COAGULOPATHY ASSOCIATED WITH COVID-19 IN PATIENTS INFECTED WITH SARS-COV-2.

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Abstract: Coronavirus infection (COVID-19), considered an acute infectious disease caused by the SARS-CoV-2 virus, is characterized by activation of the hemostasis system. As a result of this, severe cases can develop coagulopathy. Whether COVID-19 is the direct cause of this condition or whether they occur with the development of an infectious process remains unclear for the time being. The frequency of occurrence of asymptomatic and clinically specific thrombotic, thromboembolic complications in COVID-19 remains uncertain. This condition is largely associated with difficulties in diagnosis. The purpose of the work to study the significance of coagulopathy markers in patients with COVID-19 and their prognostic role in various clinical forms of the disease. This study was a single-center retrospective cohort study. The usual blood tests: the number of leukocytes (WBC), the number of lymphocytes (LYM), the number of mononuclears (MONO), the number of neutrophils (NEU), platelets were performed on blood samples. Coagulation functions (fibrinogen (Factor I), (prothrombin time (PT), activated partial thromboplastin time (APTT), (international normalized ratio (INR) were determined using the MINDRAY BA - 88A analyzer (China). The concentration of D-dimer was determined using the ELISA method using reagent kits for enzyme immunoassay determination of the concentration of D-dimer in blood plasma D-dimer - ELISA-BEST. The concentration of antibodies to IgM IgG phospholipids was determined using the ELISA method.

However, according to some data, patients with COVID-19 have a much higher frequency of venous and arterial thrombosis. In this case, the peculiarities of the course of the disease, the search for the factors that causes it and the interest in them from the point of view of study, aroused interest and gave rise to many discussions.

Keywords: COVID-19, SARS-CoV-2, D-dimer, MONO, fibrinogen (Factor I), prothrombin time, international normalized ratio, thrombotic, activated partial thromboplastin time, thromboembolic complications, venous and arterial thrombosis.

Introduction. Coagulopathy (also called a bleeding disorder) is a condition in which the blood's ability to coagulate (form clots) is impaired. This condition can cause a tendency toward prolonged or excessive bleeding (bleeding diathesis), which may occur spontaneously or following an injury or medical and dental procedures. Complications of a new coronavirus infection (COVID-19) are characterized by very different clinical manifestations. Among them, thromboembolic complications play the most important role [1,2]. Soon after the start of the pandemic, doctors noticed that patients with COVID-19 often develop thrombosis with different localization. They were often arterial, and in some cases venous thrombosis. It was found that deep vein thrombosis can reach up to 79% in patients hospitalized with a new coronavirus infection [3,4,5]. Several changes in the coagulogram have been described in patients with COVID-19. SARS-CoV-2 virus, in particular, causes abnormalities such as decreased prothrombin time, increased levels of fibrinogen and D-dimer in the blood. It should be noted that the degree of deviation of these signs is also directly related to the severity of the patient's condition: for example, elevated levels of D-dimer are more common in patients lying in intensive care units, and its average level is the category is higher than in non-resuscitated patients [6,7,8]. The use of anticoagulant therapy in hospitalized patients with a new coronavirus infection has significantly reduced mortality [9,10,11]. Accumulating data indicate that more than 80% of COVID-19 patients are treated with antibiotics, as it is difficult to identify COVID-19 patients without concomitant bacterial infection who could safely stop taking antibiotics. However, recent clinical data show that procalcitonin can help assess the condition of these patients and reduce unnecessary use of antibiotics [12,13]. At the same time, when assessing the time parameter of an increase in platelet activity in patients with a new coronavirus infection, an impression is made of its secondary nature in relation to the activation of plasma hemostasis. Plasma hemostasis is activated from the first days. And platelet activity is 9 of the disease- Increases significantly in the 10th days [14,15,16]. The activation of plasma hemostasis appears to be the main cause of coagulopathy caused by a

new coronavirus infection. SARS-CoV-2 causes sufficient tissue damage caused by the virus. This in turn leads to the activation of the immune system. As a result of this, the tissue factor is activated. Eventually causes activation of plasma hemostasis, due to hyperproduction of various anti-inflammatory IL-6, TNF-a cytokines. The rotational thromboelastometry and thrombodynamics test is used to assess global processes of thrombosis formation and lysis. With these methods, it is possible to determine the exact hypercoagulation in patients with a new coronavirus infection. They showed high density and volume of the thrombus, as well as high rates of its formation [17,18]. Serum levels of CRP and PCT have a significant correlation with the severity of COVID-19 and can be used to as independent factors for predicting disease risk. Serum levels of CRP and PCT can effectively assess the severity of the disease and predict the outcome in patients with COVID-19. The study of the level of CRP in the blood serum is a mandatory laboratory study. Since the level of CRP correlates with the severity of the course, the prevalence of inflammatory infiltration and the prognosis for pneumonia. PCT is a well-known diagnostic marker of bacterial infection. [19]

In COVID-19, changes in indicators that characterize the state of the hemostasis system and are associated with the severity of the disease and its prognosis, an increase in D-dimer levels in the blood, an increase in prothrombin time, as well as an increase in thrombin and partially activated thromboplastin time (APTT) were studied. At first, an increase in the concentration of fibrinogen can be observed in this case. After that, the level of fibrinogen and antithrombin in the blood decreases. This condition is also associated with the severity of thrombocytopenia and its prognosis, and is rarely severe. It is one of the factors that helps to activate this halo that is called immunotrombosis. That is, an increase in the concentration of cytokines produced as anti-inflammatory of the blood clotting system [20,21,22]. He was in the intensive care unit of 3 hospitals in Denmark. 13% of 184 patients with COVID-19 have died. While arterial thromboembolism was fatal in 31% of these patients, severe complications such as deep vein thrombosis, pulmonary embolism, ischemic stroke, myocardial infarction were reported in the remaining patients. Meanwhile, objectively confirmed venous thromboembolic complications prevailed over arterial thrombosis. That is, pulmonary artery thromboembolism (O'ATE) accounted for

27%, while arterial thrombosis boron fat accounted for 3.7%. In a retrospective study of the only center in China, severe COVID-19 patients (n=81) lying in an intensive care unit had a 25% incidence of deep vein thrombosis (CHVT). In an analysis of 107 patients with COID-19, time pneumonia who were successively admitted to the resuscitation unit in Lille (France), O'ATE incidence was 20.6%. This case in the same period of 2019, there was a much higher rate of 6.1% compared to patients of exactly the same weight. In autopsies, microthrombs have been described in the capillary vessels of the lung. As the main causes of these disorders, the specific effects of viral infection, inflammation, were considered progressive coagulopathy [23,24,25]. In a one-center retrospective study in China, with covid-19 lying in an intensive care unit, 81 patients with severe pneumonia had a D-dimer> 1500 ng / ml with sensitivity of 85.0% and specificity of 88.5 [26,27,28]. Patients with COVID-19 without strict guidelines, given the inadequacy of the usual instrumental examinations, most experts now believe that screening is not necessary to prove whether there are venous thromboembolic complications (TEA)in asymptomatic patients with very high D-dimer levels [30,31,32]. It has been proposed to use two widely used scales in sepsis to assess the nature of hemostasis system disorders in patients with COVID-19. It appears that the first of these characterizes the activation of blood clotting processes during coagulopathy caused by sepsis and indicates a stage of the process that is not yet coagulopathy. There is evidence that this scale can be used to select patients with COVID-19 who are more likely to benefit from the use of anticoagulants.

Thus, there were severe manifestations of COVID-19 that were successively admitted to Tongji University Hospital in Wuhan, China A retrospective study of the electronic medical records of 499 patients revealed 28 of the patients who received mainly preventive doses of heparin. In cases where the sum of scores on the Sepsis-induced coagulopathy scale was >4 or there was a significant increase in blood D-dimer levels, daily mortality was low [33,34,35]. The presence of disseminated intravascular coagulation syndrome (DVS) indicates the development of coagulopathy when it is necessary to replenish the missing components of the blood clotting system. The occurrence of DVS is associated with poor prognosis. Thus, of the 183 patients with COVID-19 confirmed during

hospitalization, DVS was recorded in 71.4% of deaths and only 0.6% of those discharged [36,37,38] in the study cited above.

Results. All patients with COVID-19 included in this study were diagnosed in accordance with the recommendations for the diagnosis and treatment of pneumonia caused by infection with the new coronavirus. All patients had laboratory confirmed infection with SARS-CoV-2 (the result of real-time RT-PCR, specific for SARS-CoV-2, was positive). From the hospitalized patients from January 5 to November 10, 2021, 120 patients were selectively examined at the Bukhara Regional Infectious Diseases Hospital. The patients were divided into severe patients (n=76) and patients with moderate forms (n=44). Of these, 22 (28.9%) patients were hospitalized in the intensive care, 8 (6.6%) patients died. According to the results of laboratory data, it was found that 41 patients had leukopenia, 20 patients had leukocytosis; 98 patients had lymphocytopenia, 4 patients had an increase in the number of lymphocytes, and 18 had normal lymphocyte levels.

The platelet count and coagulation parameters were analyzed in this study.

Of the 120 patients included in the study, thrombocytopenia less than 150x109/l was detected in 109 (90.8%), thrombocytosis - in 6 (5.0%). Indicators of hemostatic homeostasis in patients with coronavirus infection at admission show that the concentration of D-dimer is increased in 57.9% of patients with moderate form, and in patients with severe form it is detected in 75%. A similar pattern was found in the study of prothrombin time, the indicators are responsibly equal to 89.5% and 79.5%. 50% of patients with moderate form have increased fibrinogen concentrations, and patients with severe form account for 75%. APTT was prolonged in 26.3% of patients with a moderate form of the disease, and in 46.9% with severe. APHL IgG and APHL IgM are respectively elevated in 40.9.3% and 52.3% in moderate, 51.3% and 52.3% in severe patients. Based on the data obtained, scientists are wondering whether patients with severe COVID-19 should be tested for antiphospholipid antibodies to assess their risk of thrombosis and progression of respiratory failure. In addition, whether antiphospholipid syndrome treatment methods, such as plasmapheresis, anticoagulant therapy and complement inhibition, will be effective for COVID-19 patients with high titers of antiphospholipid antibodies.

Thus, the SARS-CoV-2 virus leads to activation of the hemostasis system at different levels. Especially from damage to lung tissue, local endothelial damage can lead to plasma hemostasis and platelet activation in the course of the disease. In patients hospitalized with a new coronavirus infection, regular use of anticoagulant therapy seems to be guaranteed. These questions require further research.

Conclusion

1. In the pathogenesis of COVID-19, thrombus activation and thromboembolic complications are an important element. Their severity is related to the severity of the manifestation of COVID-19 and its prognosis. Much remains unclear in the prevention and treatment of TEA in COVID-19.

2. Taking into account previously known facts about the selection of methods of treatment of a particular patient, the feedback of the expert community, which is quickly summing up data on the results of COVID-19 and their various interventions, these experiments remain the priority of the currently operating attending physicians.:Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. JACC. 2020. doi:10.1016/j.ac. 2020.04.031.

3. Thus, such indicators of hemostatic homeostasis as platelet levels, D-dimer, fibrinogen and antiphospholipid antibodies are predictors of COVID-19 associated coagulopathy and indicates the severity of the disease in patients. Further research is required to better understand the pathogenesis of COVID-19 associated coagulopathy.

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