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Risk factors assessment of venous thromboembolism in patients after COVID-19

SUMMARY

COVID-19 is a systemic disease characterized by dysregulation of the immune system and increased coagulability. COVID-19-related coagulopathy is a crucial aspect of the disease, and its early diagnosis, prevention, and treatment may limit its evolution toward potentially irreversible pulmonary and systemic diseases. Difficulties in diagnosing VTE in the course of COVID-19, during the acute period of the disease and after *SARS CoV-2* infection, are caused by the common symptomatology of pneumonia and pulmonary embolism and/or DVT, as well as the frequent co-occurrence of other lung or circulatory system diseases. Based on the existing literature, it is known that *SARS CoV-2* infection intensifies prothrombotic processes in the vessels, which may result in the worsening of the disease and even death of the patient in the case of absence or delayed diagnosis. However, it is not yet known what factors may influence the pathogenesis of chronic inflammation in patients with persistent clinical symptoms after *SARS-CoV-2* infection, which may be responsible for the occurrence of thromboembolic complications.

The presented study aimed to analyze the factors that may be responsible for developing thromboembolic complications and assess the incidence of VTE in patients after COVID-19. Patients after *SARS CoV-2* infection were subjected to detailed clinical and biochemical analysis to detect possibly existing factors influencing the risk of these complications.

The study was prospective. Consecutive patients admitted to the Pulmonary Department of the Institute of Tuberculosis and Lung Diseases (IGiChP) to establish the diagnosis of persistent clinical symptoms such as shortness of breath, cough, chest pain, and DVT symptoms and/or who were diagnosed with venous thromboembolism during or after suffering from COVID-19 and signed an informed consent form were qualified for the study.

One hundred eight patients were enrolled: 39 (36,11%) women and 69. (63,89%) men. The mean age was 57,52±13,14 years; the youngest patient was 29 years old, and the oldest was 82 years old. Patients were assigned to two groups: with a diagnosis of venous thromboembolism – 43 people (39,81%) and without a diagnosis of this disease – 65 people (60,19%). Both groups did not differ significantly in terms of demographics, severity of the course and treatment of COVID-19, and the period of testing since the *SARS-CoV-2* infection.

All patients had biochemical blood tests twice, with a median time between tests of 8 months (min. 5 – max. 15). The levels of pro-inflammatory cytokines IL-1ß, IL-6, IL-8, IL-10, TNF-α, and the concentrations of ferritin and PAI-1 were determined twice.

Each patient underwent an ultrasound examination of the veins of the lower limbs. In patients without previously diagnosed PE, who were at risk of developing embolism, chest computed tomography with pulmonary angiography was performed.

Both groups did not differ statistically significantly in terms of demographics, the severity of the course and treatment of COVID-19, and the period of testing since the SARS-*CoV-2* infection.

All patients with *SARS CoV-2* were detected by PCR or antigen tests. The most common method of confirming *SARS-CoV-2* was the PCR test, which detected infection in 71% of patients.

The incidence of VTE in patients after *SARS CoV-2* infection in the study was as high as 40% (39,81%). In the acute period of COVID-19 disease, VTE was diagnosed in 16,67% of patients. After the SARS-CoV-2 infection, 6,48% of cases were diagnosed on an outpatient basis, and the other 16,67% of cases of this disease were diagnosed during the first visit to our department.

The median period from the diagnosis of COVID-19 to the measurement of selected parameters was 150 days (10-630). In the group with VTE, it was 120 days (min. 11 – max. 630 days), and in the group without VTE, it was also 180 days (min. 10 – max. 630). The difference was not statistically significant.

Among all patients participating in the study, at least one comorbid disease occurred in 50,93% of patients—48,84 % in the group with VTE and 52,31% in the group without VTE. The most common concomitant disease was hypertension, which occurred in 50,93% of patients. 18,52% of patients had diabetes, 15,9% had heart failure, and 13,8% had interstitial lung disease. No significant difference was found between both groups with and without VTE.

The median TNF-α concentration during the first visit was significantly higher in the group of patients with VTE than in the group of patients without VTE, respectively to 37,23 pg/ml (3,33-206,49) and 27,94 (13,97-206,49) pg/ml (p=0.015).

During the second visit, after eight months (eight-month median), TNF-α concentration in the group of patients with VTE was still higher and respectively was 28,96 pg/ml (2,21-281,62) vs.– 25,22 pg/ml (11,86-74,73) in the group without VTE. However, the difference was not significant.

A ROC curve for TNF-α concentration was determined. The area under the curve (AUC) was 0,6179. The sensitivity of VTE detection using TNFα concentration was 62,9%, and the specificity was 62,5% for the concentration of >30.15 pg/ml.

The mean d-dimer concentration during the first visit was higher in the VTE group than in the group without VTE, amounted 2177,22 ± 3490,27 ng/ml and 802,36 ± 1262,52 ng/ml, respectively. No significant difference was found between both groups. There were no statistical differences in the concentrations of the remaining parameters: IL-6, IL-8, IL-10, PAI-1, and ferritin during both visits.

According to our knowledge, for the first time, this work showed an increased concentration of TNF-α within approximately 120 days from the onset of COVID-19 in patients with VTE. Testing the TNF-α concentration at this time after COVID-19 and finding a value above 30,15 pg/ml, together with probable clinical symptoms of VTE (PE or DVT), should result in a diagnostic procedure for venous thromboembolism. The D-dimer concentration in both study groups was elevated but did not differ significantly or differentiate between patients with and without VTE.

The results of this study provided significant information, which may imply diagnostic and therapeutic activities dedicated to symptomatic patients after COVID-19. It seems that increased TNF-α concentration may be an additional factor in making diagnostic decisions.

It is worth highlighting that this study is the first significant piece of information of this type in the literature.