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PATHOGENETIC ASPECTS OF POST-COVID-19 COMPLICATIONS IN THE BLOOD COAGULATION SYSTEM

Disorders in the blood coagulation system play an important role in the pathogenesis and clinical manifestations of COVID-19 both during the acute phase of the disease and in the post-infectious period. The coronavirus disease is associated with a high risk of thrombotic and thromboembolic complications due to a prolonged state of hypercoagulation, which can occur even after recovery. Despite the extremely large amount of scientific data, the pathophysiological aspects of SARS-CoV-2 infection remain uncertain. The presented review summarizes the results of modern scientific research on pathological changes in the hemostasis system that can occur against the background of the transferred coronavirus disease, and considers the main mechanisms of the development of COVID-19-associated coagulopathies. From scientometric databases PubMed, Scopus, Web of science, ScienceDirect, Google Scholar, etc. the latest publications devoted to this issue were selected and analyzed. Hemostasis is a dynamic, tightly regulated process which is provided by three closely interrelated links: coagulation, anticoagulation, and fibrinolytic. Activation of the coagulation cascade and the platelet link of hemostasis, which causes a prothrombotic state in convalescent patients with COVID-19, is primarily associated with dysregulation of the renin-angiotensin system, a long-term local and systemic inflammatory reaction, an increase in the immune response due to the release of pro-inflammatory mediators that interact with platelets, stimulate the expression of tissue factor, suppress the fibrinolytic system and lead to dysfunction of the endothelial cells of blood vessels, triggering thrombogenesis. Understanding the pathogenetic mechanisms of post-COVID-19 complications and monitoring the main markers of hemostasis (level of D-dimer, fibrinogen, prothrombin time, platelet count, etc.) are important for the timely detection of disorders in the blood coagulation system, and make it possible, depending on the clinical situation, to take timely measures for their correction at various stages of pathology development.

Keywords: COVID-19, SARS-CoV-2 infection, post-COVID-19 complications, coagulopathy, hemostasis, thrombosis.

The coronavirus disease (Coronavirus disease 2019, COVID-19), which is caused by the SARS-CoV-2 virus, has so far affected more than 674 million people and caused more than 6.8 million deaths worldwide, and their number continues to grow steadily. The clinical manifestations of COVID-19 can be diverse, including both mild and moderate symptoms of the disease of the upper respiratory tract, and life-threatening pathological conditions of many organs. Among the most common causes of serious consequences of SARS-CoV-2 infection, which cause serious concern, are respiratory failure, excessive inflammatory response (the so-called cytokine storm), activation of coagulation, thrombosis, disseminated intravascular coagulation (DIC-syndrome), as well as multiorgan syndrome. Subsequently, it turned out that the transfer of the acute phase of the coronavirus disease does not yet mean complete recovery, but is only its initial stage, the severity of which depends on the prevalence of lesions and biological changes in various organs. According to the World Health Organization, the average period from the onset of COVID-19 to clinical recovery in mild cases is about 14 days, in case of severe or critical disease, more than 3-6 weeks. However, in many infected people, the symptoms of COVID-19 in the form of various clinical manifestations can persist much longer and last more than 6 months, in some cases, exacerbations are possible [1]. That is why the terms "Long-COVID-19", which implies the persistence of the SARS-CoV-2 virus, and "Post-COVID-19" when it comes to the preservation of the pathological state of the organism after the transferred coronavirus disease in the absence of an identified pathogen are increasingly used in the professional literature.

Despite the extremely large number of scientific research devoted to the study of pathogenetic mechanisms of SARS-CoV-2 infection and multisystemic aspects of its acute form, a clear understanding of the distant consequences of COVID-19 requires clarification and careful analysis [2, 3]. As is known, structural and functional disorders of many organ systems are often observed in patients who have recovered from the coronavirus disease, including respiratory, cardiovascular, nervous, digestive, and musculoskeletal [4]. Pathological symptoms include rapid fatigue, shortness of breath, headache, arthralgia, myalgia, chronic cardiovascular complications such as heart failure, arrhythmia, atherosclerosis, pulmonary hypertension, arterial aneurysms, etc. [5, 6]. Post-COVID-19 syndrome is a pathological condition that can occur even after a mild or asymptomatic course of the disease caused by SARS-CoV-2 infection, and its development cannot be predicted in advance. Prediction of the degree of severity, duration, risk of complications after suffering from COVID-19 remains a relevant issue, especially in patients with comorbid conditions. Individuals with cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, chronic renal failure, diabetes, metabolic syndrome, and obesity have the greatest risk of negative consequences of SARS-CoV-2 infection [7, 8]. Among the possible reasons for the development of complications are the persistence of the pathogen, oxygen insufficiency, a long-term state of hyperinflammation, autoimmune processes, individual characteristics of the patient's immune response, impaired endothelial functions and increased blood coagulation (hypercoagulation), which leads to numerous micro- and macrothrombosis. According to various sources, complications in the form of arterial and venous thrombosis occur in almost 30% of patients with confirmed COVID-19 and post-COVID-19 syndrome [9, 10].

Disturbances in the hemostasis system play an important role in the pathogenesis and clinical manifestations of COVID-19 both during the acute phase of the disease and in the post-infectious period [11, 12]. As you know, hemostasis is a dynamic, well-regulated process that is ensured by several interconnected structural and functional components, which include the procoagulant link (blood coagulation factors), the anticoagulant link and the fibrinolytic system. Among the most common pathologies of the blood coagulation system in patients who have undergone SARS-CoV-2 infection, there is both latent hypercoagulation, which can be established only by the

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results of laboratory tests, and severe clinical manifestations in the form of pulmonary embolism, deep vein thrombosis, ischemic stroke, myocardial infarction, DIC-syndrome [13]. However, in the majority of published scientific studies devoted to violations in the hemostasis system during the coronavirus disease, attention is mainly focused on thrombohemorrhagic complications during the acute phase of the disease [14]. Only recently, isolated reports on the features of the functioning of the hemostasis system in the post-infectious period began to appear [15-17]. Fan, et al. showed that in convalescent patients with COVID-19, even in the absence of significant risk factors for the development of cardiovascular diseases and thromboembolic complications, persistent hypercoagulation, endotheliopathy, and inflammation may persist for a year after recovery [18]. There is an assumption that similar consequences of COVID-19 in some cases can lead to the development of acute thrombosis, even after a long period of time from the first clinical manifestations of the coronavirus disease [19]. According to studies by Patel, et al., in convalescent patients with confirmed SARS-CoV-2 infection who did not receive anticoagulant therapy, 30 days after hospitalization, the cumulative frequency of thrombosis (including arterial and venous thrombosis) was 2.5%, while the frequency clinically significant bleeding – 3.6% [20].

As is known, at the basis of intravascular thrombus formation, regardless of where it occurs – in the arteries, veins or microcirculatory channel, there are pathological factors that combine into the classic Virchow's triad: a change in blood properties (a state of hypercoagulation), damage to the endothelium of the vascular wall, and impaired blood flow (stasis). Usually, the etiology of coagulopathies is associated with microvascular dysfunction, the interaction of leukocytes and platelets, increased expression of tissue factors in response to the release of inflammatory mediators, and also with the effect of hypoxia on the regulation of transcription factors [21]. To explain the occurrence of coagulopathy caused by COVID-19, various mechanisms are considered, among which the so-called "immunothrombosis" is identified as one of the key ones, the basis of which is the close relationship between inflammation and the blood coagulation system. In particular, systemic inflammation can induce coagulation and cause the development of pathological venous and arterial thrombosis, which, in turn, directly increase the inflammatory process [22].

Structural and functional disorders of the endothelium, which lines the inner surface of blood vessels and ensures their reactivity, play a key role in the development of coagulopathy and activation of the thrombus formation process associated with the coronavirus disease. Persistent endothelial injury is quite common in convalescent patients with COVID-19 [23]. Damage to the vascular endothelium can be caused by a long-term effect of a viral infection, chronic hypoxia, and an inflammatory reaction. Endothelial cells, as it turned out, are the most susceptible to infection with the SARS-CoV 2 virus. Vascular endothelial cells and pericytes, like pulmonary alveolocytes, to a more significant extent, compared to cells of many extrapulmonary tissues, express the angiotensin-converting enzyme-2 (ACE-2), which the coronavirus uses as the main receptor to enter the cell, causing its damage [24]. *In vitro* experimental studies, in which a soluble form of human recombinant ACE-2 (hrsACE-2) was used, proved that SARS-CoV 2 can directly infect cells of blood vessels [25]. The causative agent of COVID-19 by binding to the receptor, modulates its activity, which leads to a decrease in the expression of ACE-2 in tissues, and a further increase in the level of its endogenous substrate – angiotensin II (AT-II), which exhibits vasoconstrictor, inflammatory, procoagulant and antifibrinolytic effects [26]. In general, the renin-angiotensin system (RAS) is one of the main regulatory systems of the oragnism, which participates in the regulation of many physiological and pathophysiological states, is responsible for homeostatic processes, such as vascular tone, blood pressure level, water-electrolyte balance, etc.

Direct damage by the SARS-CoV-2 virus to endothelial cells or the indirect action of the infectious agent through immune reactions, cytokines and free radicals leads to their dysfunction and the development of endotheliitis/endotheliopathy [27]. The main manifestations of endothelial dysfunction are a violation of the bioavailability of nitric oxide, an increase in the synthesis and expression of procoagulant factors by endothelial cells, in particular tissue factor (TF), von Willebrand factor (vWF), selectin, plasminogen activator inhibitor (PAI-1), endothelin-1. Violation of the functions of endothelial cells is accompanied by a change in their properties to procoagulant due to damage to the glycocalyx and loss of anticoagulant proteins; inflammation of the inner lining of blood vessels, which complicates blood flow and may result in microcirculation disorders; narrowing of blood vessels with subsequent development of ischemia of organs, inflammation and swelling of tissues; as well as pathological changes in the blood coagulation system, which are manifested by a decrease in the number of platelets (thrombocytopenia), thrombosis, etc. [27, 28].

The pathophysiological mechanisms that underlie the activation of coagulation due to COVID-19 still require more in-depth study. It is likely that they depend more on the intensity of the individual inflammatory reaction, and not on direct specific viral activity. There is an assumption that the hyperimmune reaction, which can develop during the acute phase of the coronavirus disease, causes the development of long-term systemic "smoldering" inflammation, which results in vascular endothelium damage and complications in the blood coagulation system in the post-COVID-19 period [29]. Clinical studies have shown increased levels of pro-inflammatory cytokines such as interleukin (IL)-17, IL-12p70, IL-1β, pro-angiogenic macrophage inflammatory protein-1 (MIP-1β), and vascular endothelial growth factor 6 months after COVID-19, which indicated the development of chronic inflammation and the process of angiogenesis in more distant terms after SARS-CoV-2 infection [30].

The relationship between the blood coagulation system, the immune system, and inflammation is now being actively studied in various contexts [31]. It is known that SARS-CoV-2, after entering the organism, activates the innate immune system, which leads to the release of a large number of cytokines, chemokines, growth factors and cell adhesion proteins, in particular monocyte chemotactic protein 1 (MCP-1), a transforming growth factor (TGF-β1), tumor necrosis factor alpha (TNF-α), and IL-1β, IL-2, IL-6, IL-8, IL-17, etc. [32]. Excessive synthesis of pro-inflammatory molecules is one of the possible mechanisms underlying endothelial damage and uncontrolled activation of coagulation. Other potential factors include virus-specific mechanisms, including the interaction of the virus with components of the fibrinolytic pathway and RAS, and the influence of comorbid conditions is also important [33]. It is likely that the SARS-CoV-2 virus can directly infect cells of the innate link of the immune system, that leads to immune dysregulation and disorders in the blood coagulation system [34].

Cytokines have a procoagulant effect by activating platelets, releasing tissue factor from macrophages/ monocytes and damaged endothelial cells, inhibiting the anticoagulant link, and inhibiting fibrinolysis. As a result of the coagulation cascade, thrombin is generated, which cleaves fibrinogen with the formation of fibrin, enhances platelet activation, and is a powerful stimulator of protease-activated receptor-1 (PAR-1), which leads to the development of thrombosis both in the microcirculatory channel and in large vessels [35]. It should be noted that persistent prothrombotic changes associated with increased thrombin generation, inhibition of plasma fibrinolysis, increased levels of factor VIII, vWF, and PAI-1 persisted in convalescent COVID-19 patients 4 months after SARS-CoV-2 infection which could indicate the platelets activation and prolonged intravascular coagulation in the post-COVID-19 period [19]. In addition, phosphatidylserine is expressed on various damaged cells and microvesicles, which enhances the coagulation process [36].

An important prognostic value for the development of immunoinflammatory reactions during viral diseases is the complement system, which includes more than 30 proteins and has an effect not only at the level of systemic circulation, but also directly in the cells. Complement is considered as one of the key factors in the pathogenesis of severe form of COVID-19 [37]. *In vitro* studies have shown the activation of the complement system with the participation of the SARS-CoV-2 spike protein [38]. It is indisputable that excessive activation and dysregulation of the complement system during coronavirus infection leads to the development of endothelial dysfunction, acute and chronic inflammation, induction of all links of the hemostasis system, including platelet and plasma, which may result in post-COVID-19 complications. It has been established that increased vascular permeability caused by complement activation, which was observed after SARS-CoV-2 infection, led to severe, often irreversible changes in tissues and organs [39]. However, the functioning of the complement protein system under the conditions of post-COVID-19 syndrome is still a controversial issue. Activation of the complement system under conditions of COVID-19 can occur in several ways, including the well-described – lectin, classical or alternative ways [37]. Some complement factors, anaphylatoxins C3a and C5a, and the membrane attack complex activate immune cells, inducing a significant pro-inflammatory response, releasing the IL-1β, IL-6, and TNF-α, which stimulate TF expression on endothelial cells and monocytes, thus leading to a hypercoagulable state. In turn, platelets, which on their surface contain receptors that bind C3 and C1-q components of complement, and in granules – heparin-binding chemokine and other proteins of the thrombosis system, induce complement activation of thrombosis [40].

Platelets play a key role in maintaining hemostasis and thrombosis, and also take part in inflammatory processes, cytokine synthesis, release of vasoactive substances, angiogenesis, interaction with neutrophils, etc. Activated platelets release a number of biologically active molecules (ADP, polyphosphates, blood coagulation factors) and mediators of the immune system (complement factors), which cause further activation of platelets and strengthening of the immune response by a positive feedback mechanism, contributing to the hemostatic process [41]. Thrombocytopenia is a fairly common complication of pathological conditions caused by viral and bacterial infections, which is often found in critically ill patients and is associated with an unfavorable clinical prognosis of the disease course. A decrease in the number of platelets in the longer term after infection with the SARS-CoV-2 virus is a relatively rare phenomenon. Usually, patients with COVID-19 may have thrombocytopenia of a mostly mild degree, which worsens as the disease progresses. The exact mechanisms by which COVID-19 causes thrombocytopenia still need to be investigated. Among the proposed potential mechanisms of the decrease in the number of platelets, direct damage to SARS-CoV-2 cells through CD-13 receptors, immune system dysfunction and autoimmunity, reduction of thrombopoietin production due to impaired liver function, aggregation and consumption of platelets during the formation of microthrombi in the lungs are considered [42].

In some studies, which are already becoming one of the priority scientific directions, disorders in the blood coagulation system during SARS-CoV-2 infection, as well as in the post-COVID-19 period, are associated with the formation of neutrophil extracellular traps (NETs) and the development netosis in response to the persistence of the pathogen and increased synthesis of pro-inflammatory mediators [43]. Middleton, et al. convincingly prove the involvement of NETs in the development of immunothrombosis and thrombotic complications in patients with COVID-19 [44]. The release of NETs is a tightly regulated process involving a number of proteolytic enzymes and peptidyl-arginine deaminase 4 (PAD4), which catalyzes histone citrullination, leading to chromatin decondensation, nuclear membrane disruption, and cytolysis. An elevated level of extracellular chromatin and specific markers of NETs – DNA of myeloperoxidase (MPO-DNA) and citrullinated histone H3 (Cit-H3) [45] was found in blood serum samples of patients with COVID-19. NETs exhibit both pro-inflammatory properties and can exert a cytotoxic effect on endotheliocytes, damage the endothelium, activate platelets, enhance thrombin generation, and inhibit fibrinolysis by "capturing" a specific tissue factor pathway inhibitor (TFPI), indicating their thrombogenic properties [46]. The important role of NETs in blood clot formation is evidenced by their detection in blood clots of patients with myocardial infarction and stroke [47].

Among the important factors contributing to the development of thrombosis both by stimulating neutrophils to release NETs and by activating endothelial cells and platelets antiphospholipid autoantibodies (aPLs) are noted. aPLs, including lupus anticoagulant, anticardiolipin, and antibodies to β-2-glycoprotein I, stimulate the formation of immune complexes and inflammation of the blood vessel wall (vasculitis), causing its damage [48]. However, the relationship between the level of aPLs and thrombotic complications, the duration of their storage and the role in the pathogenesis of post-COVID-19 complications remains a controversial issue that requires further research.

The International Society on Thrombosis and Haemostasis (ISTH) recommends that all patients diagnosed with COVID-19, as well as convalescents, undergo mandatory laboratory monitoring of the main indicators of pathological changes in the blood, which allows establishing predictors of negative consequences of SARS-CoV-2 infection. A generally accepted tactic is to determine D-dimer, fibrinogen, prothrombin time, the number of platelets, C-reactive protein (CRP), ferritin, which makes it possible to predict the course of the disease, its duration and the risk of complications, as well as to carry out adequate therapeutic measures in a timely manner. An important step is the development of effective and safe protocols for thromboprophylaxis during a disease with COVID-19. However, when analyzing indicators characterizing hemostasis, one should take into account the

presence of concomitant pathological conditions and the use of anticoagulants, which may cause the risk of an unfavorable prognosis of the course of the disease [49]. Among the key markers of coagulation activation and fibrinolysis, the most commonly used is the level of D-dimers circulating in the blood –products of cleavage of stabilized fibrin polymers with a wide range of molecular weights. An increase in the level of D-dimer is observed in various inflammatory and infectious diseases. In the conditions of COVID-19, a significant long-term increase in fibrin degradation products is associated with the severity of the course of the disease, the risk of coagulation complications and thrombus formation [50, 51]. It was established that even 4 months after the disappearance of the manifestations of an acute SARS-CoV-2 infection in about 25% of convalescent patients, an increase in the concentration of D-dimer in blood serum was noted, despite the normalization of the level of inflammatory markers and other coagulation indicators [52]. However, the value of D-dimer cannot be used only as a prognostic marker of the threat of intravascular thrombosis since its accumulation can occur both with thrombosis and with hemorrhagic complications.

Thus, disorders in the blood coagulation system are one of the most important risk factors for adverse consequences both in acute SARS-CoV-2 infection and in the post-infectious period. The pathogenesis of post-COVID-19 complications is closely related to endothelial dysfunction, activation of RAS with the release of procoagulant PAI-1, activation of the coagulation cascade and inhibition of fibrinolysis, hyperimmune response with activated platelets, systemic inflammation and release of neutrophil extracellular traps. Understanding the mechanisms that underlie the pathological changes in the hemostasis system after recovery from COVID-19 is crucial for the targeted therapy of complications and makes it possible to take measures to prevent them, especially in patients with a severe clinical course of the coronavirus disease and various comorbid conditions, primarily with diseases of the cardiovascular system.

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ПАТОГЕНЕТИЧНІ АСПЕКТИ ПОСТКОВІДНИХ УСКЛАДНЕНЬ У СИСТЕМІ ЗГОРТАННЯ КРОВІ

Порушення у системі згортання крові відіграють важливу роль у патогенезі та клінічних виявах COVID-19 як під час гострої фази захворювання, так і у постінфекційний період. Коронавірусна хвороба асоціюється з високим ризиком розвитку тромботичних і тромбоемболічних ускладнень унаслідок тривалого стану гіперкоагуляції, який може траплятися і після одужання. Незважаючи на надзвичайно велику кількість наукових даних, патофізіологічні аспекти SARS-CoV-2 інфекції залишаються достеменно невизначеними. У представленому огляді узагальнено результати сучасних наукових досліджень щодо патологічних змін у системі гемостазу, які можуть виникати на тлі перенесеної коронавірусної хвороби. Розглянуто основні механізми розвитку COVID-19-асоційованих коагулопатій. З наукометричних баз даних Pub Med, Scopus, Web of science, Science Direct, Google Scholar обрано та проаналізовано найновіші публікації, присвячені цій проблематиці. Гемостаз є динамічним, чітко регульований процесом, який забезпечується трьома тісно взаємопов'язаними ланками: згортальною, протизгортальною та фібринолітичною. Активація коагуляційного каскаду та тромбоцитарної ланки гемостазу, що спричиняє протромботичний стан у реконвалесцентних пацієнтів з COVID-19, передусім пов'язана з дисрегуляцією ренін-ангіотензинової системи, тривалою місцевою й системною запальною реакцією, посиленням імунної відповіді через вивільнення прозапальних медіаторів, які взаємодіють із тромбоцитами, стимулюють експресію тканинного фактора, пригнічують фібринолітичну систему та призводять до дисфункції ендотеліальних клітин кровоносних судин, запускаючи тромбогенез. Розуміння патогенетичних механізмів постковідних ускладнень і проведення моніторингу основних маркерів гемостазу (рівня D-димеру, фібриногену, протромбінового часу, кількості тромбоцитів та ін.) є важливими для вчасного виявлення порушень у системі згортання крові й надають змогу, залежно від клінічної ситуації, своєчасно вжити заходів для їхньої корекції на різних етапах розвитку патології.

Ключові слова: COVID-19, SARS-CoV-2 інфекція, постковідні ускладнення, коагулопатія, гемостаз, тромбоз.