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CHANGES IN THE BLOOD COAGULATION SYSTEM IN POST-COVID PATIENTS

Ruziyev Z. M.
Hematology and clinic laboratory diagnostics department
Bukhara State Medical Institute Bukhara, Uzbekistan

ABSTRACT

COVID-19 is a systemic infection that has a significant impact on the hematopoietic system and hemostasis. Modern approaches to prevention are considered and treatment of thrombotic/thromboembolic complications in COVID-19. The review considers changes in the parameters of the hemostasis system in patients with COVID-19 and analyzes their practical significance.Our data confirm that chronic inflammation leads to disorders of the blood coagulation system towards hypercoagulation, and subsequently to thrombosis, and the more experience and age of patients with COVID-19 and the higher the activity of the underlying disease, the more pronounced are the changes in coagulation hemostasis towards hypercoagulation.

Keywords: hemostasis, antithrombotic therapy, coagulation system, thrombosis, vascular-platelet system, SARS-CoV-2, COVID-19.

INTRODUCTION

One of the most common complications of COVID-19 is hypercoagulation. Gradual increase in the level of D-dimer during the course of the disease is closely associated with the deterioration of the patient's condition and poor prognosis. Lymphopenia is one of the most significant manifestations of this infection and has prognostic potential. The ratio of neutrophils to lymphocytes and the peak ratio of platelets to lymphocytes may also have predictive value in identifying a severe course of the disease. Monitoring the dynamics of the number of lymphocytes and inflammatory markers such as lactate dehydrogenase (LDH), C-reactive protein (CRP) and interleukin-6 (IL-6) can help predict critical illness and facilitate the timely provision of intensive care. Biomarkers such as procalcitonin and ferritin in the blood serum were unsuccessful prognostic factors [1,3,5].

Patients infected with COVID-19, whether hospitalized or treated on an outpatient basis, are at high risk of developing venous thromboembolism (VTE), and therefore early and long-term pharmacological thromboprophylaxis with low molecular weight

heparin is strongly recommended [2,4,6]. In viremia, SARS-CoV-2 mainly affects tissues expressing high levels of ACE2, such as the lungs, heart, and gastrointestinal tract [7,8]. Approximately 7-14 days after the initial symptoms, clinical manifestations of the disease are detected with a pronounced systemic increase in pro-inflammatory cytokines, which can even be called a "cytokine storm". At this point, lymphopenia becomes quite obvious. Although the etiology of lymphopenia in the case of COVID-19 is not fully understood, some factors can be identified that lead to this condition. Activation of cytokines can also be associated with atrophy of lymphoid organs, incl. spleen, which also reduces the number of circulating lymphocytes [9,10,15].Other markers of hypercoagulability, such as prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), increased fibrin breakdown products, severe thrombocytopenia, lead to the development of disseminated intravascular coagulation (DIC) requiring constant vigilance or immediate intervention.

Guan and coll. published clinical blood test data of 1,099 confirmed cases of COVID-19 during the first two months of the epidemic in China. On admission, the vast majority of patients had lymphocytopenia (83.2%), while 36.2% had thrombocytopenia and 33.7% had leukopenia. In the case of a severe course of the disease, these disorders were more pronounced compared with the moderate course of the disease (96.1% vs. 80.4% - lymphocytopenia; 57.7% vs. 31.6% - thrombocytopenia; and 61.1% vs. 28.1 % - leukopenia). These results were in good agreement with four other studies (201 cases of confirmed COVID-19, respectively) over the same period in China [11,12,20]. In particular, two such studies highlighted the association between lymphopenia and the need for intensive care, while Wu et al. revealed an association between lymphopenia and the development of acute respiratory distress syndrome (ARDS). Lymphopenia has also been reported in about 40% of the first hospitalized COVID-19 patients in Singapore. Later, the percentage of patients with lymphocytopenia was confirmed. 69% of patients with low lymphocytes had a reactive lymphocyte population, including a subset of lymphoplasmacytoid cells that was not present in the peripheral blood of patients with SARS in 2003. Evaluation of the dynamics of the number of lymphocytes can help predict the outcome of the disease. Tan and coll. proposed a predictive model based on lymphocyte counts at two time points: at 10-12 days from the onset of symptoms, patients with less than 20% of lymphocytes and less than 5% at 17-19 days have an unfavorable prognosis [13,14,16].

A meta-analysis of nine studies showed that thrombocytopenia is closely associated with the severity of the course of COVID-19: a more pronounced decrease in the number of platelets was noted in the case of deaths. According to multivariate

analysis, the ratio of platelets to lymphocytes during the platelet peak appeared to be an independent prognostic factor for long-term hospitalization. It has been suggested that a high ratio of platelets to lymphocytes is indicative of a more intense cytokine storm caused by increased platelet activation [17,18,21].

Aim of the study: To study indicators of coagulation hemostasis depending on the degree of activity of COVID-19 disease.

Material and research methods. In the hemostasis laboratory of the Bukhara Regional Multidisciplinary Medical Center, a hemostasiological examination of patients was carried out, which included an assessment of the following links of this system:

Coagulation hemostasis - PT, PTI, APTT, INR, Fibrinogen using a coagulometer. As well as vascular-platelet hemostasis - PLT, PCT, MPV, PDW using a hematological analyzer. To study the indicators of hemostasis, our study was carried out on a single-channel coagulometer (HumaClot Junior).

According to a retrospective analysis, the case history from the Bukhara Regional Multidisciplinary Medical Center is a dependent risk factor for worsening the disease to critical (the need to stay in the intensive care unit, mechanical ventilation, death or transfer to sepsis) in 120 patients with confirmed COVID-19 along with blood saturation oxygen and C-reactive protein >200 mg/l was the level of D-dimer >2500 ng/ml (RR 5.8 at 95% CI limits: 3.2-15.2) [14]. In general, it is believed that of the studied indicators characterizing the state of the hemostasis system, D-dimer is the most attractive as a marker of severity and poor prognosis in COVID-19 — its definition is widely available and standardized, and the differences between the groups of the living and the dead are well pronounced [7]. Prothrombin time also has a prognostic value, however, during hospitalization, its changes in patients with an unfavorable prognosis are not as pronounced as in D-dimer, and, in general, slightly exceed the upper limit of normal. Experts of the International Society of Thrombosis and Hemostasis recommend that during hospitalization, determine the level of D-dimer in the blood, prothrombin time, fibrinogen concentration and perform a detailed complete blood count, including the level of platelets, followed by regular monitoring of these indicators (daily or more often with a pronounced increase in D-dimer, increased prothrombin time, blood platelet level 1000 ng/ml [15].

Results of the study and discussion

The study of the level of PT, PTI, APTT, INR, fibrinogen in the study group was carried out. In our study, the activity of PT, APTT and INR in COVID-19 patients were lower than the values of the control group ($p1<0.05$). The superiority of such factors as

APTT, higher values of PTI and fibrinogen in COVID-19 were more accurately observed in comparison with the group, which included patients without COVID-19 pathology (p1<0.05).

As you know, normally most platelets are in an inactive form in all vessels of the bloodstream. However, under pathological conditions, such as systemic inflammation, platelets can spontaneously activate without contact with the subendothelium [17]. Under physiological conditions, there is a low spontaneous aggregation, which increases significantly with inflammation or vascular pathology. Its intensity depends on many factors and, as a rule, is associated with the release of thromboxane A2, a powerful marker of hemostatic potential, indicating the presence of active platelets in vivo [14]. The process of aggregation consists in the attachment of activated platelets in the blood stream to each other and to previously fixed platelets in the area of damage, mediated by fibrin and von Willebrand factor [10, 12]. For our study, an accessible informative marker of activation of the platelet link of hemostasis is the level of HAT. We have found that in patients with COVID-19, not only the number of platelets is statistically significantly higher compared to healthy individuals, but also their functional activity. Low GAT and high platelet thrombocrit is an important indicator of thrombogenic endotheliosis. In connection with the increase in the functional activity of platelets, multiple platelet aggregates are formed, leading to impaired microcirculation and deterioration of myocardial blood supply. To determine the activity of growth hormone, the levels of HAT, MPV, Pct, PDW were examined in the blood. Of the listed GAT values, the values were lower, and Pct and PDW values were higher than the control group and the group of patients with COVID-19 (P<0.05). The superiority of these indicators was also observed when comparing the groups with COVID-19 and not with COVID-19 (P1<0.05), except for the values of the average platelet volume.

Indicators of vascular-platelet hemostasis in patients with COVID-19 Table 1

Indicators	Patients with COVID -19 n = 94	Patients without COVID -19 n=40	Control, n=30	P
GAT 102 sec	13 ± 1,91	16±1.8	**17±1.02**	P<0.05 P1<0.05
Degree of anisocytosis %	**16,9** ± 1,02	12,6 ± 1,02	**9.5±0.5**	P<0.05 P1<0.05
Thrombocrit %	**0,312** ± 0,04	0,217 % ±0,1	**0,10±0.02**	P<0.05 P1<0.05
Average platelet volume %	**9,5** ± 1,06	8,2 ± 1,02	**6,5 ±0.02**	P<0.05 P1=nr

Note: p-differences from control; p1-differences between groups of the first and second groups

CONCLUSION:

Thrombosis activation and, less commonly, thrombotic or thromboembolic complications are an important element in the pathogenesis of COVID-19. Their severity is associated with the severity of the manifestations of COVID-19 and its prognosis. Much in the prevention and treatment of thrombosis in COVID-19 remains unclear. The choice of treatment options for a particular patient remains the priority of the attending physicians, who are currently acting on the basis of previously known facts, considerations of the expert community, rapidly accumulating data on the results of various interventions for COVID19, and their own experience.

According to the literature, patients with COVID-19 showed significant activation of the coagulation and vascular-platelet hemostasis. Revealed not only an increase in the number of platelets, which is a reflection of severe systemic inflammation, but also the activation of the functional activity of platelets. This was confirmed by a significant increase in the performance of this system in patients with COVID-19. Thus, the indicators of coagulation and platelet hemostasis in association with COVID-19 are characterized by a more pronounced destabilization towards high activity of the studied parameters of these systems in comparison with patients who did not fall ill with COVID-19.

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