhel Hospital. All the data were taken between January, 2020 till May, 2021 who were presented in OPD or inpatient department with symptoms of DVT and required admission. Presence or absence or concomitant COVID-19 was tested by RT-PCR test.

**Result:** There were a total of 52 patients admitted as DVT, among which 26(50%) were male and 26(50%) were female. Twenty patients (38.5%) were COVID-19 positive and 32 (61.5%) were COVID-19 negative. Mean age for among those patients was 50.50±4.8 years, average hospital stay was 6.4±0.6 days, after anticoagulation therapy target INR was reached in 3.8±0.17 days and CVI was present in 14(70%) for COVID positive with DVT. Similarly, mean age was 46.80±3.3 years, average hospital stay was 4.6±0.3 days, after anticoagulation therapy target INR was reached in 3.3±0.21 days and CVI was present in 18(56.65%) with COVID negative with DVT.

**Conclusion:** COVID-19 is still the mysterious virus and exact mechanism of this disease is still a debate which may need many years to solve. Sometimes DVT can be the only presentation of this disease.

**Key Words :** COVID-19; CVI; DVT.

### INTRODUCTION

On December 31st 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was found in Wuhan China which caused the acute respiratory illness and became the pandemic as declared by World Health Organization in March 11, 2020.<sup>1</sup> Coronavirus, which enters the human cell by binding to angiotensin converting enzyme-2 (ACE-2), found mainly on alveolar epithelium and endothelium. This leads to activation of endothelial cells and is thought to be the primary driver for the increasingly recognized complication of thrombosis. Viral inclusion bodies have been identified in endothelial cells in a variety of organs, from the lung to the gastrointestinal tract.<sup>2</sup> These leads to symptoms such as fever or chills, cough, shortness of breath or difficulty breathing, fatigue,

muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting and diarrhea.<sup>3</sup> Beside these symptoms few atypical symptoms have also been reported such as Deep Vein Thrombosis(DVT) which is thought to be triggered by endothelial dysfunction and exacerbated by hypoxia in patient suffering from COVID-19.<sup>4</sup> DVT can be asymptomatic, as well as it can present with extremity pain, calf tenderness, and extremity swelling.<sup>5</sup> DVT occurs when three factors of Virchow's Triad predisposes a vessel towards thrombosis. Hypercoagulopathy, stasis, and endothelial injury of the vessel are the three components.<sup>6</sup> Risk factors for DVT have been reported in detail. Increased age, previous history of DVT, malignancy,

history of surgery, trauma, diabetes mellitus (DM), hypertension (HTN), chronic renal failure, pregnancy, hormone therapy, varicose vein, major heart failure, and prolonged immobilization are the most prominent ones.<sup>7</sup> In a study, COVID-19 patients who were admitted in ICU were found to have 42% incidence rate of venous thromboembolism (VTE).<sup>8</sup> Similarly in another study on critical COVID-19 patients at Wuhan, China has found incidence of DVT as 46% that included proximal DVT at 9%.<sup>8,9</sup> And in another metaanalysis it has shown that patients with higher age, increased BMI and severe symptoms of COVID-19 have higher chances of VTE.<sup>10</sup> In one study DVT as the presenting feature of COVID-19 was found to be 1.5% and was associated with worse prognosis.<sup>11</sup> Infection induced inflammatory changes have been considered as cause of VTE.<sup>11,12,13</sup>

So, the aim of the study is to know the proportion of cases of DVT with concomitant COVID-19. The study also aims to know any major differences between DVT patients with and without COVID-19 status.

### METHODOLOGY

This was a single center retrospective study in Kathmandu University Dhulikhel Hospital, Dhulikhel, Kavre Nepal. All the cases who presented with the symptoms of DVT between January 2020 till May 2021 were recorded. Non-compressibility of the vein was taken as a major criteria, and similarly secondary echogenic thrombus in the vein lumen, distention of the thrombosed vein, complete absence of spectral or color Doppler signal in the lumen, absence of flow phasicity, and absence of response to the Valsalva maneuver or manual augmentation were taken as a secondary criteria.<sup>14</sup> Ultrasonography techniques, including compression ultrasound, Duplex ultrasonography and color flow duplex imaging were performed on all patients who were suspected for DVT using 7-10MHz linear probe in Kalamed KUP-211 ultrasound system (Kalamed GmbH).<sup>15</sup> Regarding anatomical site of DVT, the most proximal site of DVT is mentioned. Other diagnostic modalities of DVT such as D-dimer, clinical scoring such as Caprini Score, Well's score was not done as Doppler ultrasonography is gold standard for diagnosis and monitoring of DVT.<sup>16</sup>

After diagnosis of DVT all the patients were sent for PCR for COVID-19 was done according to protocol asked by Ministry of health and population, National Public Health Laboratories Nepal. One or more of the major symptoms like presence of persistent edema, secondary varicose veins, venous ulcers, lipodermatosclerosis following deep venous thrombosis are taken as criteria for chronic venous insufficiency (CVI).<sup>16,17</sup> The data was entered in SPSS software package program (SPSS Inc., version 13,

chicago, IL, USA) and was used for statistical analysis. Descriptive data were given as mean, standard deviation, median, number, or percentage. The continuous variables of the groups were compared using the Student's t test.

### RESULT

A total of 52 patients with DVT were admitted between January 2020 to May 2021. Among them 26 (50%) were male and 26(50%) were female. Clinical and demographic parameters are shown in Table 1. There were a total 20(38.5%) of cases were COVID-19 positive patients whose PCR were sent as a screening for COVID-19 before admission and the rest 32(61.5%) were the case of DVT without COVID-19. Overall mean age was 48.92±3.2 and mean age for COVID-19 positive with DVT was 50.50±4.8 and for DVT with COVID-19 negative was 46.80±3.3 years (p value 0.649). Left lower limb was common in both COVID-19 positive DVT and non COVID-19 patients. Average number of hospital stay for DVT with COVID positive patients was 6.4±0.6 days and for DVT with COVID negative patients were 4.6±0.3 days. However p-value was 0.11 which was statistically not significant.

**Table 1: Clinical and Demographic Variables**

Variables	DVT with COVID Positive (N=20)	DVT with COVID Negative (N=32)	p-value
Age (Years)	50.50±4.8	46.80±3.3	0.649
<b>Gender</b>			
Male	10 (50%)	16 (50%)	0.612
Female	10(50%)	16 (50%)	
<b>Side of Lower Limb</b>			
Left	12(60%)	22(68%)	0.187
Right	6(30%)	10(31.3%)	
Bilateral	2(10%)	0(0%)	
Days of Hospital Stay	6.4±0.6	4.6±0.3	0.110
Target INR Achieved (Days)	3.8±0.17	3.3±0.21	0.119
Presence OF CVI	14 (70%)	18 (56.65%)	0.389

Similarly, after anticoagulation therapy average days for INR to reach its target for DVT with COVID positive patients was 3.8±0.17 and for DVT with COVID negative

patients were  $3.3 \pm 0.21$  days (Fig 1), with p-value of 0.119 it was also not statistically significant. Interestingly there were a total 32 (61.5%) patients among all the DVT patients who had CVI symptoms in telephone follow up. Among 20 patients who were DVT patients and COVID positive patients 14 (70%) developed CVI and for DVT with non COVID patients 18 (56.65%) from a total of 32 patients developed CVI, however p-value was 0.389 and was statistically not significant among DVT with COVID and non COVID patients. None of the patients had symptoms suggestive of pulmonary embolism during hospital stay or during follow-up.

In relation to symptomatology, none of the patients had common symptoms of COVID-19 such as fever, dry cough, shortness of breath. All the cases improved after medical treatment. There was no mortality till the day (minimum follow-up of a month).

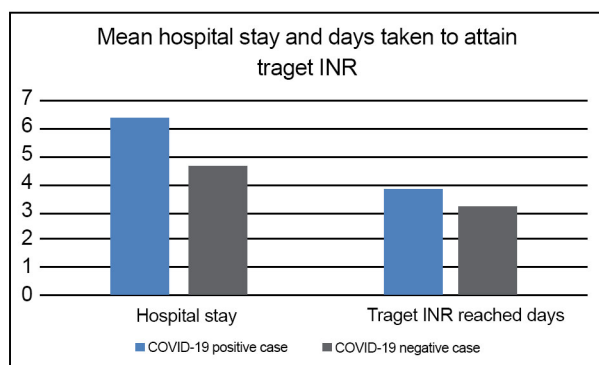


Figure 1: Mean hospital stay and days taken to attain target INR in two groups.

## DISCUSSION

Of the presented cases of DVT in our study, 38.5% of patients were COVID-19 positive. None of the cases had typical symptoms of COVID-19. Lofollah Davoodi, Md et al, in 2020 reported a similar case report stating that DVT can be the only symptom in COVID-19 patients with no other common symptoms of COVID-19 as a presentation.<sup>18</sup> Similarly another cohort study done published on 2020 by Hanny Al-Samkari et al showed only 4.8% incidence of DVT in patient with COVID-19 patients.<sup>19</sup> However, the incidence was reported as high as 85% in those undergoing ultrasound screening examinations regardless of clinical suspicion.<sup>20</sup> We could not find other study that mentions DVT as the only presentation of COVID-19. There have been multiple studies to find associated DVT in COVID-19 cases. Previously DVT was thought to be secondary to COVID-19 and many studies have been conducted in patients who had typical symptoms for COVID-19, whether they had or developed DVT or any thromboembolic events during admission or post admission. Evren Karaalietal in 2021

had done a similar study regarding increased DVT in patients with COVID-19.<sup>21</sup> In a study done in Italy, among 200 patients, 15% of patients with COVID-19 had DVT.<sup>22</sup> Similarly another study done in China has stated that 41.5% of patients with DVT were COVID positive patients.<sup>23</sup> A study done in Turkey amongst COVID-19 positive people in quarantine period, there was increased prevalence of DVT compared to normal population.<sup>18,21</sup>

In our study although mean age in DVT with COVID-19 positive was slightly higher than that with COVID-19 negative, significance was not found. However the mean age in this study is very similar to our earlier study involving 67 cases.<sup>24</sup> Similarly, Mean age of male patients was  $50.50 \pm 4.8$  years and for non COVID-19 with DVT patients was  $46.80 \pm 3.3$ . Distribution of male and female distribution was 50% in both COVID-19 positive and negative DVT patients. In a study done by Kakkos SK et al in 2021, it was found that the distribution of DVT in both male and females is almost equal, which also supports our study.<sup>25</sup> Left side of the lower limb was a common site for DVT in both COVID-19 positive and negative with DVT patients. In a study done on May 2000 by Kenneth Ouriel MD et al, it has also stated that left side of lower limb was a common site in DVT.<sup>26</sup>

Another interesting fact in our study was days of hospital stay was longer in case of COVID-19 patient ( $6.4 \pm 0.6$ ) days compared to non COVID patient ( $4.6 \pm 0.3$ ) days with DVT. Similarly in other study patients having both DVT and COVID-19 patients there hospital stay was 10.8 days on average.<sup>27</sup> The difference between hospital stay among our cases and the other above research might be due to associated comorbid conditions or might have other severe symptoms as well. Similarly, another significant finding of our study was presence of Chronic Venous Insufficiency in patients with DVT either with COVID positive (70%) or with non COVID-19 (56.6%). However, we were not able to find the studies regarding presence of Chronic Venous Insufficiency after COVID-19 with DVT. Similarly, in an article published in vascular society of Great Britain and Ireland, has stated that there were more than 50% chances of having the symptoms of venous insufficiency in patient post DVT, but the article also stated that it may take up to 1 year to have all the symptoms.<sup>28</sup> In our study, the days taken to reach therapeutic INR were similar in both the groups. Although the coagulation function panel can be altered in COVID-19 patients, this was noted in severe cases.<sup>29</sup>

## CONCLUSION

COVID-19 is still the mysterious virus and exact mechanism

of this disease is still a debate which may need many years to solve. So, all the health workers need to be vigilant and aware about the pathophysiology and symptoms of the disease. Of the diagnosed cases of DVT, we found 38.5% percent of patients with COVID-19 positive and none had typical symptoms of COVID-19. So with this study we would like to emphasize that DVT can be the only presenting symptoms of COVID-19.

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