JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Short Communication DOI: https://doi.org/10.23950/jcmk/12277

# Preventive ultrasound diagnosis of deep vein thrombosis of the lower extremities in patients with COVID-19

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Received: 2022-03-29.
Accepted: 2022-06-23



J Clin Med Kaz 2022; 19(4):59-63

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**Abstract**

**Aim:** The aim of the study was to determine the risk group for detecting early signs of thrombus formation in the veins of the lower extremities during preventive ultrasound examination in patients with COVID-19.

**Materials and methods:** The study included three groups of patients who were in intensive care units for COVID-19, of which 50 with acute venous thrombosis, 50 with venostasis in the veins of the lower extremities, and 50 patients without vein pathology, which constituted the control group. All patients were determined the level of D-dimer, fibrinogen and underwent duplex ultrasound scanning examination of the veins of the lower extremities.

**Results:** A close correlation was established between the presence of venous thrombosis and the levels of D-dimer and fibrinogen (2.33, 4.66, p=0.0001). According to the data obtained, in the examined patients values >=2.33 μg/ml for D-dimer is a sign of thrombus formation with 87.76% sensitivity and 97% specificity. For fibrinogen values 0. >=4.64 g/L are indicative of thrombus formation with 83.67% sensitivity and 83.00% specificity. The two studied parameters D-dimer (AUC area = 0.9458) and fibrinogen (AUC area = 0.9024) were a very high-quality classifier model.

**Conclusion:** The results of this study make it possible to form risk groups for the development of deep vein thrombosis (DVT) and to carry out timely prevention of this pathology. In patients with COVID-19 with severe respiratory failure and elevated levels of D-dimer (more than 2.33 mg/l) and fibrinogen (more than 4.64 g/l) duplex ultrasound is indicated.

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

## Introduction

A new coronavirus infection, now classified as COVID-19 and first identified in December 2019 in the Chinese city of Wuhan, is accompanied by an exponential increase in the number of infected people and significant mortality in many countries [1].

The ongoing COVID-19 (SARS-CoV-2) pandemic demonstrates not only the high aggressiveness of a new infectious agent, but also its ability to cause severe cardiovascular complications. One of them is the high prevalence of thrombotic complications, especially in the group of patients with a severe course of the infectious process [2].

COVID-19 predisposes to thrombosis and venous thromboembolism (VTE) due to excessive inflammation, platelet activation, endothelial dysfunction and stasis. An increase in the level of fibrinogen and factor VIII, activation of coagulation and a direct damaging effect of the virus on the endothelium play an important role in the development of thrombotic complications [3]. The incidence of DVT and pulmonary embolism (PE), according to prospective population studies is 160 and 60 cases respectively per 100,000 population per year [4, 5]. To refer to these diseases in foreign literature, the term "venous thromboembolism" (VTE) is used in the domestic literature "venous thromboembolic complications" (VTEC) [6, 7].

Deep vein thrombosis (DVT) of the lower extremities is one of the main causes of death from PE [8]. Most venous thrombi are not clinically manifested [9]. The "gold standard" for early diagnosis of DVT in COVID-19 is ultrasound using B-mode, color and power Doppler mapping as the most informative method [10]. According to the literature, the accuracy of diagnosing thrombosis of the veins of the femoral-popliteal segment is more than 90%, of the veins of the lower leg from 50 to 90%. [11].

Prevention of VTEC is one of the main problems of modern medicine, given the complexity of diagnosis the severe consequences of this pathology and significant economic losses [12]. Currently, the search for a screening method for the early diagnosis of DVT, which must meet two criteria objectivity and accessibility - is relevant. In this regard, the aim of this study was to determine the risk group for detecting early signs of thrombus formation in the veins of the lower extremities during preventive ultrasound examination in patients with COVID-19.

## Material and methods

The design of the study was comparative. In working with patients, all the ethical principles required by the Declaration of Helsinki of the World Medical Association "Ethical principles of scientific and medical research involving humans (as amended in 2008) were observed. The study plan was approved by the local bioethical committee at NJSC "Astana Medical University". The study included three groups of patients who were in intensive care units for COVID-19. Patients of all groups underwent ultrasound scanning of the lower extremities, regardless of the presence of symptoms of DVT. The first (main) group consisted of 50 patients with thrombosis of the main veins of the lower extremities, the second group (comparison) included 50 patients with signs of venous stasis, and the third (control) group consisted of 50 patients without DVT. The age of the patients of the first group was from 40 to 94 years (mean age 69.18±14.50 years), in group 2 - from 40 to 92 years (mean age - 69.4±10.90 years), in group 3 - from 31 to 97 years (mean age - 69.06±12.84 years).

Duplex ultrasound was performed on LOGIQ P6 ultrasound scanners (GE Healthcare, USA) using linear transducers operating in the frequency range of 3–10 MHz. The veins from the inguinal ligament to the ankle were examined, including the common femoral vein (CFV, DFV, and SFV), popliteal vein (PV), posterior tibial vein (PTV), peroneal vein and intermuscular vein of the calf. DVT was diagnosed according to the ultrasound protocol in accordance with the recommendations of the Society of Ultrasound Sonographers for deep vein thrombosis of the lower extremities [13].

The studies were carried out in the supine position at rest, using a compression test. Duplex ultrasound examination was carried out in B mode in transverse scanning of the vein, if necessary power and color Doppler mapping mode were used. The standard criterion for assessing the patency of a vein is the level of its compressibility. Complete or partial incompressibility of the vein (indirect sign) is the only parameter required for the diagnosis of DVT. Mild progressive compression of the veins limited the risk of iatrogenic embolization. Compression testing was repeated every 2 cm over a 12 cm segment at each level [14, 15]. Signs of flotation of the thrombus head and the degree of occlusion were checked using power and color Doppler mapping. The advantages associated with 4-point ultrasound are that it is a simple, safe (i.e. no ionizing radiation) procedure, affordable, inexpensive, reliable (with sensitivity and specificity on the order of 90 to 100%) and fast (from 3 to 5 minutes), limiting potential exposure to the virus and the risk of infection.

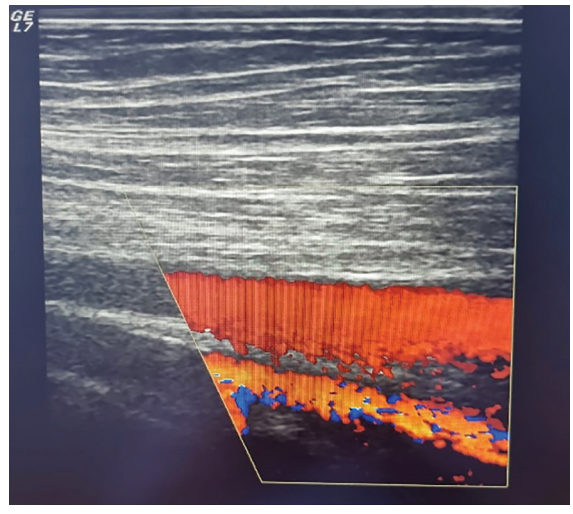
Laboratory data were collected at the first evaluation after the patients were admitted to the intensive care unit. The level of D-dimer was determined by a rapid quantitative method (D-dimer test, Finecare, China), fibrinogen on the analyzer Sysmex CA-1500 (semi-automatic coagulometer Start 4.0, Japan). Plasma samples were collected during the first 24 hours after hospitalization. The threshold value of D-dimer below 0.5 μg/ml, fibrinogen 1.8-3.5 g/l recommended by the manufacturer to exclude VTE was considered normal plasma levels.

MS Excel and Stata 14.2 (StataCorp) were used for data analysis and processing. Quantitative parameters are presented as mean, standard deviation, minimum and maximum values. To determine a statistically significant difference between groups of a continuous variable, a parametric one-way ANOVA (one-way analysis of variance) study was used if the variable was normally distributed. If not, an analog of one-way ANOVA related to the non-parametric research method the Kruskal-Wallis test was used. The difference in indicators is statistically significant at $p<0.05$.

## Results

The criterion for inclusion of patients in the control group was the absence of ultrasound signs of venous pathology. The lumens of the deep veins of the lower extremities completely subsided during the compression test. Valves in the form of thin hyperechoic strips moved away from the wall of the vein during inhalation and pressed against it during exhalation. The lumen of the veins was homogeneous and anechoic (Figure 1).

**Figure 1** - Ultrasound signs of the absence of thrombosis: complete staining of vein on color flow Doppler




With incomplete vein compression in obese patients and in patients with severe edema of the lower extremities, the absence of thrombosis was checked using the power and color Doppler. Full mapping of the lumen during the test with distal compression testified to the absence of thrombosis. The average values of D-dimer in the control group corresponded to the values of 0.89±0.52 [0.22-2.783] μg/ml, and fibrinogen 3.55±0.65 [1.2-4.53] g/l.

In the second group of patients with ultrasound, the "effect of spontaneous contrasting" of the lumen of the veins was observed. This effect consists in the visualization of an inhomogeneous hypoechoic lumen of the veins, due to multiple

**Figure 2** - The effect of "spontaneous contrast" in the lumen of the femoral vein

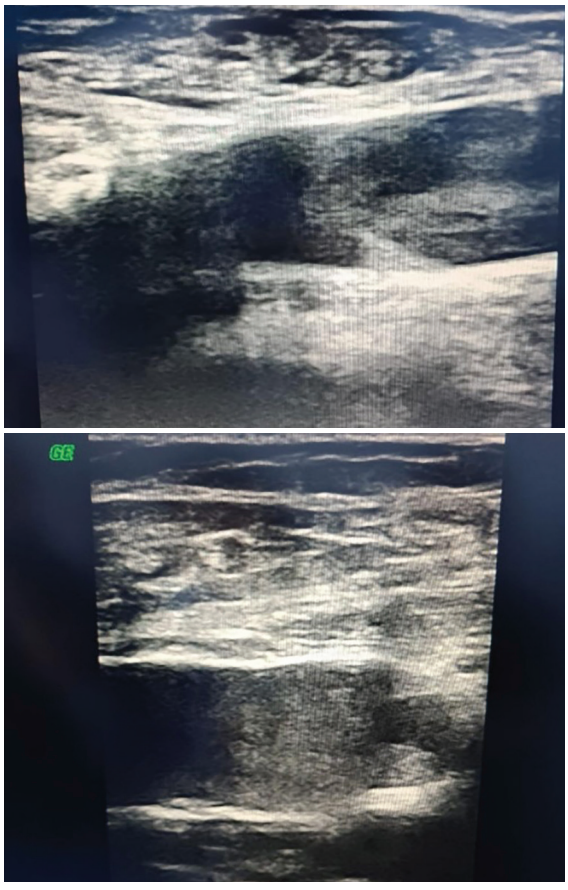


**Figure 3** - Occlusive and non-occlusive thrombosis of the femoral vein

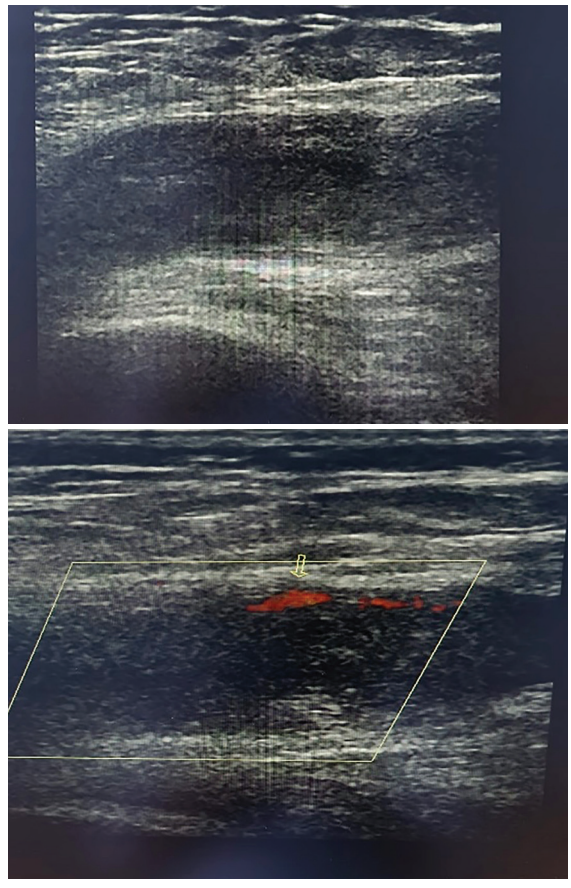


**Table 1** Level of D-dimer and fibrinogen in groups of examined patients

| | Group 1 | Group 2 | Group 3 | p-value |
|---|---|---|---|---|
| D-dimer | 4.94±2.57[0.318-10.58] | 1.26±0.60 [0.396-3.8] | 0.89±0.52 [0.22-2.783] | 0.0001 |
| Fibrinogen | 6.07±2.53 [3.81-20.2] | 4.42±0.74 [3.18-6.4] | 3.55±0.65 [1.2-4.53] | 0.0001 |

**Table 2** Sensitivity and specificity of D-dimer and fibrinogen in patients with COVID-19

| | AUC | Cutoff | Sensitivity | Specifity | Youden index |
|---|---|---|---|---|---|
| D-dimer | 0.9458 | ≥ 2.33 | 87.76% | 97.00% | 0.8476 |
| Fibrinogen | 0.9024 | ≥ 4.64 | 83.67% | 83.00% | 0.6667 |

echo-positive inclusions that are displaced during a compression test. This effect is due to the accumulation of blood cells, slowing of blood flow and the phenomena of its turbulence (Figure 2). Turbulent blood flow in the area of the sinuses contributes to venostasis and in the case of an imbalance between the coagulation and fibrinolytic systems, a thrombus subsequently forms in the niche of the valvular sinus and spreads further along the vein [16, 17].

The average values of D-dimer in the 2nd group of patients with venostasis corresponded to the values of 1.26±0.60 [0.396-3.8] µg/ml, and fibrinogen - 4.42±0.74 [3.18-6.4] g/l

The group with thrombosis was characterized by the absence of compressibility of the vein heterogeneous hypoechoic thrombus masses were visualized in its lumen, which completely occluded the lumen. However, no lumen mapping was observed using the power and color Doppler mapping. Non-occlusive venous thromboses were diagnosed with incomplete compression of the vein while parietal blood flow was recorded in the color flow mode and in the power mode along the walls free from a blood clot.

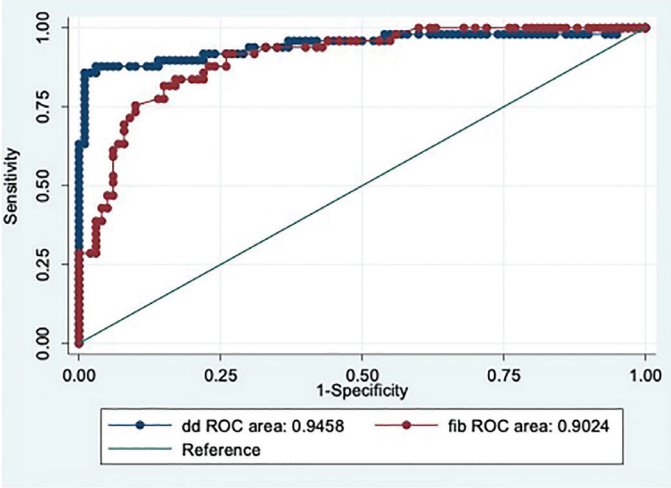
The average values of D-dimer in the group of patients with thrombosis was 4.94±2.57 [0.318-10.58] µg/ml, and fibrinogen - 6.07±2.53 [3.81-20.2] g/l.

According to the data obtained, the level of D-dimer and fibrinogen was statistically significant between the three compared groups ($p=0.0001$, $p=0.0001<0.05$, respectively) (Table 1).

To solve the problem of determining the value of the level of D-dimer and fibrinogen in homogeneous groups of patients with COVID-19 differing in outcome the presence of thrombosis, the presence of venostasis and the absence of thrombosis, the ROC analysis method was used. Using the ROC-analysis data the prognostic values of the method for determining the level of D-dimer and fibrinogen in the above groups of patients were obtained and cut-off value points were determined for the level of D-dimer and fibrinogen in each group of patients, above which an increase was observed number of outcomes (formation of thrombosis).

In the group of patients with COVID-19 and the presence of deep vein thrombosis of the extremities the D-dimer cut-off

**Figure 4** - ROC curve for detecting possible thrombosis when using the level of D-dimer and fibrinogen in the laboratory diagnosis of complications in patients with COVID-19




point was determined to be 2.33 µg/ml. When using this level of the laboratory marker of venous thrombosis the area under the curve (AUC) was 0.94 (95% CI (0.899; 1.002), which means a high degree of efficiency of the classifier [18]. Sensitivity was 87.76%, specificity 97% for D-dimer (Table 2), the positive predictive value = 93.478%, diagnostic efficiency = 93.96% [19].

For fibrinogen values >=4.64 g/L were indicative of thrombus formation with 83.67% sensitivity and 83.00% specificity. For fibrinogen, positive predictive value = 70.69%, diagnostic efficiency = 83.221% [19].

Thus, the two studied parameters D-dimer (AUC area = 0.9458) and fibrinogen (AUC area = 0.9024) were a very high-quality classifier model.

## Conclusion

The results of our study may allow the formation of risk groups for the development of deep vein thrombosis and timely prevention of this pathology. In patients with COVID-19 with severe respiratory failure and elevated levels of D-dimer (more than 2.33 µg/l) and fibrinogen (more than 4.64 g/L), preventive ultrasound of the veins of the lower extremities is indicated, even in asymptomatic patients.

Outside of intensive care, there is no indication for systematic screening for venous thromboembolism in patients with COVID-19 in the absence of clinical symptoms, as stated in French and European guidelines [20]. This will unnecessarily expose medical and nursing staff to the risk of infection and transmission, as well as the risk of nosocomial infections in patients. However, systematic testing of D-dimer and fibrinogen may be a valuable tool for predicting the severity of COVID-19 and the risk of thromboembolic complications.

**Disclosures:** There is no conflict of interest for all authors.

**Acknowledgements:** None.

**Funding:** None.

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