Sonographic Evolution of Lower Extremities Deep Vein Thrombosis in Patients with COVID-19

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Abstract

Covid-19 is a serious virus related to severe illness courses. The main complication of this virus is venous thromboembolism which includes pulmonary embolism and deep vein thrombosis. Doppler ultrasound is becoming increasingly accepted as an accurate, non-invasive modality of imaging in suspected DVT. To evaluate the prevalence of DVT using Doppler sonography among COVID-19 patients concerning clinical and laboratory findings at Taif City, Saudi Arabia, and to determine the D-dimer elevation in DVTs patients and its association with the high-altitude regions. This is a retrospective study conducted at King Faisal Hospital, Taif. Including 150 Patients. Lower limb Doppler ultrasound was performed on all patients admitted either to the ward or intensive care unit between April to December 2021. Clinical and laboratory features, thrombotic complications, and outcomes were assessed.150 patients were screened in this study including 96 female and 54 male. DVT was found in 86 patients (57.3%) while those who didn't complain of DVT represented (42.7%). The mean age was (>64) years, and most of the respondents were inpatients (70.0%), while Isolation, ICU, and ER accounted represented (12.7%, 11.3%, and 6.0%) respectively. Also, (54.7%) of patients who complained of DVT had an increase in D-dimer values, compared to inpatients that didn't complain of DVT. Ultrasound is a helpful tool for detecting DVT in COVID-19 patients., based on the large percentage of people with venous thrombosis. Also, this study proved that there is a statistically significant association between DVT and elevated D-dimer among confirmed COVID-19 patients who live in Taif City.

Keywords: COVID-19, Deep vein thrombosis, Ultrasonography, High altitude, Taif

INTRODUCTION

In 2019, an epidemic spread around the world causing millions of deaths and affecting many people [1]. In February 2020, the World health organization (WHO) called the virus coronavirus disease 2019 (COVID-19) [2]. The primary symptoms of the virus were similar to any other flu, counting fever, cough, shortness of breath, and pneumonia, which further developed into an acute respiratory disease [3, 4].

Since the emergence of the surge COVID-19 pandemic, there is cumulative confirmation suggesting that hospitalized patients due to this infection are more likely to have VTE [5]. The incidence of VTE complications in COVID-19 patients ranged from 1.7 to 16.5% in 35 observational studies reported from around the world (total N=9249) [6], VTE is including pulmonary embolism (PE) and deep vein thrombosis (DVT) [7, 8]. DVT has often been discussed as a common cardiovascular complication in COVID-19 patients [9]. Deep vein thrombosis (DVT) is a common pathological condition, and its incidence has increased significantly in recent times. It occurs when a blood clot (thrombus) forms in one or more of the deep veins in the body, usually in the legs [10]. It is a serious condition that can cause permanent damage to the vein or a life-threatening pulmonary embolism (PE). DVT usually begins around the leaflets of venous valves, especially in the calves, and can propagate superiorly [11]. The main affecting factor in DVT is the D-dimer value, which is considered a thrombosis marker [12]. Several previous research has proven that the D-Dimer test is very sensitive (>95%) in acute deep vein thrombosis or pulmonary embolism. Continuous wave Doppler is accurate and can be used as the main method for diagnosing DVT [13]. So, this study aims to evaluate the prevalence of DVT in the lower extremities using Doppler sonography among COVID-19 patients concerning clinical and laboratory findings at Taif City, Saudi Arabia, and to determine the D-dimer elevation in DVTs patients and its association with the high-altitude regions.

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MATERIALS AND METHODS

This is a retrospective study conducted at King Faisal Hospital, Taif. Including 150 Patients. The inclusion criteria were Patients over 18 years of age with confirmed COVID-19 and suspected DVT who were hospitalized either in the general ward, Isolation, or ICU. A diagnosis of COVID-19 pneumonia was defined as a positive reverse transcription polymerase chain reaction (RT-PCR) test in a nasopharyngeal swab or sputum specimen along with radiological findings consistent with pneumonia. Patient data was collected via their Electronic Medical Records (EMR) and the image archiving and communication system (PACS) in the radiology department of baseline characteristics (mainly those predisposing for DVT), radiographic clinical factors related features of the US, analytical features (D-dimer to COVID-19, disease complications, laboratory features "Liver enzymes"). Lower extremity ultrasound (US) was performed on all patients admitted to our hospital due to COVID-19 between April to December 2021. The exams were performed at the bedside, using a Doppler technique consisting of assessing compressibility of the popliteal vein (PV) and common femoral vein (CFV) in search of clots. Categorical variables were presented as frequency and percentage. Continuous quantitative variables were presented as mean and standard deviation (SD) in the case of a normal distribution or as median and interquartile range. The Statistical Package for the Social Sciences (SPSS version 26) For data analysis in this study, a p-value of 0. 05 was considered statistically significant. The figures preparation was conducted using Microsoft Excel 2010. 01. Frequency, and percentage, to identify the personal data and items of Dimensions 2. Mean and standard deviation have been accomplished 3. t. tests were conducted to examine the differences in mean 4. One-way ANOVA was conducted to examine the mean differences.

RESULTS AND DISCUSSION

Table 1 shows that most of the respondents aged >65 years old were (38.0%), while (46-64), (26-45), (18-25) years old were (32.7%, 27.3%, 2.0%), respectively, the majority of respondents were female (64.0%), whilst male represented (36.0%) during infection with COVID-19 and there was suspected of DVT in the lower extremities however, most of the respondents were in patients (70.0%), while, isolation, intensive care unit (ICU), emergency (ER) and they represented (12.7%, 11.3%, 6.0%), respectively, whereas the vast majority of respondents had patient history and risk factors (84.7%). **Table 2** shows that the commonest history and most risk factors among the respondents was Diabetes Mellitus 46.0%, whereas respiratory diseases (45.3%), cardiac disease (16.7%), and neurological disease (4%) hypertension (40%), and other; (chronic kidney disease, anemia, chronic liver disease, history of thrombosis, hypothyroidism, malignancy, history of venous thromboembolism, smoker) recorded (32.7). **Table 2** shows that the commonest Respondents' Signs and Symptoms among the respondents were Shortness of breath 66.7%,

whereas Cough, Fever, Leg pain, Headache, Swelling, and Other (Abdominal pain, Diarrhea, Nausea, Vomiting, Chest pain, dysgeusia and anosmia, High blood pressure,) recorded (61.3%, 50.0%, 14.0%, 13.3%, 12.7%, and 12.0 %), respectively.

Table 1. Participants' demographic information (N= 150)

Variables	Frequency (%)
Age (y)	
(18-25)	3(2.0)
(26-45)	41(27.3)
(46-64)	49 (32.7)
(>65)	57(38.0)*
Gender	
Male	54(36.0)
Female	96(64.0)*
Patient Type	
ER	9(6.0)
ICU	17(11.3)
Inpatient	105(70.0)*
Isolation	19(12.7)
Patients history and risk factors	
Yes	127(84.7)*
No	23(15.3)

*Indicates the highest percent

Table 2. Respondents' history and risk factors (N=150)

Respondents' history	Yes F (%)	No F (%)	Mean ±Std
Hypertension	60(40.0)	90(60.0)	1.40±0.49
Diabetes	69(46.0)	81(54.0)	1.46±0.50
Cardiac disease	25(16.7)	125(83.3)	1.17±0.37
Respiratory diseases	68(45.3)	82(54.7)	1.45±0.49
Neurological disease	6(4.0)	144(96.0)	1.04±0.19
Other*	49(32.7)	101(67.3)	1.33±0.47
Respondents' Signs and Symptoms	Yes F (%)	No F (%)	Mean ±Std
Fever	75(50.0)	75(50.0)	1.50±0.50
Cough	92(61.3)	58(38.7)	1.61±0.49
Leg pain	21(14.0)	129(86.0)	1.14±0.35
Swelling	19(12.7)	131(87.3)	1.13±0.33
Shortness of breath	100(66.7)	50(33.3)	1.67±0.47
Headache	20(13.3)	130(86.7)	1.13±0.34

Other**	18(12.0)	132(88.0)	1.12±0.33

* (Chronic kidney disease Anemia, Chronic liver disease, History of thrombosis, Hypothyroidism, Malignancy, History of venous thromboembolism, Smoker)
**(Abdominal pain, Diarrhea, Nausea, Chest pain, dysgeusia and anosmia, High blood pressure, Vomiting)

Table 3. The Prevalence of DVT and D-dimer value (N= 150)

Variables	Frequency (%)
US imaging finding	
DVT	86 (57.3%)
No DVT	64 (42.7%)
D-dimer	Frequency (%)
D-dimer (<0.5 mg\l)	26 (17.3%)
D-dimer (>0.5 mg\l)	82 (54.7%)
No D-dimer	42 (28%)
Total	150 (100%)

*Indicates the highest percent

Table 3 shows that the majority of the sample according to US finding have DVT (57.3%), while those who didn't complain of DVT represented (42.7%), however, D-dimer level during infection with COVID-19 and there was suspected of DVT in the lower extremities. The number of patients whose D-dimer level was greater than (0.5 mg\l) was (82) patients out of the total sample (150 patients), and the percentage was (54.7%), which is an indication of the presence of thrombosis. And those with a D-dimer level smaller than (0.5 mg\l) were 26 patients, and their percentage was (17.3%), which means that the D-dimer level is normal and is an indicator of the absence of blood clots. And there were several patients for whom the D-dimer analysis was not found in the laboratory, and their numbers were 42 patients, or (28%).
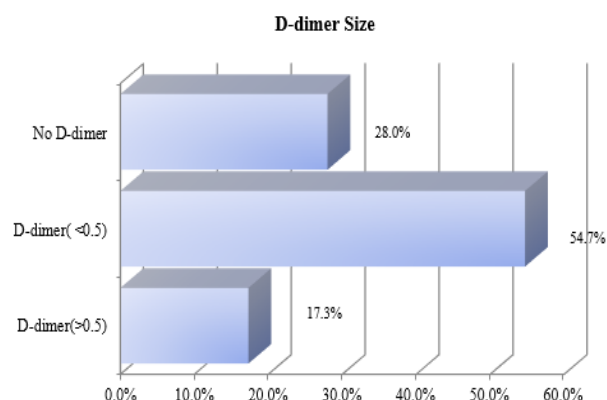

Figure 1. Depicts a pedigree. The volume of the D-dimer for patients with Covid-19 was (>0.5), which is larger than the usual size, and the percentage of patients who had high D-dimer levels was 54.7%, confirming the occurrence of DVT in a substantial percentage.

Table 4. D-dimer levels in relation to the sample age groups

Age	D-dimer			Total
	D- dimer (>0.5)	D-dimer (<0.5)	No D-dimer	
(18-25) y	3	0	0	3
(26-45) y	12	10	19	41
(46-64) y	25	15	9	49
(>65) y	42	1	14	57
Total	82	26	42	150

Table 4 shows the age groups and their relationship to the d-dimer, where it is observed that the age (>65 y) with the D-dimer (>0.5) represented (28%), which is the largest percentage, while the category (46-64y) was (16.66%).

Table 5. Shows the relationship between gender and the prevalence of DVT, and the correlation to gender (N=86)

Gender * US finding Crosstabulation

Gender	US findings		Total
	Presence of DVT	No DVT	
Male	26(17.33%)	28(18.66)	54
Female	60(40%)	36(24%)	96
Total	86	64	150
Gender	D-dimer		P. value
	D-dimer (<0.5)	D-dimer (>0.5)	
Male	7(8.14%)	19(22.1%)	0.034*
Female	8(9.30%)	41(47.7%)	

Table 5 shows the number of females and men diagnosed with DVT, the total number of females was 96, including 60 females with DVT. While the total number of males was 54, 26 of them were diagnosed with DVT. Also, showed that the highest percent was 41(47.7%) in favor of female) in D-dimer (>0.5). Also, the table proved that there was a statistically significant relationship between Gender and D-dimer size (X2=6.746, p. value= 0.034).

While DVT prevalence in patients setting has been a controversial topic, some series point out that DVT prevalence might be increased in the course of COVID-19. Moreover, scores of data have been published about the incidence of DVT in patients with COVID-19 [14]. This study investigated 150 confirmed COVID-19 patients and performed at least a single US scan of the lower limb veins. (38%) of the sample were 65 y and above, followed by age

group 46-64 y with (32.7%), (64%) of them were female, and (70%) inpatient, are shown in **Table 1**.

The prevalence of DVT in this study was 57.3% (n=86). The investigation found a high prevalence of DVT on ultrasound scans and an association between DVT and D- dimer (> 0.5 mg\l) **(Figure 1 & Table 3)**. The 57.3% was proof of the study's aim. It is interesting to note that 70% of DVT patients were recorded from the inpatient department at the variance of recent studies, in close connection with several factors as bedridden time (91. 3%) had a huge effect on them. Our findings suggest a high infection rate in females rather than males ranging between (40 %-17.23%). On the opposite side a study by Demelo-Rodríguez *et al*. (2020) run on (65.4%) of male patients, but their study was limited to screening for asymptomatic DVT [15]. Symptoms and signs were monitored for each patient, symptoms varied between cough, fever, and shortness of breath, and the highest value for shortness of breath was 66.7% **(Table 2)**. A recent study established raised of hepatic enzymes (AST and GGT) related to 40% elevated VTE prevalence so we considered liver enzymes to be screened, the results were not confined to a specific range, so liver enzymes were excluded from the factors affecting DVT in this study [16]. Also, regarding the medical history of each patient, the results showed that; (84.7 %) of the sample had a history of chronic disease. We were surprised to find diabetes the highest percentage of chronic disease with a score of (46.0%), are shown in **Table 2**.

This study shed light on the D-dimer factor based on the majority of recent studies and its effect on blood thrombosis, the results got in touch with high levels of D-dimer in DVTs patients in numbers 82 patients detected with D-dimer up of 0.5, most of them in the age of (>65) while the patients in (18-25) years old got the lowest percentage **(Table 4)**, and this is agree with one previous study [17]. COVID-19 has also link to D-dimer elevation based on previous studies. D-dimer is commonly elevated in patients with COVID-19 correlate with its severity [18]. Through our study, D-dimers were high, especially among females (47.7%) but this association is linked with more than one factor, is shown in **Table 5**. Basims R.'s study (2018). has shown D-dimer levels elevated in females and pregnant patients, the study includes 35 patients diagnosed with malignant breast cancer in their age range between 25 and 65 years, results show twenty of the patients had an elevated D-dimer levels [19].

Our study suggests that there is an additional approach could be the major factor for the elevation of the D-dimer in our sample which is the high altitudes. Several studies indicate that high altitude regions cause a significant rise in D-dimer due to the nature of the atmosphere and the high atmospheric pressure with the psychology of the body, such as Taif, Saudi Arabia in which the research was conducted [20]. This raised our question: Is the elevation of D-dimer in our sample not only related to DVT but also to high altitude areas. In a recent review study entitled 'Travelling to High Altitudes Could be Thrombogenic!", they detected a high level of D-

dimer at high altitudes [20]. In Xiaokang He, *et al*. (2021), a prospective, observational, actively controlled study on 849 patients with COVID-19 hospitalized in Romania between 1.03.2020– 30.11.2020. Determined other parameters that constitute the risk profile for severe COVID-19 evolution, the D-dimer dosing at admission proved to be extremely useful in the management of COVID-19 [21].

In summary, while DVT prevalence in patients setting has been a controversial topic, some series point out that DVT prevalence might be increased in the course of COVID-19. The prevalence of DVT was (57.3%) **(Table 3)**. A high level of d-dimer in DVTs patients is detected which supports a lot of research. Symptoms varied between cough, fever, and shortness of breath, and the highest value was shortness of breath. D-dimers were high especially among females (47.7%). Out of 82 patients with D-dimer up to 0.5 mg\l, most of them are in age (>65) **(Table 5)**. This study stated that; high-altitude regions cause a significant rise in D-dimer among confirmed COVID-19 patients, who had DVT. As a result; age, D-dimer and the altitude of the place are being a significant risk factors for DVT in COVID-19 patients in this study.

CONCLUSION

Ultrasound is a helpful tool for detecting DVT in COVID-19 patients. This study found a relationship between DVT and several risk factors, specifically D-dimer levels greater than 0.5 g/mL Because the prevalence of DVT is higher in this study, we hypothesize that COVID-19 is an additional risk factor for DVT in patients who live in Taif city, which considered a high-altitude city, and by virtue of the geography of the place, it had an effect on some enzymes and hormones in the body, such as the D-dimer, which usually rises in the high areas. The most common age group was 65 years old and above. The association of Covid-19 with DVT depends on several additional factors, including age, D-dimer levels, and the altitude of the place, beside the uses of anticoagulants, but statistically in this study DVT is one of the diseases associated with Covid-19 patients. Finally, this study revealed that sonographic imaging screening for deep thrombosis in patients with substantially higher D-dimer levels is extremely relevant and beneficial. We support the need for ultrasound screening all the more.

Recommendation

More research is needed to explain the increased risk of thrombo-embolic diseases in high altitude areas.

ETHICS STATEMENT: This study was approved by Ethical Committee in both the Radiological Sciences Department, College of Applied Medical Sciences, Taif University, and Directorate of Health Affairs, Ministry of Health at Taif City. The participants will not receive any compensation. Confidentiality and anonymity will be ensured.

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