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Assessment of risk factors for thrombosis in ICU patients with COVID-19

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Abstract

Introduction: High incidence of thrombotic events has been reported in hospitalized patients with COVID-19. Less than 50% of pulmonary embolisms (PE) are associated with signs of deep vein thrombosis (DVT) of the lower extremities.

Objective: To assess the risk factors of deep vein thrombosis (DVT) in intensive care patients with COVID-19 by comparing the clinical features of patients in groups with thrombosis, venous stasis and without deep vein thrombosis.

Material and methods: A prospective cross-sectional study was conducted that included all consecutive adult patients with laboratory-confirmed COVID-19 admitted to the intensive care unit. We investigated chronic comorbid conditions in patients, including arterial hypertension, diabetes mellitus, obesity, chronic kidney failure (CRF), chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF), and cancer which may be a risk factor for thrombosis.

Results: A total of 465 patients were included in the study. Comorbidities were present in 435 of 465 patients (93.55%). Doppler ultrasound (DUS) confirmed deep vein thrombosis in 60 patients (13.8%), which was associated with older age (71.12±13.98 vs. (79.57%), chronic heart failure - 196 (42.15%), obesity - 161 (34.62%), diabetes mellitus - 144 (30.97%), chronic renal failure (CRF) -58 (12.47%) and oncological diseases - 25 (5.38%). Hypertension (p=0.02), diabetes mellitus (p=0.041) and obesity (p=0.01) were significant risk factors for DVT. D-dimer was a statistically significant predictor of DVT formation (p<0.001), an increase in D-dimer per unit increased the risk of DVT by 14%.

Conclusion: The study identified risk factors for deep vein thrombosis in intensive care patients with COVID-19. These include: age, high levels of D-dimer, and comorbidities such as hypertension, obesity, and diabetes mellitus.

Key words: COVID-19, deep vein thrombosis (DVT), thromboembolism, ultrasound diagnostics

Introduction

After the first case of coronavirus (COVID-19) in Wuhan, China in late December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread to more than 200 countries in about 3 months. On March 11, 2020, the World Health Organization (WHO) declared the outbreak a pandemic [1-3].

A high incidence of thrombotic events has been reported in hospitalized patients with COVID-19 [4–17]. Most patients suffer from venous thromboembolic events, with pulmonary embolism (PE) playing a major role and this has an impact on the outcome of the disease [10-17].

One hypothesis is that isolated pulmonary microcirculatory thrombosis of the lung may be the cause of severe atypical cases of acute respiratory distress syndrome (ARDS) of COVID-19 pneumonia. However, PE may occur in patients with COVID-19, especially if clinical suspicion is confirmed by instrumental diagnosis of deep vein thrombosis (DVT) of the lower extremities. Several studies have specifically examined the incidence of DVT in patients with COVID-19 pneumonia or the role of blood tests such as D-dimer in detecting DVT [5–9].

Several mechanisms may contribute to the procoagulant state in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First, it has been demonstrated that an inflammatory condition occurs during COVID-19 that causes endothelial cell dysfunction and leads to increased thrombin production and impaired fibrinolysis. Second, hypoxia can stimulate thrombosis by increasing blood viscosity and inducing signaling pathways dependent on transcription factors [18, 19].

Purpose of the study: To identify significant risk factors for deep vein thrombosis (DVT) in intensive care patients with COVID-19.

Material and methods

We conducted a prospective cross-sectional study that included all adult patients with a laboratory-confirmed diagnosis of COVID-19 admitted to 3 intensive care units of 3 hospitals in Astana with previously undiagnosed DVT or pulmonary embolism (PE). A total of 465 patients were included in the study who developed PE followed by death.

The inclusion criteria for study subjects were patients 18-98 years of age with deep vein thrombosis in COVID-19, of any nationality, who signed an informed consent to participate in this study or was signed from relatives, since 65% of patients were in critical condition (who were on ventilator), with several of the signs and symptoms suggestive of DVT in COVID-19 (swelling of the lower extremities, bluish skin tone, and pain with movement of the lower extremities), with severe and unstable comorbid somatic pathology (diabetes mellitus (DM) , arterial hypertension (AH), obesity, chronic renal failure (CRF), chronic heart failure (CHF), chronic obstructive pulmonary disease (COPD) and cancer. The study also included patients with COVID-19, with elevated plasma levels of D-dimer or changes in the coagulogram (fibrinogen, factor VIII).

Exclusion criteria were patients under 18 years of age, pregnant women, patients after trauma, after surgery, patients with prolonged immobilization prior to COVID-19 infection, patients who had arteriovenous fistula as well as all other patients without COVID-19 with deep vein thrombosis. The inclusion period was 04/22/2020-11/26/2020. Our study was approved by the Local Ethics Committee (Figure 1).

Oropharyngeal swabs were taken upon admission to the hospital in accordance with the protocol of the Republic of Kazakhstan. Condition assessment and disease monitoring were performed along with serological testing for SARSCoV-2 PCR RNA or detection of antibodies against SARSCoV-2, as well as on the basis of the results of a complete blood count, coagulogram, D-dimer, fibrinogen, saturation determination.

Upon admission to the emergency department, all patients underwent computed tomography (CT) of the chest, which revealed bilateral lung disease (ground-glass syndrome, interstitial lung disease) corresponding to viral pneumonia. The degree of lung involvement was classified as ≤ 30%, 31–50%, and ≥ 50% of the total lung area. Lung CT angiography was performed in all patients with high clinical suspicion of pulmonary embolism/deep vein thrombosis (PE/DVT).

166 patients were examined using duplex ultrasound (DUS) in B-mode and, if necessary, with color Doppler blood flow mapping. The studies were carried out on a LOGIQ - 6 and VOLUSON 730 EXPERT device (GE Healthcare, USA) using linear sensors operating in the frequency range of 5–10 MHz. The state of the deep veins of the lower extremities was assessed by ultrasound diagnostic doctors with more than 5 years of experience. The deep veins included in the study were the femoral, popliteal, and distal veins (posterior tibial, peroneal, gastrocnemius, and soleus veins) of the lower extremity. The examined superficial veins were also the great and small saphenous veins of the lower extremity. Lack of compressibility or direct identification in the lumen of a thrombus was used as criteria for the diagnosis of thrombosis. Compression was performed in the transverse plane to avoid slipping of the probe from the vessel wall along the longitudinal axis, which can lead to false negative results. In addition, testing was considered or possibly repeated if DVT was clinically suspected.

During the examination, we took into account the presence of chronic concomitant diseases in the studied patients, such as arterial hypertension, diabetes mellitus, obesity, chronic renal failure (CRF), chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF) and oncological diseases.

For categorical variables, a chi-square test and Fisher's exact test (for subgroups of 5 or fewer people) were used. For quantitative variables, analysis of variance (ANOVA) and Pearson and Spearman correlations were used. For multiple variables, ordered logistic regression models were built, with likelihood ratio tests performed to compare the models. Two-tailed p-significances <0.05 were presented as statistically significant. All calculations were performed using STATA MP 17.0 software (StataCorp LLC).

Results

The mean age (+-SD) of all examined patients was 70.58±11.84 years (range 25 to 98 years), these were all adult patients admitted to the intensive care unit during the pandemic, among which only 2 patients were over the age of 90 years. The sex ratio was 272 (58.49%) : 193 (41.51%) (male: female). The average body mass index was 29.7 kg/m2. Of 465 (44.3%) patients, 206 had a BMI greater than or equal to 30. Of these, 34 (16.5%) patients had DVT.

We selected 166 patients who underwent ultrasonography of the deep veins of the lower extremities and were divided into 3 groups (Table 1).

Table 1 Association of quantitative variables with DVT (mean ± standard deviation (min; max))

	Patient groups			Total	p-value
	No DVT	Venous stasis	DVT		
Age	65.20±11.16 (25;100)	67.23±13.06 (31;91)	71.12±13.98 (36;94)	70.58±11.84 (25;100)	0.006
BMI kg/m2	29.22±6.46 (12.30;60.55)	30.24±6.85 (12.80;49.13)	32.57±10.92 (15.10;70.86)	29.78±7.30 (12.30;70.86)	0.358
D-dimer (µg/ml)	3.24±3.88 (0.1;38.49)	2.96±2.60 (0.12;16)	6.46±3.66 (1;18.5)	3.62±3.87 (0.1;38.49)	0.001
Fibrinogen (g/l)	5.13±1.75 (0.39;15.80)	4.83±1.41 (2.55;9.60)	5.36±2.38 (2.80;20.20)	5.12±1.80 (0.39;20.20)	0.001
SpO2 (%)	78.74±12.71 (34;98)	77.39±11.59 (34;93)	68.22±12.05 (30;94)	77.22±12.95 (30;98)	<0.001
CT (%)	46.35±21.03 (4;98)	47.39±18.79 (13;90)	63.98±16.72 (25;95)	48.75±21.07 (4;98)	0.003

BMI - body mass index, SpO2 saturation, CT - computed tomography

According to the results of the obtained ultrasound data, all patients were divided into 3 groups: with DVT - 60 patients (13.8%) (mean age 71.12±13.98 years), without DVT – 349 patients (74.2%) (67.20±11.16 years), with venostasis – 56 patients (12%) (67.23±13.06) (Figure 1).

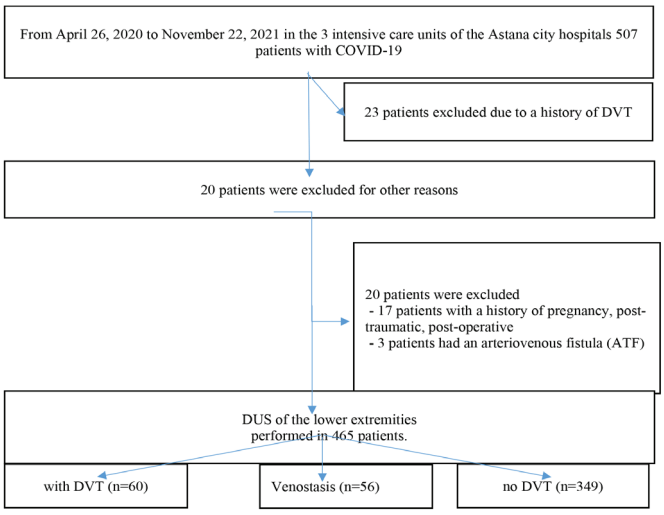

Figure 1 - Selection of patients for study. DVT - deep vein thrombosis; DUS- Doppler ultrasonography

It should be noted that in the group with DVT, the mean age of patients was significantly older than in the group without DVT (p<0.006). When comparing the body mass index in the study groups, it turned out that in patients in the group with DVT and in the group with venostasis, BMI was more than 30 kg/m2 than in the group without DVT (32.57±10.92, 30.24±6.85 versus 29.22±6.46) (Table 1).

In the majority of cases, DVT was detected in the tibial segment 26 (43.33%), in 18 (30%) patients it was diagnosed in the popliteal veins and in 14 (23.33%) cases in the femoral segment.

Coagulation tests showed that D-dimer levels were significantly higher in the DVT group compared to the non-DVT group (6.46±3.66 vs. 3.24±3.88 µg/mL, p<0.001). We obtained a similar difference when assessing the level of fibrinogen in the group with DVT and in the group without DVT (5.36±2.38 versus 4.83±1.41 g/l, p<0.002).

Fibrinogen (5.1 g/L; range 4.5–7.2) and D-dimer (3.6 µg/L; range 0.5<) levels were high. The level of D-dimer ranged from 0.1 µg/ml to 38.49 µg/ml with an average value of 3.62±3.87 µg/ml (Table 1). An increase in D-dimer (≥ 0.50 mg/l) was observed in 90.75% (422/465) of patients.

In all patients, CT scanning of the chest revealed bilateral ground-glass changes and consolidation of the lung tissue. In the

Table 2 Association of qualitative variables with DVT

	Patient group			Total	p-value
	No DVT	Venous stasis	DVT		
Gender					0.809
Female	202 (57.88%)	35 (62.50%)	35 (58.33%)	272 (58.49%)	
Male	147 (42.12%)	21 (37.54%)	25 (41.67%)	193 (41.51%)	
PCR					0.338*
Yes	343 (98.28%)	54 (96.43%)	58 (96.67%)	455 (97.85%)	
No	6 (1.72%)	2 (3.57%)	2 (3.33%)	10 (2.15%)	
Vaccination					0.691
Yes	30 (8.6%)	6 (10.71%)	7 (11.67%)	43 (9.25%)	
No	319 (91.4%)	50 (89.29%)	53 (88.33%)	422 (90.75%)	
X-ray					0.813*
Pneumonia	333 (95.42%)	53 (94.64%)	57 (95%)	443 (95.27%)	
Pleural effusion	16 (4.58%)	3 (5.36%)	3 (5%)	22 (4.73%)	
Hypertension					0.289
Yes	278 (79.66%)	41 (73.21%)	51 (85%)	370 (79.57%)	
No	71 (20.34%)	15 (26.79%)	9 (15%)	95 (20.43%)	
Diabetes mellulitis					0.004
Yes	103 (29.51%)	12 (21.43%)	29 (48.33%)	144 (30.97%)	
Obesity					0.006
Yes	108 (30.95%)	22 (39.29%)	31 (51.67%)	161 (34.62%)	
No	241 (69.05%)	34 (60.71%)	29 (48.33%)	304 (65.38%)	
CHF					0.424
Yes	153 (43.84%)	20 (35.71%)	23 (38.33%)	196 (42.15%)	
No	196 (56.16%)	36 (64.29%)	37 (61.67%)	269 (57.85%)	
COPD					0.581
Yes	36 (10.32%)	8 (14.29%)	8 (13.33%)	52 (11.18%)	
No	313 (89.68%)	48 (85.71%)	52 (86.67%)	413 (88.82%)	
CHF					0.011*
Yes	51 (14.61%)	1 (1.79%)	6 (10%)	58 (12.47%)	
No	298 (85.39%)	55 (98.21%)	54 (90%)	407 (87.53%)	
Cancer					0.146
Yes	15 (4.3%)	4 (7.14%)	6 (10%)	25 (5.38%)	
No	334 (95.7%)	52 (92.86%)	54 (90%)	440 (94.62%)	

Note: CHF-Chronic heart failure, COPD- Chronic obstructive pulmonary disease, CRF- Chronic renal failure

Table 3 Logistic regression. Outcome selected as 2 - DVT, 1 - venostasis, 0 - no DVT

	OR (95% CI)	p-value
Age	0.99 (0.97; 1.01)	0.176
D-dimer	1.15 (1.08; 1.22)	<0.001
Gender		0.935
Female	1	
Male	1.02 (0.64; 1.62)	
Hypertension		0.02
Yes	1	
No	0.70 (0.39; 1.25)	
Diabetes mellulitis		0.041
Yes	1.64 (1.02; 2.62)	
No	1	
Obesity		0.01
Yes	1.80 (1.15; 2.82)	
No	1	
CHF		0.382
Yes	0.81 (0.51; 1.30)	
No	1	
COPD		0.108
Yes	1.70 (0.89; 3.26)	
No	1	
CRF		0.028
Yes	0.39 (0.17; 0.90)	
No	1	
Cancer		0.081
Yes	2.15 (0.91; 5.07)	
No	1.00 (;)	

Note: CHF-Chronic heart failure, COPD- Chronic obstructive pulmonary disease, CRF- Chronic renal failure

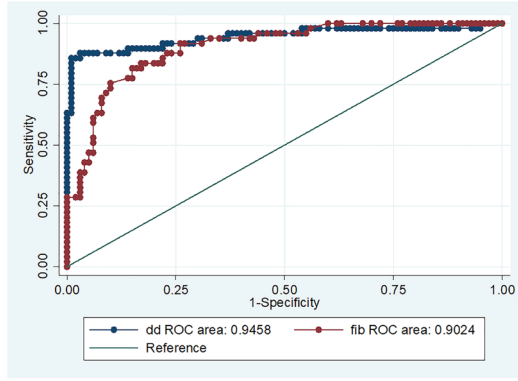

Figure 2 - Dependence of D-dimer and the degree of lung damage on CT

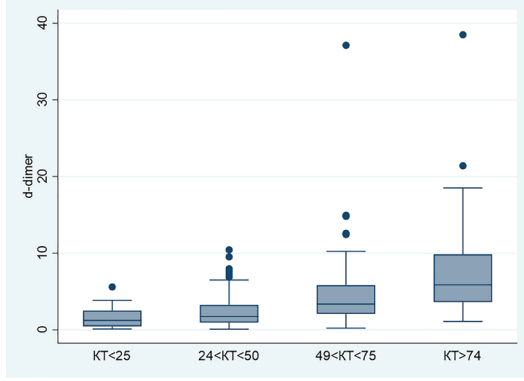

Figure 3 - ROC analysis for statistically significant variable (D-dimer, Fibrinogen

Table 4 Studies to identify venous thromboembolic complications. 2021 meta-analysis results

Authors	Country	Study design	Number of patients	Male	Age	Severity	Anti-coagulants	End points	CT-angio-graphy	PE (%)	DVT (%)
Grillet	France	single center	100	70	66±13	Severe	Unknown	PE	100	23	12.6
Leonard-Lorant	France	single center	106	70	62.5±14.3	Mixed	Yes	PE	100	30.2	23.0
Gervaise	France	single center	72	54	62.3±17.8	Mixed	No	PE	100	18.1	14
Klok	Netherlands	prospective multicenter	184	139	64±12	ICU	Yes	PE, DVT	unknown	35.3	0.5
Al-Samkari	USA	multicenter	400	228	62	Mixed	Yes	PE, DVT	unknown	2.5	2.5
Zhang	China	single center	143	74	63±14	Mixed	Yes	PE, DVT	2.1	0.7	46.2
Ren	China	multicenter	48	26	70 (62-80)	ICU	Yes	DVT	unknown		85.4
Llitjos	France	multicenter	26	20	68 (51.5-74.5)	ICU	Yes	PE, DVT	unknown	23.1	50
Helms	France	prospective multicenter	150	122	63	ICU	Yes	PE, DVT	66.7	16.7	2
Demelo-Rodriguez	Spain	prospective singlecenter	156	102	68.1±14.5	Mixed	Yes	DVT	unknown		14.7
Middledorp	Netherlands	single center	198	130	61±14	Mixed	Yes	PE, DVT	unknown	6.6	12.6
Cui	China	single center	81	37	59.9±14.1	ICU	No	DVT	unknown	-	13.7
Poissy	France	single center	107	78	60.8±14	ICU	Yes	PE, DVT	31.8	20.6	4.7
Bompard	France	multicenter	135	94	64 (65-76)	Mixed	Yes	PE	100	23.7	-
Cattaneo	Italy	singlecenter	64	35	70 (58-77.5)	Mixed	Yes	PE	unknown	-	0
Maatman	USA	multicenter	109	62	61 ±16	ICU	Yes	PE, DVT	unknown	4.6	22
Hekimian	France	singlecenter	51	38	51.9±11	Mixed	Yes	PE	64.7	15.7	-
Artifoni	France	multicenter	71	43	64 (46-75)	ICU	Yes	PE, DVT	45.1	9.9	21.1
Grandmaison	Switzerland	singlecenter	29	18	64.5 ±10	ICU	Yes	PE, DVT	41.4	6.9	38.6
Fraisse	France	singlecenter	92	73	61 (55-70)	ICU	Yes	PE, DVT	29.3	28.3	13
Lodigiani	Italy	singlecenter	362	264	66 (55-85)	Mixed	Yes	PE, DVT	8.3	2.8	1.7
Longchamp	Switzerland	singlecenter	25	16	68±11	ICU	Yes	PE, DVT	36	24	24
Poyiadji	USA	multicenter	328	186	62±15	Mixed	Yes	PE	100	22	-
Fang	Great Britain	singlecenter	93	60	62 (56-69)	Mixed	Yes	PE	100	44.1	-
Valle	Italy	multicenter	114	84	61 (51.2-66)	Mixed	Yes	PE	100	57	18
Manjunath	USA	singlecenter	23	15	61.7	ICU	Yes	PE	43.5	26.1	16,3
Kerbikov	Russia	singlecenter	75	36	63.4	Severe	Yes	PE	unknown	-	20
Ozerman	Kazakhstan	prospective singlecenter	465	193	70.58±11.84	ICU	Yes	PE, DVT	unknown	34.4	13.8

DVT group, the percentage of lung involvement was higher than in the other two study groups (63.98±16.72 vs. 46.35±21.03, 47.39±18.79). Figure 2 shows the D-dimer values in accordance with the degree of lung damage detected on CT. D-dimer values in patients with CT-4 COVID-19 were 4 times higher than in patients with CT1 COVID-19 (median 7.12±5.65 μg/mL versus 1.53±1.20 μg/mL, respectively).

According to the ROC analysis, values for D-dimer >=2.33 μg/ml in the studied patients with a sensitivity of 87.76% and a specificity of 97.00% affect the risk of thrombosis. We also found that 55/60 (91.7%) patients with DVT had D-dimer levels >2.33 μg/mL, while 5/60 patients (8.3%) with DVT had D-dimer levels <2.33 μg /ml Fibrinogen values >=4.64 g/L indicate thrombus formation with a sensitivity of 83.67% and a specificity of 83.00% (Figure 3). Of the two parameters studied, D-dimer (AUC area = 0.9458) is more accurate than fibrinogen (AUC area = 0.9024).

Comorbidities 435 of 465 patients (93.55%) had at least one comorbidity. The most common were arterial hypertension in 370 patients (79.57%), chronic heart failure in 196 patients (42.15%), obesity in 161 patients (34.62%), diabetes mellitus in 144 patients (30.97%), chronic renal failure (CRF) in 58 patients (12.47%) and oncological diseases in 25 patients (5.38%) (Table 2).

Logistic regression analysis showed that the level of D-dimer may indicate the risk of developing DVT. According to our study, D-dimer was a statistically significant predictor of DVT formation (p<0.001), an increase in its value by one unit increases the risk of DVT formation by 14%. Diabetes mellitus (p=0.041) and obesity (p=0.01) were also significant risk factors for DVT. Diabetes mellitus is associated with a 64% increased risk of DVT (Table 3). Obesity increases the chance of DVT by 80%. As for chronic renal failure, in our case, patients with CRF were less likely (by 61%) to suffer from DVT, compared with those who did not have CRF (p=0.028).

Discussion

Due to the high mortality of patients with COVID-19, the first study we conducted in Kazakhstan revealed the main risk factors for the development of thromboembolic events. In this study, we identified the incidence, prevalence, and risk factors for DVT in critically ill patients with COVID-19. DVT is a complication and one of the causes of death in intensive care patients with COVID-19. According to the results of our study, DVT 13.8% occurred as often as in neighboring countries such as Russia (20%) and others (Table 4). Elderly patients who either have comorbidities (obesity, arterial hypertension, diabetes mellitus, chronic heart failure (CHF), chronic obstructive pulmonary disease (COPD), chronic renal failure (CRF)) or are in intensive care (mortality 21.9% in patients over 80 years of age) are at particularly high risk of developing thromboembolic complications [20-21]. In our study, DVT was associated with older age compared with patients without DVT (71.12±13.98 vs. 67.20±11.16, p<0.006).

According to Zhou, F. and al. comorbidities in DVT may increase the risk of pulmonary embolism [22], which is consistent with our results where almost all patients (435 of 465 patients) (93.55%) had at least one comorbidity. This proves that comorbidities such as arterial hypertension, diabetes mellitus, CHF, obesity, which have a high frequency in our study, may also play a role in the development of DVT.

Several researchers have drawn attention to the potential over-prevalence of arterial hypertension among patients with COVID-19 [22-25]. Moreover, hypertension appears to be strongly associated with age, becoming one of the strongest predictors of death associated with COVID-19 [26]. In particular, observational and retrospective studies conducted near the Wuhan area have actually shown that hypertension is the most common comorbidity seen in COVID-19 patients, ranging from 15% to over 30% [25,26]. In our study, in 370 patients (79.57%) with COVID-19, arterial hypertension was the most common comorbidity. Although it was observed in 51 patients (85%) in the group with DVT, however, it was not a significant risk factor for the development of DVT in our case. However, we believe that other comorbidities, such as diabetes mellitus and obesity, may increase the risk of venous thromboembolic complications against the background of arterial hypertension.

Diabetes mellitus is a common comorbidity and causes a worse prognosis in patients with COVID-19 [31-33]. In patients with COVID-19, the incidence of diabetes is twice as high in intensive care units with severely ill patients [27–30]. Indeed, in our study in the group with DVT, 51 patients (85%) had diabetes mellitus and it was a significant risk factor for the occurrence of DVT. In our study, logistic regression proved that diabetes mellitus (p=0.041) was associated with a 64% increased risk of DVT.

Patients with CHF are also at high risk of mortality from COVID-19. According to foreign researchers, heart failure changes the blood coagulation system, which leads to edema of the lower extremities [31-32]. Based on the results of the study, CHF was observed in second place in terms of frequency of occurrence among concomitant diseases, after arterial hypertension (196/465 (42.15%) patients). Moreover, in the group without DVT, CHF was more common than in the group with DVT, and therefore, according to our data, it is not a significant risk factor for the occurrence of DVT (p=0.424).

According to the literature, it is known that if a person's BMI is more than 30 cm2 or a person is obese, then he has an increased risk of severe disease or mortality from SARSCoV-2 infection, and is also at risk of thrombosis [33]. We found a similar relationship in our study: in the group with DVT, 31/60 patients (51.67%) had obesity and was a significant risk factor for the occurrence of DVT. This means that more than half of the patients with thrombosis were obese, while in the group without DVT, obesity was observed in only a third of patients. (p=0.006).

In a cohort study of adults with COVID-19 admitted to intensive care units at 68 US medical centers, CKD was observed in 18.4% of patients at the time of admission to the intensive care unit [34]. In our case, in 58 patients (12.47%), CRF acted as a concomitant disease and demonstrated an inverse relationship with thrombosis. In the group with DVT, CRF was less common (p=0.011). And among patients with venous stasis, only one person (1.79%) suffered from CRF, out of 12.47% of patients with CRF among the entire sample. Thus, CRF was a protective factor against DVT, that is, patients with CRF were less likely (by 61%) to suffer from DVT compared to those who did not have CRF.

One study reported that despite ongoing prophylactic anticoagulant therapy, DVT was detected in 40% of hospitalized patients with COVID-19, and in severe patients with COVID-19, the incidence of DVT reached 65%. [35]. In other studies, the incidence of DVT in intensive care patients with COVID-19 was 27% [36]. A meta-analysis showed that the combined incidence of pulmonary embolism (PE) and deep vein thrombosis (DVT) in patients with COVID-19 was 16.5% and 14.8%, respectively [37], despite anticoagulant therapy.

In a study conducted in Russia during USAS of the veins of the lower extremities, DVT was found in 15 patients (20%), the effect of spontaneous echo contrast (SC) in 53 (70.7%) patients, which indicated blood stasis and a pronounced decrease in venous blood flow velocity in common femoral veins. In most patients, thrombi were found in the tibial segment in 13 patients (86.7%) and in 2 patients (13.3%) in the femoral segment [38].

In our study, DVT was detected in 60 (13.8%) resuscitation patients who underwent ultrasonography of the lower extremities. In most cases, DVT was detected at the level of the tibial segment. And the effect of spontaneous contrasting, indicating the presence of venostasis, was detected in 56 (12%) patients. The effect of spontaneous contrast enhancement of vein lumen in patients with coronavirus disease is associated with increased viscosity, i.e., blood clotting, an increase in the frequency of thrombotic events and complications. Assessing the presence of spontaneous echo contrast (SC) on ultrasound is a promising strategy and may be a useful alternative to laboratory measurements [39].

According to the results of the meta-analyses carried out by Jean-François Llitjos et al. and Li J et al., high D-dimer was found to be a major risk factor for DVT and that patients at high risk of DVT are more likely to be admitted to the intensive care unit [40, 41]. This could be due to a syndrome of systemic inflammatory response to activation of blood coagulation, defined as a high level of fibrinogen. In our study, high levels of fibrinogen and D-dimer were found in COVID-19 patients with respiratory failure as an indicator of hypercoagulability. These indicators were significantly higher in the group of patients with thrombosis, so it is necessary to take into account their significance when prescribing DUS even when there are no clinical symptoms of DVT. Elevated D-dimer and DUS values will be able to timely detect asymptomatic DVT and prevent thromboembolic complications in intensive care patients with COVID-19 in the future. In patients at low risk of DVT, the diagnosis can be safely ruled out if D-dimer levels are normal. On the other hand, if in patients at high risk of DVT, D-dimer analysis will be insufficient and ultrasound examinations are necessary.

In our study, all patients were in intensive care and we also found a D-dimer cut-off value, which indicates thrombosis with high sensitivity and specificity.

Because clinical signs do not allow diagnosis of DVT to be assessed, D-dimer levels can be used in combination with other parameters to provide timely ultrasound, making our study unique.

The study has many strengths. Firstly, the study was conducted prospectively and there were many opportunities to investigate risk factors for thrombosis at a glance. Second, this study is the largest study to date in the Republic of Kazakhstan, specifically designed for the timely diagnosis of DVT and assessment of the frequency of DVT in patients with COVID-19 undergoing venous ultrasound. The high frequency of DVT found in our patients with severe COVID-19 who were on prophylactic treatment and the correlation with respiratory parameters and some important laboratory data suggest that they can be used as a screening tool for patients who should undergo ultrasound. In these patients, ultrasound can be considered a useful and reliable tool for the early detection of DVT.

The present study had several limitations. DUS has been performed in a limited number of patients, largely due to the lack of available resources to scan all patients with elevated D-dimer levels and associated risk of death. Moreover, DUS was performed earlier in patients with DVT, and patients without DVT received a higher dose of heparin, so underestimation of DVT can be suspected in some cases. This suggests that clinical and laboratory suspicion before the study is always required. Also, the study was limited to screening for asymptomatic DVT, so the incidence of PE and the role of D-dimer in the diagnosis of PE remain unknown. The limited sample size may have limited the significance of our results. As for chronic renal failure, in our case, patients with CRF were less likely (by 61%) to suffer from DVT, compared with those who did not have CRF (p=0.028). If the study included a large number of patients, chronic renal failure may have shown another statistically significant predictor of DVT, which is a limitation in our study.

Conclusion

Our study confirmed that COVID-19 is associated with a high incidence of deep vein thrombosis (13.8%) in critically ill patients, in line with global statistics. Significant risk factors for DVT in patients in intensive care with COVID-19 are older age, high levels of D-dimer, and comorbidities such as obesity, diabetes mellitus. The identified factors must be taken into account for the formation of high-risk groups of patients with the development of thromboembolic events.

The threshold value of D-dimer calculated by us (>-2.33 μg/ml) is a predictor of thrombosis, which is an indication for the timely appointment of ultrasonic scanning of deep veins of the lower extremities. Timely correction of thrombolytic therapy based on coagulogram parameters and ultrasound results will help reduce the number of thromboembolic events in critically ill patients with COVID-19

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