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# The prevalence of deep vein thrombosis and associated risk factors among patients with COVID-19 in the North of Iran

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**Aim:** We aimed to investigate the associated risk factors of deep vein thrombosis (DVT) among COVID-19 patients. **Materials & methods:** In this cross-sectional study the demographical data and clinical characteristics of 382 COVID-19 patients were collected and analyzed. **Results:** The DVT was observed in 53 patients (14.1%). The rate of death was significantly associated with the incidence of DVT, 48.1 versus 32.2% in non-DVT cases;  $p = 0.034$ . Also, BMI ( $p = 0.0001$ ), renal failure ( $p = 0.001$ ), lower-limb edema ( $p = 0.0001$ ) and intubation ( $p = 0.004$ ) were associated with the risk of DVT. **Conclusion:** COVID-19 patients with a higher BMI, renal failure, lower-limb edema and need for intubation were at a higher risk of DVT.

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**Keywords:** COVID-19 • deep vein thrombosis • DVT • SARS-CoV-2 • venous thromboembolism

COVID-19 is a highly infectious disease and an ongoing global public threat that results in more than 500,000 deaths worldwide [1]. Older age and comorbidities are major risk factors for morbidity and mortality in patients with COVID-19 [2]. The SARS-CoV-2 virus induces an inflammatory state and increases inflammatory factors. This systemic inflammation causes damage to several organs and endothelial tissue and increases the risk of cardiovascular complications and deep vein thrombosis (DVT) [3–6].

A review of research demonstrated an increased risk of DVT, venous thromboembolism (VTE) and potential pulmonary embolism (PE) in respiratory settings. During the coronavirus disease pandemic, a high prevalence of DVT was reported in severe COVID-19 patients, particularly in the intensive care unit (ICU) [4,7,8]. DVT is the presence of a thrombus in the deep venous system, commonly encountered in the lower extremities. It is not only limb-threatening but also threatening life due to the chances of PE [9].

According to recent reports during 2020–2021, the incidence of DVT in hospitalized patients with COVID-19 was reported around 46% [10,11]. The prevalence of confirmed DVT in the lower limbs was 17.4% or 1.74 in 1000 people. The patients with COVID-19 were different in developing DVT based on their history of surgery, trauma, history of chronic obstructive pulmonary disease and previous DVT [12]. The rate of DVT complications in COVID-19 patients was high (69%), besides receiving prophylactic or therapeutic anticoagulation [13]. Patients with DVT were older and had a higher rate of cardiac injury, and worse prognosis, including an increased proportion of deaths [10]. The patients with COVID-19 were different in developing DVT based on their history of surgery, trauma, history of chronic obstructive pulmonary disease and previous DVT [12].

There are a few studies investigating DVT incidence and risk factors specifically in patients with COVID-19. Determining the prevalence of DVT and its risk factors can prevent or cause severe and critical disease and death. Also, it can help with prognosis, screening and preventive strategies. In this study, we investigated the prevalence of DVT and associated risk factors among patients with COVID-19 in a referral hospital in the North of Iran.

Table 1. Patients' demographic and clinical information by two groups (deep vein thrombosis and non deep vein thrombosis).

Variable	DVT (n = 53)	Non-DVT (n = 329)	Total (n = 382)	p-value	
Sex	Male	29 (53.7%)	157 (47.9%)	186 (48.7%)	0.426
	Female	25 (12.8%)	171 (87.2%)	196 (53.1%)	
Age	61.14 ± 11.8	59.2 ± 36.1	59.4 ± 25.1	0.18	
BMI	25.2 ± 22.7	27.3 ± 11.1	26.3 ± 12.7	0.002 <sup>†</sup>	
BP	29 (53.7%)	162 (49.4%)	191 (50%)	0.557	
DM	15 (27.8%)	110 (33.5%)	125 (32.7%)	0.403	
Hyperlipidemia	10 (18.5%)	86 (26.2%)	96 (25.1%)	0.227	
CVD	11 (20.4%)	71 (21.6%)	82 (21.5%)	0.832	
Renal failure	12 (22.2%)	32 (9.8%)	44 (11.5%)	0.008 <sup>†</sup>	
Respiratory disease	13 (24.1%)	45 (13.7%)	58 (15.2%)	0.049 <sup>†</sup>	
Rheumatic disease	6 (11.1%)	10 (3%)	16 (4.2%)	0.006 <sup>†</sup>	
surgery history	10 (18.5%)	46 (14%)	56 (14.7%)	0.387	
Limb transplant	1 (1.9%)	5 (1.5%)	6 (1.6%)	0.858	
DVT history	3 (5.6%)	1 (0.3%)	4 (1%)	0.0001 <sup>†</sup>	
Malignancy	–	16 (4.9%)	16 (4.9%)	–	
Cerebrovascular disease	4 (7.4%)	33 (10.1%)	37 (9.7%)	0.541	
Hypothyroid	4 (7.4%)	19 (5.8%)	23 (6%)	0.644	
The lower-limb edema	52 (96.3%)	41 (12.5%)	93 (24.3%)	0.0001 <sup>†</sup>	
O <sub>2</sub> saturation	80.1 ± 41.2	84.8 ± 53.8	83.9 ± 25.9	0.057	
Respiration count (min)	24.4 ± 14.8	22.5 ± 14.4	22.5 ± 14.6	0.015 <sup>†</sup>	
The length of hospitalization	13.1 ± 2.9	7.6 ± 4.8	8.7 ± 2.9	0.022 <sup>†</sup>	
ICU	26 (48.1%)	64 (19.5%)	90 (23.6%)	0.001 <sup>†</sup>	
Intubation	26 (48.1%)	63 (19.2%)	89 (23.3%)	0.001 <sup>†</sup>	
Prophylaxis	40 (74.1%)	203 (61.9%)	243 (63.6%)	0.085	
Death	26 (48.1%)	109 (32.2%)	135 (35.3%)	0.034 <sup>†</sup>	

<sup>†</sup>The significant level <0.05.

BP: Blood pressure; CVD: Cardiovascular disease; DM: Diabetes mellitus; DVT: Deep vein thrombosis; ICU: Intensive care unit.

## Materials & methods

The present study was conducted as a cross-sectional study. The study population included patients with COVID-19 admitted to Razi Hospital of Rasht, in the North of Iran, from February 2020 to the end of August 2020. All procedures performed in studies involving human participants were in accordance with the ethical code of human genome/gene research at the Guilan University of Medical Science (IR.GUMS.REC.1399.453). They were included in the study by simple random sampling. The data were gathered by using patients documented files. Inclusion criteria were age over 18 years, definitive diagnosis of COVID-19 by PCR, the presence of at least one of the criteria of severe or critical illness: RR  $\geq$ 30/min, SPO<sub>2</sub> <90%, PaO<sub>2</sub>/FiO<sub>2</sub> <300, respiratory failure or need for mechanical ventilation, shock, multiple organ failure or need for ICU hospitalization, and no pregnancy or lactation. DVT patients with severe COVID-19, who died from embolism before the diagnosis of DVT and those without a definitive diagnosis were excluded from the study.

Patient data (age, gender, BMI, underlying disease, etc.) and clinical characteristics (vital signs and symptoms, etc.) were recorded in a checklist (Table 1). Also, the patients clinical course and the occurrence of complications were evaluated daily. For all patients, the lung CT scan at least once and blood tests (including complete blood count, lactate dehydrogenase, CRP) at least three-times (at admission, the next day after the end of treatment and at discharge) were performed. In COVID-19 patients, intravenous color Doppler ultrasound of both the lower extremities and, if symptomatic, the upper extremity was performed by an expert radiologist for DVT diagnosis during hospitalization. Patients without color Doppler ultrasound were excluded. Then, patients with COVID-19 were divided into two groups with and without DVT. Finally, two groups were compared regarding clinical symptoms, the length of hospital stay, the need for mechanical ventilation, intensive care, receiving or not receiving anticoagulant prophylaxis, para-clinical findings, inflammatory markers and death. It is worth noting that the first vaccination of COVID-19 in Iran was in February 2020, and it was only for healthcare workers and some patients

**Table 2. Patients laboratory data by two groups (deep vein thrombosis and non deep vein thrombosis).**

Variable	DVT (n = 53)	Non-DVT (n = 329)	Total (n = 382)	p-value	
WBC count at admission	11.5 ± 3.9	10.5 ± 8.7	10.5 ± 9.4	0.934	
WBC count before discharge or death	10.4 ± 8.9	10.4 ± 2.3	10.4 ± 3.4	0.708	
Platelet count at admission	311.14 ± 15.3	284.1 ± 45.7	288.1 ± 22.09	0.335	
Platelet count before discharge or death	298.1 ± 85.7	274.1 ± 28.07	277.1 ± 47.24	0.276	
LDH level at admission	1214.74 ± 85.7	1003.5 ± 35.9	1033.5 ± 25.5	0.015 <sup>†</sup>	
LDH level before discharge or death	1076.5 ± 17.8	916.4 ± 77.2	939.5 ± 3.9	0.078	
CRP level at admission	1+	11 (20.4%)	82 (25%)	93 (24.3%)	0.61
	2+	26 (48.1%)	135 (41.2%)	161 (42.1%)	
	3+	17 (31.5%)	111 (33.8%)	128 (33.5%)	
CRP level before discharge or death	1+	12 (22.2%)	105 (32%)	117 (30.6%)	0.351
	2+	27 (50%)	143 (43.6%)	170 (44.5%)	
	3+	15 (27.8%)	80 (24.4%)	95 (24.9%)	

<sup>†</sup>The significant level <0.05.  
DVT: Deep vein thrombosis; LDH: Lactate dehydrogenase; WBC: White blood cell.

with severe conditions. The overall development happened after August 2019, and the duration of this study was between February and August 2020, so the vaccination data of the patients were not available.

The data were analyzed via SPSS software (version 21). The frequency with percentage for qualitative variables, mean with standard deviation for quantitative variables in the case of normal, and median with interquartile range (IQR) in the case of non-normal distributions was used for describing data. ANCOVA, t-test and repeated measures ANOVA were used for between groups comparisons. Chi-square was used for qualitative associations. Multiple logistic regression was also used to capture the confounders' effect and p-values less than 0.05 were considered statistically significant.

## Results

The data from 382 hospitalized patients with COVID-19 were analyzed, of which 53 patients had DVT and 329 patients were non-DVT. The mean age in DVT patients was  $61.14 \pm 11.8$  years and 16.6% of them (31 cases) were in age over 60 years. Most DVT patients were males (53.7%) with a BMI of more than 25 kg/m<sup>2</sup> (29 cases, 10.6%). The lower-limb color doppler ultrasound was performed for all patients. Out of the total number of patients, DVT was found in 53 patients (14.1%). In total, 243 patients (63.6%) received anticoagulants drug and 74.1% of DVT patients received prophylaxis. In DVT patients, death occurred in 48% (26 cases). The rate of death in patients with COVID-19 was significantly associated with the incidence of DVT ( $p = 0.034$ ). The prevalence of DVT in COVID-19 patients in terms of the underlying disease is depicted. The high prevalence of DVT was related to lower-limb edema (96.3%) and blood pressure (53.7%), respectively (Table 1).

In a univariate analysis, DVT was associated with BMI, renal failure, respiratory and rheumatic diseases, DVT history, lower-limb edema, respiration count (min), length of hospitalization, ICU, intubation and death. There was no significant relation between DVT and laboratory findings (Table 2) except for lactate dehydrogenase at admission, which was more in DVT patients ( $p = 0.015$ ).

The results of multiple logistic regression to determine the risk factors associated with DVT in patients with COVID-19 indicated that BMI, renal failure, lower extremity edema and intubation were potential risk factors for DVT in patients with COVID-19. Patients with higher BMI, a history of renal failure, lower extremity edema and who required intubation were at a higher risk of DVT. The higher BMI about 1.5-times (OR: 1.5;  $p = 0.0001$ ), history of renal failure about 6.2-times (OR: 6.25;  $p = 0.001$ ), lower extremity edema about 2.9-times (OR: 2.9;  $p = 0.0001$ ), and requiring intubation about 4.6-times (OR: 4.6;  $p = 0.004$ ) were reported in COVID-19 patients with DVT (Table 3).

## Discussion

COVID-19 patients, with very severe diseases, could exhibit a higher risk of venous thromboembolism. There are a few studies investigating DVT incidence and risk factors specifically in patients with COVID-19. The results of our study indicated that DVT was found in 14.1% of COVID-19 patients, which was in line with the estimated incidence of 14.7% in a study by Demelo-Rodriguez *et al.*, in 2020 [14]. Regarding other studies conducted by

**Table 3. The results of multiple Logistic regression to determine the associated risk factors for deep vein thrombosis.**

Variable	Estimation ( $\beta$ )	SD	OR	p-value <sup>†</sup>	CI: 95% for OR	
					Lower	Upper
BMI	0.398	0.106	1.5	0.0001	1.2	1.8
Renal failure	1.835	0.573	6.25	0.001	0.052	0.49
The lower-limb edema	6.308	0.887	2.9	0.001	0.9	3.8
Intubation	1.545	0.54	4.7	0.004	1.6	6.5

<sup>†</sup>The significant level <0.05.

OR: Odds ratio; SD: Standard division.

Middeldorp *et al.* [15], Yuan Yu *et al.* [16], Zhang *et al.* [10], Nahum *et al.* [17] and Ren *et al.* [18], the prevalence of DVT between 20–85% was higher than that obtained from our study. Based on systematic review and meta-analysis reports in 2021, the pooled incidence of DVT in patients with COVID-19 was estimated at 14.8%, which was closest to our study [19].

According to other multiple results of logistic regression in this study, the variables of BMI, renal failure, lower extremity edema and intubation were related risk factors for DVT in patients with COVID-19. In our study, patients with higher BMI (OR: 1.5) were at a higher risk of DVT. Similar results were reported in the study by Ren *et al.* [18] and also, in the study by Nahum *et al.* [17] BMI was more in DVT patients, which was following the results of this study. In our study, patients with a history of renal failure (OR: 6.25) were at a higher risk of DVT. While in studies by Zhang *et al.* [10] and Yuan Yu *et al.* [16], the prevalence of renal failure (1.5–2%) was lower in DVT patients than that in non-DVT (2.2–3.9%); however, the difference was not significant. These results were in accordance with the results of our study. The results of this study also showed that the prevalence of lower extremity edema was more in DVT patients (96.3 vs 12.5%) and those with lower extremity edema (OR: 2.9) were at a higher risk of DVT. In line with our study, Zhang *et al.* demonstrated that lower extremity edema was higher in DVT patients (13.6 vs 11.7%), although it was not significant [10].

According to other results of our study, the frequency of intubation was more in DVT patients (48.1 vs 19.2%) and patients who required intubation (OR: 4.6) were at a higher risk of DVT. In line with our study, Zhang *et al.* [10] and Yuan Yu *et al.* [16] reported that the frequency of intubation was significantly higher in DVT patients (28.8–70%) than that in non-DVT (5.2–31.5%). Similar results were reported in the study by Ren *et al.* with an intubation percent of 83% in DVT patients with severe COVID-19 compared with 42.9% in non-DVT [18].

Severe infection and inflammation might be important contributors to the development of DVT in patients with severe COVID-19. Coagulation activation could also have been related to a sustained inflammatory response [20]. In this study, despite prescribing anticoagulation drugs to about 63.6%, and prescribing prophylaxis in DVT patients to about 74.1%, DVT was found in 14% of COVID-19 patients (54 cases).

Also, the VTE prognostic scores perform only modestly regarding VTE prediction [21] and ultrasound screening seems to be the only way to detect the high occurrence of DVT in hospitalized COVID-19 patients. Furthermore, DVT rates seem to differ regarding the timing of performing ultrasound with higher rates being observed if screening for DVT prior to hospital discharge at the end of hospitalization [22]. In contrast to the occurrence of symptomatic VTE events that are significantly associated with more severe COVID-19 presentation [23], the occurrence of asymptomatic DVT events does not seem to be associated with CRP levels as confirmed in the current study.

In addition to various coagulation complications related to SARS-CoV-2 infection, the adenoviral COVID-19 vaccination as a prophylactic method to decrease the risk of future infection or reduce the worsening of subsequent infection can also lead to different complications such as coagulation disorders. It has been reported that among the adenoviral COVID-19 vaccinated population, the occurrence of thrombosis with thrombocytopenia syndrome as one of the adverse outcomes of this vaccine, has led to a high risk of morbidity and mortality [24]. Although, the patients vaccination details were not available at the time of our study, it would be useful to have this information in future studies and further investigations.

## Conclusion

The results of this study showed that COVID-19 patients with a higher BMI, a history of renal failure, lower extremity edema and who required intubation were at a higher risk of DVT. Besides, the results of this study

indicated that intravenous color Doppler ultrasound should be performed in DVT patients with COVID-19 or at least in high-risk patients. It is recommended to perform multicenter studies to identify other risk factors and to evaluate the incidence of DVT when prescribing anticoagulants with therapeutic doses in high-risk COVID-19 patients.

### Summary points

- The demographical data and clinical characteristics of 382 hospitalized patients with COVID-19 were analyzed and compared in two groups with (n = 53) and without (n = 329) deep vein thrombosis (DVT).
- A total number of 243 patients (63.6%) received anticoagulants drug and 74.1% of DVT group patients received prophylaxis.
- The rate of death in COVID-19 patients with DVT was higher than non-DVT group (p = 0.034).
- The high prevalence of DVT was related to lower-limb edema (96.3%) and blood pressure (53.7%).
- The results of logistic regression showed that BMI (OR: 1.5; p = 0.0001), renal failure (OR: 6.25; p = 0.001), the lower extremity edema (OR: 2.9; p = 0.0001) and intubation (OR: 4.6; p = 0.004) were associated risk factors for DVT in patients with COVID-19.
- The COVID-19 patients with a higher BMI, a history of renal failure, lower extremity edema and who required intubation were at a higher risk of DVT.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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### Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval from Guilan University of Medical Science (IR.GUMS.REC.1399.453) or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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