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Thrombotic storm, hemostasis disorders and thromboinflammation in COVID-19

Alexander D. Makatsariya[1], Ekaterina V. Slukhanchuk[1,2], Viktoria O. Bitsadze[1], Jamilya Kh. Khizroeva[1], Maria V. Tretyakova[3], Andrey S. Shkoda[4], Svetlana V. Akinshina[5], Nataliya A. Makatsariya[1], Valentina I. Tsibizova[6], Jean-Christophe Gris[1,7], Ismail Elalamy[1,8,9], C. Ay[10], E. Grandone[1,11]

[1]Sechenov University; 2 bldg. 4, Bolshaya Pirogovskaya Str., Moscow 119991, Russia;

[2]Petrovsky National Research Centre of Surgery; 2 Abrikosovskiy Lane, Moscow 119991, Russia;

[3]«Medical Center» LLC; 15/1 Timura Frunze Str., Moscow 119021, Russia;

[4]Vorokhobov City Clinical Hospital № 67, Moscow Healthcare Department; 2/44 Salyama Adilya Str., Moscow 123423, Russia;

[5]«Medical Centre for Women» LLC; 62 Str. Zemlyanoi Val, Moscow 109004, Russia;

[6]Almazov National Medical Research Centre, Health Ministry of Russian Federation; 2 Akkuratova Str., Saint Petersburg 197341, Russia;

[7]University of Montpellier; 163 Rue Auguste Broussonnet, Montpellier 34090, France;

[8]Medicine Sorbonne University; 12 Rue de l'École de Médecine, 75006 Paris, France;

[9]Hospital Tenon; 4 Rue de la Chine, 75020 Paris, France;

[10]University of Vienna; 1 Universitätsring, Vienna 1010, Austria;

[11]Research Center «Casa Sollievo della Sofferenza»; 1 Viale Cappuccini, San Giovanni Rotondo 71013, Italia

***Corresponding author**: Ekaterina V. Slukhanchuk, e-mail: beloborodova@rambler.ru*

Abstract

The rate of thrombosis and disseminated intravascular coagulation (DIC) has been increasing in COVID-19 patients. Key features related to such condition include minimal or no risk of bleeding, moderate thrombocytopenia, high plasma fibrinogen as well as complement components level in the areas of thrombotic microangiopathy. The clinical picture is not typical for classic DIC. This review systematizes the pathogenetic mechanisms of hypercoagulation in sepsis and its extreme forms in

patients with COVID-19. The latter consist of the thrombosis-related immune mechanisms, the complement activation, the macrophage activation syndrome, the formation of antiphospholipid antibodies, the hyperferritinemia, and the dysregulation of the renin-angiotensin system. Taking into consideration the pathogenetic mechanisms, the biomarkers had been identified related to the prognosis of the disease development. Patients with pre-existing cardiovascular disease and other risk factors, including obesity, diabetes, hypertension, and aging pose the peak risk of dying from COVID-19. We also summarize new data on platelet and endothelial dysfunction, immunothrombosis, and, as a result, thrombotic storm as essential components of COVID-19 severe features.

Keywords: thrombotic storm, thromboinflammation, COVID-19, cytokine storm, neutrophil extracellular traps, NETs, endotheliopathy

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Тромботический шторм, нарушения гемостаза и тромбовоспаление в условиях COVID-19

А.Д. Макацария[1], Е.В. Слуханчук[1,2], В.О. Бицадзе[1], Д.Х. Хизроева[1], М.В. Третьякова[3], А.С. Шкода[4], С.В. Акиньшина[5], Н.А. Макацария[1], В.И. Цибизова[6], Ж.-К. Гри[1,7], И. Элалами[1,8,9], Ц. Ай[10], Э. Грандоне[1,11]

[1]ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский Университет); Россия, 119991 Москва, ул. Большая Пироговская, д. 2, стр. 4;

[2]ФГБНУ «Российский научный центр хирургии имени академика Б.В. Петровского»; Россия, 119991 Москва, Абрикосовский пер., д. 2;

[3]ООО «Лечебный Центр», Россия, 119021 Москва, ул. Тимура Фрунзе, д. 15/1;

[4]ГБУЗ «Городская клиническая больница № 67 имени Л.А. Ворохобова Департамента здравоохранения города Москвы»; Россия, 123423 Москва, ул. Саляма Адиля, д. 2/44;

[5]ООО «Медицинский женский центр»; Россия, 109004 Москва, ул. Земляной Вал, д. 62;

[6]ФГБУ «Национальный медицинский исследовательский центр имени В.А. Алмазова» Министерства здравоохранения Российской Федерации; Россия, 197341 Санкт-Петербург, ул. Аккуратова, д. 2;

[7]Университет Монпелье; Франция, 34090 Монпелье, Rue Auguste Broussonnet, 163;

[8]Медицинский Университет Сорбонны;
Франция, 75006 Париж, Улица медицинского факультета, д. 12;
[9]Госпиталь Тенон; Франция, 75020 Париж, Китайская улица, д. 4;
[10]Венский университет; Австрия, 1010 Вена, Universitätsring, д. 1;
[11]Исследовательский центр «Casa Sollievo della Sofferenza»;
Италия, 71013 Сан-Джованни-Ротондо, Viale Cappuccini, 1
***Для контактов**: Екатерина Викторовна Слуханчук, e-mail: beloborodova@rambler.ru*

Резюме

Число сообщений о тромбозах и диссеминированном внутрисосудистом свертывании (ДВС) у пациентов с COVID-19 растет. Ключевые особенности состояния включают отсутствие риска кровотечения, умеренную тромбоцитопению, повышенный уровень фибриногена в плазме, а также компонентов комплемента в областях тромботической микроангиопатии. Клиническая картина не типична для классического ДВС-синдрома. В данном обзоре систематизированы патогенетические механизмы формирования гиперкоагуляции при сепсисе, а также при его крайних формах у пациентов с COVID-19. К ним относятся иммунные механизмы тромбоза, активация комплемента, синдром активации макрофагов, формирование антифосфолипидных антител, гиперферритинемия, дисрегуляция ренин-ангиотензиновой системы и др. Учитывая патогенетические механизмы, выделены и биомаркеры, отражающие прогноз развития заболевания. Пациенты с уже существующими сердечно-сосудистыми заболеваниями и другими факторами риска, включая ожирение, сахарный диабет, гипертоническую болезнь и пожилой возраст, подвергаются наибольшей опасности смерти от COVID-19. В этом обзоре мы обобщаем новые данные, указывающие на дисфункцию тромбоцитов и эндотелия, иммунотромбоз и как результат – тромботический шторм, как на важные компоненты патологии COVID-19

Ключевые слова: тромботический шторм, тромбовоспаление, COVID-19, цитокиновый шторм, внеклеточные ловушки нейтрофилов, NETs, эндотелиопатия

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Highlights	Основные моменты
What is already known about this subject?	Что уже известно об этой теме?
The number of reports on thrombotic complications and disseminated intravascular coagulation (DIC) in severe patients with COVID-19 has been increasing.	Количество сообщений о тромботических осложнениях и диссеминированном внутрисосудистом свертывании (ДВС) у тяжелых пациентов с COVID-19 растет.

This condition is usually featured by no risk of bleeding, moderate thrombocytopenia, increased plasma fibrinogen and complement components levels. The clinical picture is not typical for the classic DIC syndrome.	К особенностям состояния следует отнести, как правило, отсутствие риска кровотечения, умеренную тромбоцитопению, повышенный уровень фибриногена в плазме, а также компонентов комплемента. Клиническая картина не типична для классического ДВС-синдрома.
What are the new findings?	Что нового дает статья?
The review systematizes the pathogenetic links in the development of hypercoagulability upon severe disease in patients with COVID-19.	Обзор систематизирует патогенетические звенья развития гиперкоагуляции при тяжелом течении заболевания у пациентов с COVID-19.
The review summarizes new data indicating platelet and endothelial dysfunction, immunothrombosis and, as a result, thrombotic storm, as important components of the pathology of COVID-19.	В обзоре обобщены новые данные, указывающие на дисфункцию тромбоцитов и эндотелия, иммунотромбоз и как результат – тромботический шторм, как на важные компоненты патологии COVID-19.
How might it impact on clinical practice in the foreseeable future?	Как это может повлиять на клиническую практику в обозримом будущем?
Analysis of the pathogenetic mechanisms of the severe COVID-19 course, the identification of specific markers and predisposing factors give a momentum to new understanding of the disease and development of effective therapeutic approaches.	Глубокий анализ патогенетических механизмов развития тяжелого течения COVID-19, выявления специфических маркеров и предрасполагающих факторов дает толчок к новому пониманию заболевания и разработке эффективных терапевтических подходов.

Introduction / Введение

Coronavirus infection is often accompanied by hypercoagulability, which predetermines the risk of high mortality [1]. Various phenomena can explain common micro-and macrovascular disorders in COVID-19, and new pathogenetic mechanisms are currently being evaluated.

Macro- and micro thrombosis in patients with COVID-19 develop more often in organs such as the lungs, spleen, brain, stomach, and peripheral vessels [2–5]. Moreover, thrombosis develops both in the acute phase of the disease and is delayed several weeks after the first symptoms. Pulmonary embolism and deep vein thrombosis are the most frequent thrombotic complications in COVID-19, observed in severe cases with a frequency of 20–30 % [6]. In a Dutch cohort study of 184 COVID-19 patients in intensive care unit (ICU), the cumulative incidence of large vessel thrombotic events was 49 %, the majority of which were pulmonary embolism confirmed by computer tomography in segmental and subsegmental pulmonary arteries [5].

Thrombosis occurs despite the standard thromboprophylaxis suggested in these patients and performed with nadroparin at a 2800 or 5700 IU dose once or twice

a day. The risk of death from all causes in this cohort was 5 times higher among patients with thrombotic complications. An Italian cohort of 388 patients had a lower but still significant cumulative rate of thromboembolic events – 21 % (27.6 % in the ICU, 6.6 % in the general ward), half of whom were diagnosed within the 24 hours after admission to the hospital [7]. In a French cohort, a similar cumulative incidence of thrombotic events was observed. This rate was compared with the incidence of thrombosis in two different retrospective control groups: (a) non-COVID-19 resuscitation patients admitted to the same unit in winter 2019, and (b) influenza patients admitted to the same ICU in 2019 [8]. Among patients with COVID-19 in the ICU, 20.6 % showed signs of pulmonary embolism (on average 6 days after admission to the ICU), which was more than 2 times higher than in any of the control groups. Thus, COVID-19 is a prothrombotic infectious disease among other severe viral respiratory pneumonias.

Common pulmonary microthrombosis contributes to the unique course of acute COVID-19. One study compared lung autopsy samples from seven patients who died from COVID-19 with seven patients who died from acute respiratory distress syndrome (ARDS) after H1N1 influenza [9]. In patients with COVID-19, microthrombi in the alveolar capillaries were nine times more common than in patients with influenza ($p < 0.001$), which corresponds to the increased incidence of thrombosis observed clinically in COVID-19 compared with other viral pneumonias. Severe endothelial damage and the presence of intracellular viral particles have also been noted in COVID-19 patients in areas associated with microthrombosis, suggesting that the endothelial damage and the inflammation may directly underlie thrombogenesis. Acute dysfunction of the right ventricle and cor pulmonale in COVID-19 is caused by an abundance of central or segmental pulmonary emboli or by the severity of microthrombosis in small lung vessels. This situation is aggravated by hypoxic vasoconstriction and increased intrathoracic pressure due to mechanical ventilation. This causes a sudden increase in the right ventricular afterload, which can even cause the rupture of the right ventricle and pulmonary artery. In a study involving 120 patients with COVID-19, mortality was directly related to longitudinal

right ventricular deformity and right ventricular dilatation [10]. PE and right ventricular tension can significantly contribute to increased troponin levels, the development of cardiogenic shock, and sudden death, which has been observed in patients with COVID-19 [11, 12].

Many patients with COVID-19 have been diagnosed with acute ischemic stroke, including young patients under 50 without significant previously identified risk factors [13]. According to a number of studies, the incidence of stroke in patients in the ICU was approximately 2.5 % [5, 7]. It has also been reported about mesenteric thrombosis, obstruction of peripheral arteries, obliterating arteriosclerosis of large vessels [3, 14–16], and thrombosis of the cerebral venous sinus [17]. Acroischemia (so called COVID toes) associated with microvascular thrombosis of the extremities [18, 19] has been also described in patients with COVID-19; as such,t his phenomenon may develop due to inflammatory microvascular injury without microthrombosis (Fig. 1) [20].

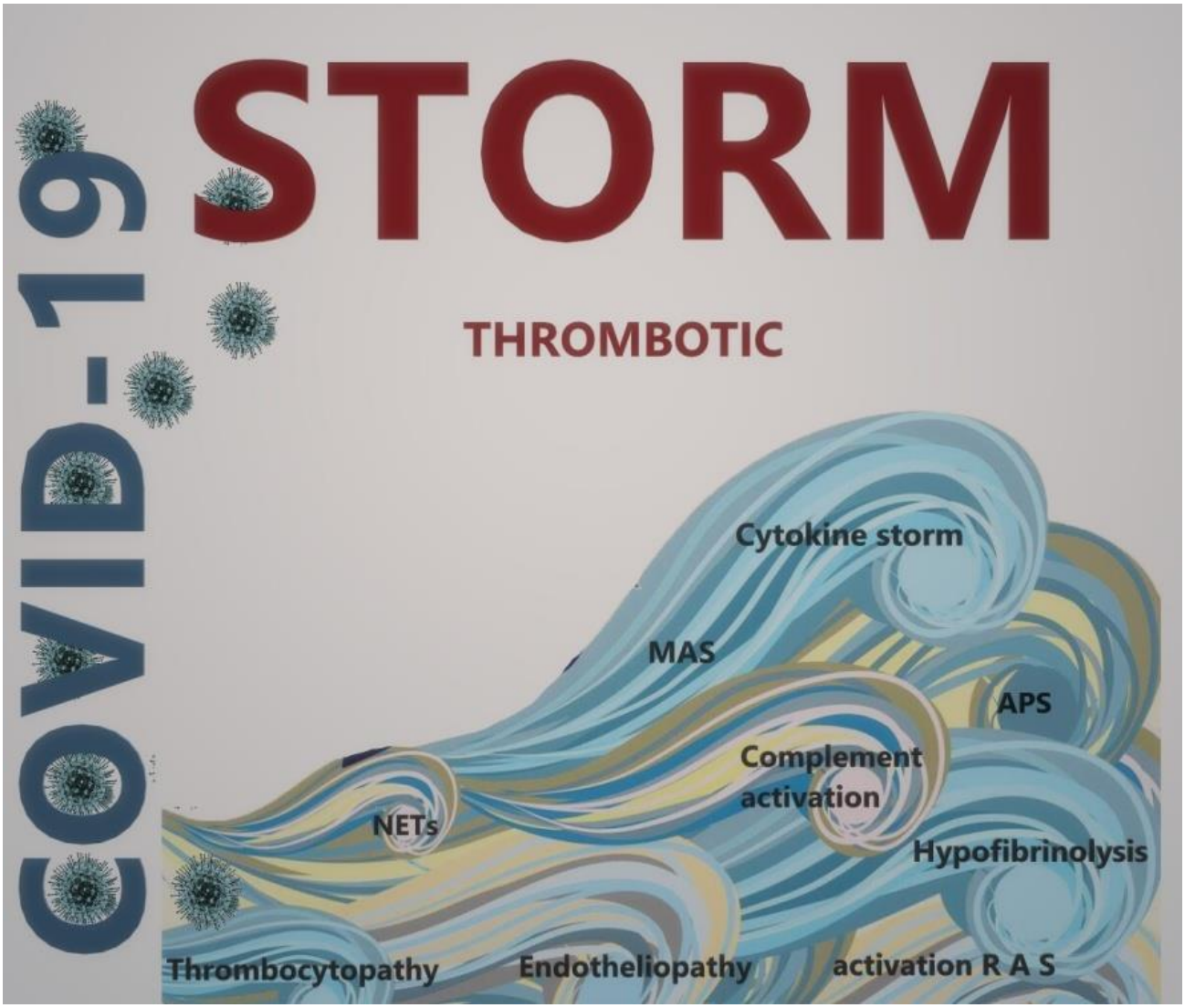

Figure 1. Thrombotic storm in COVID-19 [drawed by authors].

Note: NETs – extracellular neutrophil traps; APS – antiphospholipid syndrome; MAS – macrophage activation syndrome; RAS – rennin-angiotensin system.

Рисунок 1. Тромботический шторм при COVID-19 [рисунок авторов].

Примечание: NETs – внеклеточные ловушки нейтрофилов; APS – антифосфолипидный синдром; MAS – синдром активации макрофагов; RAS – ренин-ангиотензиновая система.

Potential pathogenetic mechanisms of thrombosis in COVID-19 / Возможные патогенетические механизмы тромбоза при COVID-19

Disseminated intravascular coagulation / ДВС-синдром

Disseminated intravascular coagulation (DIC) activates the coagulation cascade with the deposition of multiple platelet-fibrin thrombi in the

microcirculation, which ultimately leads to the consumption of platelets and coagulation factors as well as bleeding concomitant with hypocoagulation [21]. The underlying disease can aggravate hypercoagulation in DIC, including hypoxia, dehydration, and relative hypodynamia. In severe cases, DIC leads to microvascular damage and subsequent organ dysfunction. The markers for DIC diagnosis are considered as the increased concentrations of fibrin degradation products. Hypocoagulation in DIC is a consequence of secondary activation of fibrinolysis, which is not typical for other thrombotic microangiopathies (TMA), such as thrombotic thrombocytopenic purpura (TTP) or catastrophic antiphospholipid syndrome (CAPS) [22]. However, hypocoagulation in severe COVID-19 is extremely rare.

However, laboratory monitoring shows differences between COVID-19 coagulation alterations and DIC [23, 24]. Initially, DIC was proposed as a pathogenic mechanism due to the marked increase in the concentration of D-dimer and fibrin degradation products (FDP). In COVID-19, these biomarkers are significantly correlated with morbidity and mortality [1]. The concentration of D-dimer continues to increase throughout the entire period of hospitalization in surviving patients [25]. This indicates a continuing procoagulant state, which correlates with the severity of the disease. On the other hand, the increase in prothrombin time (PT) and activated partial thromboplastin time (APTT) is insignificant, while the concentration of fibrinogen and factor VIII are increased [26], which is more typical for the acute phase of the systemic inflammatory response than for DIC disorder. Thrombocytopenia is another feature of COVID-19 that is linearly related to the risk of death, but the degree of thrombocytopenia seen in the late stages of COVID-19 is less pronounced than that usually observed in DIC [27, 28].

Analysis of the procoagulant state in COVID-19 indicates that hyperactivation of hemostasis, which reaches a peak within the first week after admission to ICU, does not transform into secondary hyperfibrinolysis. In one study, thromboelastometric hypercoagulation on ICU admission continued to increase until day 5 and then slightly decreased by day 10 [29]. The fibrinogen concentration was

maximal upon admission (8.96 ± 1.1 g/L), decreasing to 3.33 ± 0.50 g/L by day 10. Hyperfibrinogenemia can be a link in the acute phase of the inflammatory response [30], or *per se* play a more complex role in the state of hypercoagulability in COVID-19. One of the major drawbacks in this study was that measurements at day 10 could only include survivors (n = 33 out of 40). It is not known whether the remaining 7 patients would have survived if they developed hyperfibrinolysis. The high mortality rate in COVID-19 in the early stages might interfere with observing later fibrinolytic forms of DIC.

Coagulopathy in COVID-19 differs from DIC and other TMA, including CAPS, hemolytic uremic syndrome (HUS), atypical hemolytic uremic syndrome (aHUS), and TTP.

Table 1. Differences between coagulopathy in COVID-19 and DIC, catastrophic antiphospholipid syndrome (CAPS), thrombotic microangiopathies – hemolytic uremic syndrome (HUS) and atypical hemolytic uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP).

Таблица 1. Отличия коагулопатии при COVID-19 от ДВС-синдрома, катастрофического антифосфолипидного синдрома (КАФС), тромботических микроангиопатий – гемолитико-уремического синдрома (ГУС) и атипичного гемолитико-уремического синдрома (аГУС) и тромботической тромбоцитопенической пурпуры (ТТП).

Sign **Признак**	**COVID-19**	**DIC** **ДВС-синдром**	**CAPS** **КАФС**	**HUS** **ГУС**	**aГУС** **aHUS**	**TTP** **ТТП**
Multiple organ failure Полиорганная недостаточность	+	+	+	+	+	+
Microthrombosis Микротромбозы	+	+	+	+	+	+
Bleedings Кровотечения	+	+	+	+	+	+/–
Trombocytopenia Тромбоцитопения	+	+++	+	++	++	+++
Complement activation Активация комплемента	+	–	+	+	+	+
Schizocytosis Шизоциты	–	+	+/–	+	+	+
Increased D-dimer concentration Повышение концентрации Д-димера	+	+	+	+	+	+
Circulating APA and LA Циркуляция АФА и ВА	+/–	–	+	–	–	+
Fibrinogen concentration Концентрация фибриногена	high высокая	low низкая	normal норма	normal норма	normal норма	normal норма

Note: APA – antiphospholipid antibodies; LA – lupus anticoagulant.

Примечание: АФА – антифосфолипидные антитела; ВА – волчаночный антикоагулянт.

Cytokine storm / Цитокиновый шторм

COVID-19-associated coagulopathy results from the host inflammatory response to viral infection and activated immune responses. The activation of hemostasis and fibrin deposition is an adaptive mechanism in the early stages of the infectious process. However, ongoing inflammation can lead to a hyperinflammatory response due to the cytokine storm and macrophage activation syndrome (MAS). Cytokine storm is a self-amplifying process determined by the release of proinflammatory cytokines, the main factor in developing of ARDS and multiple organ dysfunction syndromes in several conditions [31–33]. MAS is a cascade of proinflammatory reactions leading to a high incidence of thrombosis and death in sepsis [34, 35]. However, the precise progression from initial COVID-19 infection to an inflammatory response and hypercoagulable state is still unknown.

In admitted patients with COVID-19, blood concentrations of nonspecific inflammatory biomarkers such as C-reactive protein, erythrocyte sedimentation rate, ferritin, and several procoagulant factors such as von Willebrand factor (vWF) and factor VIII are significantly increased [26]. In addition, the concentration of proinflammatory cytokines is increasing: particularly tumor necrosis factor-alpha (TNF-α) and interleukins (IL) – IL-2R, IL-6, IL-8, and IL-10 [36, 37]. Both TNF-α and IL-6 are elevated more than in cases of bacterial sepsis or influenza [38]. There was found a correlation between increased levels of IL-6 and increased fibrinogen in intensive care patients [39]. The possible contribution of IL-6 to the development of hypercoagulability is currently being investigated by using its antagonists, tocilizumab, and sarilumab, in order to reduce the risk of thrombosis. Lupus anticoagulant (LA) was detected in patients with COVID-19 (91 % of patients tested) compared with the control group of patients with prolonged APTT without COVID-19 (26 %) [40]. The clinical significance of LA detection is not yet clear, but it increases the likelihood of antiphospholipid syndrome (APS) involvement in the pathogenesis of thrombus inflammation in patients with COVID-19.

The pathogenetic mechanisms of immune-mediated thrombosis can be studied in other severe infections. In SARS-CoV *in vitro* models, infected mononuclear cells

expressed high procoagulant activity, including fibrinogen, serine protease inhibitors (serpins), tissue factor, and factors II and X [41, 42]. The cells also expressed Toll-like receptor (TRL) 9 and thromboxane synthase genes, which promote platelet activation and aggregation, endothelial dysfunction, and vasoconstriction. These processes may underlie the endothelial damage seen during the autopsy of COVID-19 patients with multiple organ dysfunction. In addition, the mechanisms of platelet activation in COVID-19 were investigated in a proteomic analysis, which showed reduced plasma platelet factor 4 (PF4) and increased beta-thromboglobulin levels [43]. It is possible that COVID-19 is featured by combined procoagulant state associated with procoagulant factors and platelet dysfunction.

In viral infection and sepsis, several parallel mechanisms contribute to the procoagulant activity of the immune system including activation of tissue factor (TF), the complement components C3a and C5a, and vWF [44, 45]. Viruses can activate the external coagulation pathway mediated by TF and factor VIIa (FVIIa). Usually, TF/FVIIa complexes are formed at the site of endothelial injury. However, monocytes and macrophages can express TF under conditions of viral infection, mainly due to the activity of TNF-α and nuclear factor kappa B (NF-κB) [44]. Thus, elevated TNF-α concentration in COVID-19 may indicate tissue factor-mediated thrombotic activity, even though TNF-α is a pleiotropic pro-inflammatory cytokine with multiple potential prothrombotic side effects. TNF-α blockade has been used as a therapy for sepsis in several studies, and meta-analyses of the data showed improved mortality in all studies [46].

Complement activation / Активация комплемента

Activated immune system plays an essential role in the antiviral immune response triggered by type I interferons. Such activation renders TMA a link in the pathogenesis of severe forms of COVID-19 [47]. Recent studies have shown that the nucleocapsid protein of some viruses, including SARS-CoV-2, binds to the main protease of the lectin complement pathway [48].

Activation of the complement cascade promotes the recruitment and activation of leukocytes, elevated local release of pro-inflammatory cytokines IL-1,

IL-6, IL-8, and interferon-γ, and subsequent damage to the endothelium. Suppression of the complement system activation can improve the situation with hemostasis and endothelial dysfunction, which has been shown in animal models of sepsis [45]. In the lung tissue of patients with severe COVID-19 pneumonia and skin biopsies from patients with COVID-19 and purpura, it was evidenced a catastrophic endothelial damage accompanied by complement activation: C5b-9, C4d, and mannose associated lectin-associated serine protease [49]. Anti-C5 therapy with eculizumab has been considered for the treatment of COVID-19. In one open-label study, four COVID-19 patients treated with eculizumab experienced a decrease in C-reactive protein, and all patients successfully recovered from COVID-19 [50]. Further placebo-controlled studies are needed to better assess such therapy.

Thrombocytopathy / Тромбоцитопатия

Platelets are short-lived small anucleate cells that perform only limited functions; in particular, they are involved in the processes of hemostasis [51]. However, it has been proven that platelets are more complex cells with fundamental mechanisms, including autophagy [52], programmed cell death [53] and rapid *de novo* protein synthesis [54], etc. Platelets interact with other cells, including circulating blood cells, endothelial cells, and other cells in the vascular wall, either directly or through signaling mediators. Platelets can function as mediators bridging the immune system (through interactions with leukocytes) and thrombosis (through platelet activation and release of hemostatic and pro-inflammatory mediators) [55]. Thrombocytopathy is a hallmark of COVID-19 and includes thrombocytopenia, hyperactivation of platelets, leading to hypercoagulability and dysfunction of the immune response.

The incidence of thrombocytopenia in patients with severe COVID-19 (requiring mechanical ventilation or admission to an intensive care unit) reaches up to 35 % [56]. At the same time, there is a marked platelet hyperactivation [56]. Activated platelets express surface P-selectin and CD40L, interact with neutrophils, and can release α-granules and complement component C3, as well as various cytokines, including CC-chemokine ligand 2 (CCL2), CCL3, CCL7, IL-1β, IL -7, IL-

8, and hepatocyte growth factor [57, 58]. *In vitro* and *in vivo* studies have shown that in response to viral infection, platelets release IL-1β on microparticles, which increases endothelial permeability [59].

Another important factor in COVID-19 is the recruitment of neutrophils into the vasculature [60]. The phenomenon of the binding of activated platelets to neutrophils and the transfer of platelet-associated neutrophils along the endothelium, known as "secondary uptake", plays a decisive role in triggering immunothrombosis [61]. The binding of activated platelets to neutrophils facilitates platelet migration into the alveolar lumen and contributes to the formation of pulmonary edema, which, in turn, can cause further platelet activation. It has been proven that neutrophil extracellular traps (NETs) contribute to the progression of thrombus inflammation in patients with COVID-19.

Hypoxia, oxidative stress, and other factors affect the work of platelet mitochondria, leading to platelet hyperactivation and apoptosis [62]. Recent studies have shown that many of the comorbidities in COVID-19 patients (e. g., diabetes and obesity) associated with oxidative stress can contribute to platelet hyperactivity and apoptosis [63]. Thrombocytopenia can develop as a result of decreased production or increased consumption of platelets. Currently, the three main mechanisms for decline in platelet count have been identified – aging of platelets (loss of sialic acid), apoptosis, and destruction of platelets by macrophages. Platelet consumption in a growing thrombus or platelet apoptosis may account for the thrombocytopenia observed in some COVID-19 patients. Alternatively, SARS-CoV-2-induced production of autoantibodies against platelet surface antigens may cause increased platelet destruction [64]. Antiphospholipid antibodies (APA) have been also found in critically ill patients with COVID-19 [65]. Hypoxia in patients with COVID-19 can directly or indirectly contribute to developing thrombocytopathy. The study by J. Maquet et al. showed that 58 % of COVID-19 patients with thrombocytopenia at the time of admission required oxygen support compared with 41 % of patients whose platelet count was within the normal range [56]. TMA mediated by activated complement system (components C3a and C5a), can also contribute to the

development of thrombocytopathy in COVID-19 [50]. All these processes promote dysregulation of platelet function and predispose to the progression of thrombus inflammation.

The virus can directly affect platelets, leading to increased apoptosis. Studies have shown that SARS-CoV-2 results in altered platelet transcriptome [66] Whether platelets express enough angiotensin-converting enzyme 2 (ACE2) on their surface for SARS-CoV-2 entrance is not completely clear; other potential mechanisms of SARS-CoV-2 penetration have been also identified independent of ACE2 receptors [67]. Studies of influenza viral infection show that platelets have many receptors necessary for viral penetration, and platelet infection leads to platelet apoptosis [68]. In addition, taking into consideration that platelets have the properties of innate immune cells, viral penetration may occur as a part of a platelet-mediated antiviral response to SARS-CoV-2. Platelet uptake and degradation of influenza and HIV (human immunodeficiency virus) viruses, single-stranded RNA viruses, like SARS-CoV-2, occur through the TLR-mediated endosomal pathway [55]. The penetration of SARS-CoV-2 into platelets is probably associated with a similar mechanism leading to platelet activation [55].

Platelet apoptosis is associated with the release of numerous proinflammatory and procoagulant factors. Immune complexformation is another possible mechanism for platelet hyperactivation and development of thrombocytopenia in COVID-19; this mechanism may be similar to heparin-induced thrombocytopenia (HIT), which involves formation of heparin–PF4–antibody complexes recognizing the FcγR receptor on platelet surface and causing platelet activation and clearance [69]. SARS-CoV-2 can form immune complexes with reactive antibodies in the host, as it is observed in critically ill patients with influenza (H1N1) infection [70] binding platelet FcγRIIa and inducing activation platelets [71]. Virus-induced platelet activation can increase the number of platelet-leukocyte conjugates [72], potentially causing NETosis. Interestingly, platelet PF4 deposits in the lungs were found at autopsy of patients with COVID-19 and have been correlated with increased NETosis and microthrombus formation [60].

Due to the high loss of platelets, the essential work of megakaryocytes becomes of paramount importance. Autopsies revealed the abnormal distribution of megakaryocytes and the formation of prothrombocytes in the tissues of patients with COVID-19. Studies have shown that in COVID-19, megakaryocyte count increases, whereas the lungs represent the site of platelet biogenesis with intravascular and extravascular reservoirs of megakaryocytes [73]. The compensatory increase in platelet production to maintain a normal level of peripheral platelet count in patients with COVID-19 varies: some patients develop thrombocytopenia, while the others do not (**Fig. 2**) [27].

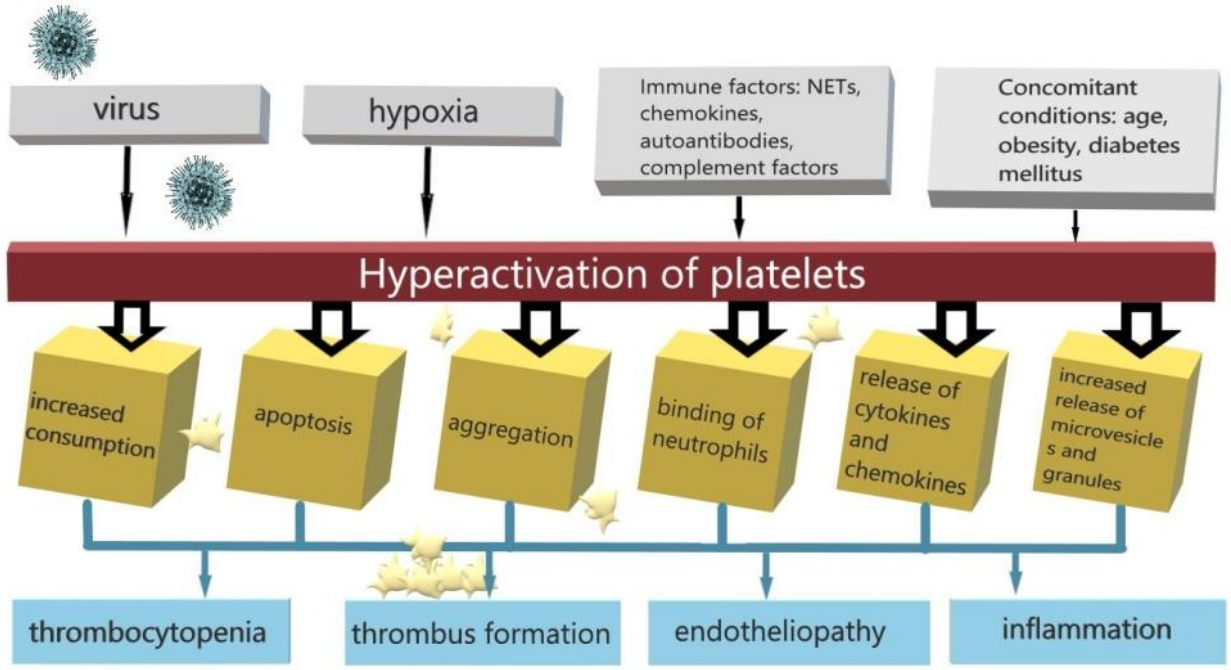

Figure 2. Thrombocytopathy in COVID-19 [drawed by authors].

Note: NETs – neutrophil extracellular traps.

Рисунок 2. Тромбоцитопация при COVID-19 [рисунок авторов].

Примечание: NETs – внеклеточные ловушки нейтрофилов.

Endothelial dysfunction / Дисфункция эндотелия

The endothelial functions are devoted to maintain the integrity of the vascular wall, create a barrier, and prevent progression of inflammatory reactions by limiting an interaction of inflammatory agents with immune cells and platelets [74].

Endotheliopathy, or endothelial dysfunction, is an important pathological feature of COVID-19. Endothelial cell damage and apoptosis were found in autopsy samples from patients with COVID-19 by using transmission electron microscopy [9, 75]. Endothelial damage plays an essential role in the stimulation of angiogenesis. Autopsy of patients who died from COVID-19 revealed an active angiogenesis in the lungs, which was detected more often than in case of influenza infection. Whether endothelial dysfunction primarily results from direct infection of SARS-CoV-2 in endothelial cells remains to be determined, but biomarkers of endothelial dysfunction such as thrombomodulin, vWF, angiopoietin 2, and plasminogen activator inhibitor-1 (PAI-1) have been found to be elevated in COVID-19 patients compared with control groups, and hadba prognostic value due to their association with severe course of the disease [76, 77].

Endothelial dysfunction is a major factor in the pathophysiology of thrombotic complications associated with COVID-19, including myocardial infarction and stroke developing due to a combination of viral damage with the endothelial response to inflammation, activation of immune responses, cytokine production, and complement production [47, 49, 50].

Plasma analysis of 68 patients hospitalized with COVID-19 revealed increased concentration of various circulating markers of endothelial damage, such as vWF, PAI-1, soluble thrombomodulin, angiopoietin 2, and follistatin [76, 77]. High levels of vWF, PAI-1, and angiopoietin 2 were observed in ICU patients as well as elevated levels of soluble thrombomodulin, PAI-1, angiopoietin 2, and follistatin in hospitalized patients with COVID-19, which all correlated with mortality.

Age is the leading risk factor for death associated with COVID-19: 304.9 deaths per 1,000 cases were reported among patients aged ≥ 85 years, compared with 0.3 deaths per 1,000 cases among patients aged 5–17 years. Age-related changes in the endothelium can be one of the causes for severe complications of COVID-19 [78]. NADPH-oxidases and mitochondria generate reactive oxygen species (ROS), and dysregulation of such pathways with age can lead to ROS accumulation [79]. In the endothelial cells of the elderly subjects, elevated ROS levels reduce the

availability of nitric oxide (NO), which is a vasodilator and antiplatelet agent with cardioprotective effects [80].

Another function of the vascular endothelium is to maintain a balance between proinflammatory and anti-inflammatory factors. Chronic inflammation is associated with age-related endothelial dysfunction, characterized by increased C-reactive protein, proinflammatory cytokines, and adhesion molecules that recruit immune cells, disrupt mitochondrial function as well as cellular energy metabolism [79]. In addition, the intensity of endothelial cell apoptosis increases with age [81]. An age-related decrease in NO bioavailability along with increased mitochondrial oxidative stress and chronic inflammation induces apoptosis of endothelial cells [81].

Neutrophil extracellular traps / Внеклеточные ловушки нейтрофилов

The development of endotheliopathy can be caused by the massive activation of neutrophils during the cytokine storm with release of abundant NETs and uncontrolled course of the thromboinflammation.

Neutrophils are attracted to the site of inflammation via several stages: activation, adhesion, and extravasation occurring with involved selectins, chemokines, including P-selectin, P-selectin glycoprotein ligand 1 (PSGL-1). P-selectin is expressed on the surface of activated endothelial cells and platelets. Integrin αLβ2 and intercellular adhesion molecule 1 (ICAM-1) are also involved in neutrophil adhesion [82].

NETs are ectopic intracellular DNA with fixed granular material, necessary for inactivation of infectious agents (fungi, viruses, and protozoa), limiting infection, especially where phagocytosis not possible. Recently, the role of NETs has been recognized as necessary not only in the pathogenesis of respiratory diseases. Intracellular material is released during the activation of neutrophils called NETosis. Previously, NETosis was thought to be a terminal event for neutrophils; however, it has been shown that some neutrophils survive this process, becoming nuclear-free, and continue to have a damaging effect on tissues. NETosis is not a single process but a multitude of events resulting in the expulsion of the nuclear contents [83].

Suicidal, vital, and mitochondrial types of NETosis have already been described in the literature [84].

NETs, produced in large quantities during COVID-19, contribute to alveolitis development, damage to the endothelium, and trigger intravascular coagulation [85, 86]. Excessive activation of neutrophils with the production of NETs contributes to acute damage to lung tissue, microthrombus formation, hemorrhage, and pulmonary failure. Histones are protein components of NETs exerting cytotoxic activity. Chromatin networks in the NETs destroy the alveolar-capillary barrier, leading to epithelial damage, epithelial damage, blood vessel integrity, and hemorrhage [87]. Overproduction or impaired utilization of NETs leads to pathological microthrombosis in sepsis [88]. Under the influence of endogenous and exogenous DNases, degradation of NETs and massive release of histones bound to DNA occur, manifested by thrombosis [89]. K. Martinod and D.D. Wagner have shown that both arterial and venous thrombi contain neutrophils and NETs [90]; NETs are always present in thrombi, especially at the organizational stage.

NETs activate the procoagulant link, disrupt fibrinolysis and anticoagulant function [88]. DNA in NETs triggers a coagulation cascade along the intrinsic pathway because negatively charged surfaces increase the activation of factor XII, the initiator of this pathway [91]. DNA in NETs acts as a cofactor for thrombin-dependent activation of factor XI [92] and promotes the successful course of reactions of the external pathway associated with TF [93]. During the endothelium activation and its death [94], caused by the cytotoxic action of histones, H_2O_2 is released, which further stimulates NETosis [83]. Weibel-Palade bodies in the endothelium undergo exocytosis and vWF, which binds to platelets and maintains thrombosis. Histones activate platelets through TLR2 and TLR4 [95] and enhance thrombin-dependent platelet activation [96]. Histone H4, by binding to prothrombin, promotes its autoactivation [97]. Histones disrupt the antithrombin-dependent inactivation of thrombin [98] and interfere with the interaction of thrombin-thrombomodulin [99]. Histones in NETs trigger the pathways of activating protein C (APC), an anticoagulant that can inhibit NETosis through protease-activated

receptors (PARs) on neutrophils [100]. In particular, neutrophil oxidase and elastase are capable of inactivating APC. Histones are able not only to activate hemostasis but also to increase the stability of the thrombus. They enhance structural changes in fibrin, making it more resistant to fibrinolysis. By activating soluble plasminogen, histones suppress plasmin, acting as competitive substrates. The protection of fibrin from the action of plasminogen is also enhanced by the covalent binding of histones to fibrin, catalyzed by activated transglutaminase, coagulation factor XIIIa. Through non-covalent interactions, histone-associated lateral aggregation of fibrin protofibrils occurs, leading to thickening of fibrin filaments followed by complications of fibrinolysis processes. Plasmin is a broadly specific serine protease that binds to arginine and lysine, implying that histones are candidates for plasmin targets. Competing with fibrin, histones interfere with plasmin activity and fibrinolysis triggered by tissue plasminogen activator (tPA). DNA increases the formation of complexes between tPA and PAI-1 [101], reducing the intensity of plasmin synthesis from plasminogen via tPA acting on the thrombus surface [98], binding proteins responsible for fibrin degradation, and reducing their release by fibrin thrombi [102], finally also penetrating fibrin filaments and blocking plasmin-mediated thrombolysis. NETs result in decreased ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity. Both extracellular DNA and histones in NETs can bind to vWF, leading to even greater recruitment of new neutrophils to the focus, enhancing the pro-inflammatory effect. Plasma von Willebrand glycoprotein ensures the delivery of platelets to the sites of damage to the vascular wall and promotes their subsequent activation and aggregation [103]. Super-large vWF multimers (UL-vWF) released from endothelial cells can spontaneously activate circulating platelets and other blood cells, promoting thrombosis development [104]. Metalloproteinase ADAMTS-13 specifically cleaves the multimer at Tyr1605–Met1606 bond in the A2 domain, thereby regulating the size and activity of vWF multimers and preventing thrombus formation [105].

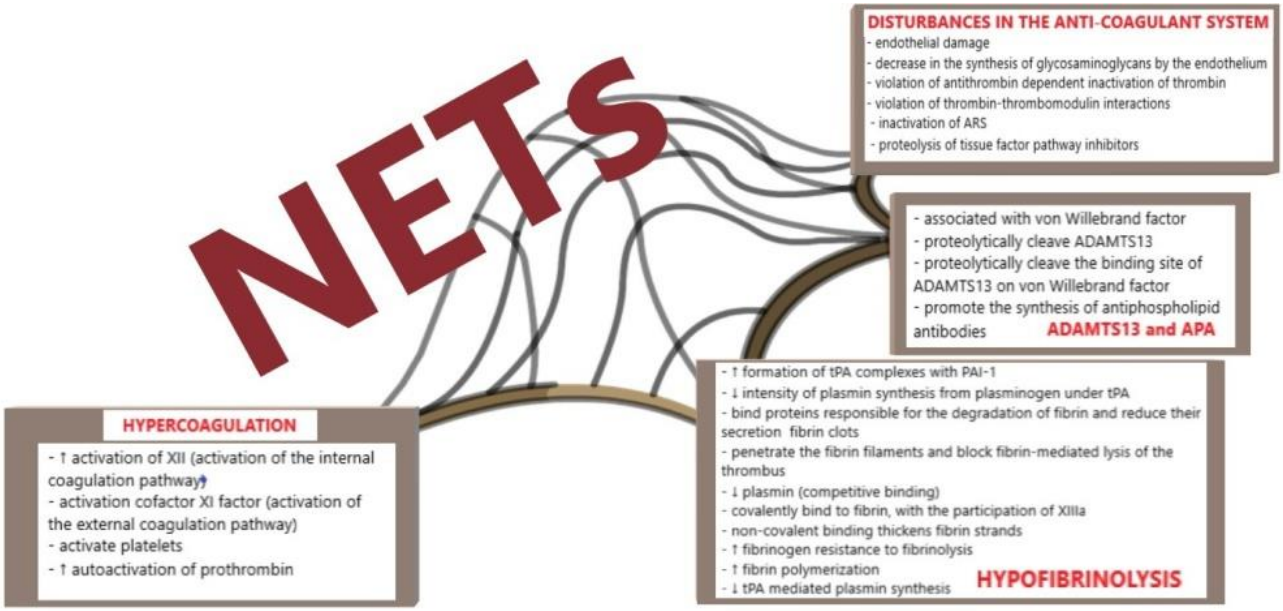

Figure 3. NETs and thrombotic storm [drawed by authors].

Рисунок 3. NETs и тромботический шторм [рисунок авторов].

Macrophage Activation Syndrome and Hyperferritinemia / Синдром активации макрофагов и гиперферритинемия

MAS can accompany the cytokine storm and hypercoagulable state seen in COVID-19. MAS develops when activated antigen presenting cells cannot be lysed by CD8 T cells or natural killer cells (NK cells) [35]. After the onset of the inflammatory response, an increased level of IL-6 lowers the cytolytic function of NK cells. As a result, a prolonged interaction between immune cells, which intensifies cytokine storms, hemophagocytosis, and multiple organ dysfunction. Two COVID-19 biomarkers could reflect the development of MAS. The first is IL-6, the concentration of which rises to levels higher than in other viral diseases. The second biomarker of MAS is ferritin, which concentration also increases during COVID-19. In two comparative studies, 653 COVID-19 demonstrated plasma ferritin level that was higher than 408 ng/ml (95 % CI = 311–505 ng/ml) in severe disease. Moreover, ferritin levels were up to 760 ng/ml that was higher in survivors vs. non-survivors (95 % CI = 561–959 ng/ml) [37]. Thus, the detection of elevated concentrations of MAS

biomarkers in severe COVID-19 points at potential involvement of MAS in pro-inflammatory, prothrombotic conditions and the hyperferritinemia syndrome [106].

Hyperactivation of the renin-angiotensin system / Гиперактивация ренин-ангиотензиновой системы

Infection with SARS-CoV-2 occurs through the binding of the virus to ACE2, similar to other SARS-CoViruses [107]. ACE2 is a membrane-bound protein in various organs and tissues, including the lungs, small intestine, heart, brain, adipose tissue, and endothelium [108]. It is especially abundant in the lungs, heart, arteries, and veins [109]. Angiotensinogen is converted to angiotensin (Ang) I by renin, Ang I is converted to Ang II by ACE, and Ang II promotes vasoconstriction and pro-inflammatory and prothrombotic effects by acting on the angiotensin II receptor type I (AT1R) and angiotensin II type IV receptor (AT4R) [110]. ACE2 reduces renin-angiotensin system (RAS) activity vi atwo mechanisms: i) ACE2 degrades Ang I and Ang II, depleting the substrate available for AT1R activation via the classic RAS cascade, ii) Ang II is directly cleaved to Ang, a vasoactive peptide with vasodilating and anti-inflammatory effects via the MAS receptor.

SARS-CoV-2 uses ACE2 to enter the cell after interaction with the serine protease TMPRSS2, which activates the viral spike protein [67]. As a result, it is possible that the pulmonary expression of membrane-bound ACE2 is suppressed that shifts the balance towards pro-inflammatory and prothrombotic effects mediated by Ang II and AT1R. This could potentially translate into increased local or circulating Ang II to Ang ratio or the absolute Ang II level. Y. Liu et al noted an increased plasma concentration of Ang II in patients with COVID-19 compared with the control group [111].

Angiotensin II has several pro-inflammatory and prothrombotic effects that COVID-19 may exacerbate. Thrombosis in microcirculation has been demonstrated in mouse models injected with Ang II [112]. Ang II is involved in the pathogenesis of endothelial dysfunction and oxidative stress [113]. AT1R activation by Ang II enhances platelet activation and impairs fibrinolysis [114]. Ang II also increases

tissue factor expression, which triggers the external coagulation pathway and PAI-1, which is the primary endogenous inhibitor of tPA and urokinase [115].

The majority of ICU patients with COVID-19 have shown hypofibrinolysis [116]. PAI-1, as the primary inhibitor of plasminogen activation along with increased concentrations in COVID-19 leads to apparent alteration of fibrinolysis processes. An increase in IL-6 levels is also associated with elevated PAI-1 [117]. Increased expression of PAI-1 leads to increased pulmonary fibrosis mediated by transforming growth factor-β [118]. PAI-1 is expressed in various tissues, including adipose tissue [119], indicating a possible link between obesity and death in COVID-19, especially in younger patients without other comorbidities.

Antiphospholipid antibodies / Антифосфолипидные антитела

Several studies in patients with COVID-19 have shown a high circulation of APAs [120]. Laboratory confirmation of APS by measuring APA, LA, anticardiolipin antibodies, and anti-β_2-glycoprotein 1, often accompanies both arterial and venous thrombosis. Clinical cases of three patients with COVID-19 and multiple cerebral infarctions with concomitantly detected APA have been described [65]. A high rate of detected APAs was noted in patients with COVID-19 and prolonged APTT [16, 121]. In another study, the percentage of patients who were positive for LA was significantly higher among patients with COVID-19 than those without COVID-19 [122]. APAs interact with endothelium, platelets, and complement factors and promote the development of thrombosis [123–126]. APAs are often detected in viral infections. Their presence may be temporary and do not always imply an increased risk of thrombosis [127]. Applying anticoagulant therapy may be also coupled to false-positive LA test [128].

Anti-thrombotic therapeutic strategies/ Стратегии противотромботической терапии

Current recommendations indicate the need for thrombosis prophylaxis in all hospitalized patients, unless contraindicated due to the high risk of bleeding.

Given the high risk of bleeding with fibrinolytic therapy, its use in severe COVID-19 is not justified.

Conclusion / Заключение

Macro- and micro thrombosis often complicate the course of Covid-19, significantly increasing mortality.

Several thrombogenic mechanisms can potentially be involved in thrombotic features in COVID-19: cytokine storm, antiphospholipid syndrome, its catastrophic variant, macrophage activation syndrome, massive NETosis, activation of the complement system, dysregulated renin-angiotensin system, hypofibrinolysis, thrombotic syndrome, microangiopathic syndrome, and intravascular coagulation.

A genetic predisposition to thrombosis can be a significant factor in the increased risk of thrombotic complications, including death, in patients with COVID-19.

Thrombophilia in these patients and poorly controlled inflammation overactivate the blood coagulation system and can result in severe forms of COVID-19 as the pathogenetic mechanism of thrombus inflammation and thrombotic storm are implicated.

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About the authors:

Alexander D. Makatsariya – MD, Dr Sci Med, Academician of RAS, Professor, Head of the Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0001-7415-4633. Scopus Author ID: 57222220144. Researcher ID: M-5660-2016.

Ekaterina V. Slukhanchuk – MD, PhD, Associate Professor, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow Russia; Obstetrician-Gynecologist, Department of Abdominal Surgery and Oncology 2, Petrovsky National Research Centre of Surgery, Moscow, Russia. E-mail: beloborodova@rambler.ru. ORCID: https://orcid.org/0000-0001-7441-2778.

Victoria O. Bitsadze – MD, Dr Sci Med, Professor of RAS, Professor, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0001-8404-1042. Scopus Author ID: 6506003478. Researcher ID: F-8409-2017.

Jamilya Kh. Khizroeva – MD, Dr Sci Med, Professor, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0002-0725-9686. Scopus Author ID: 57194547147. Researcher ID: F-8384-2017.

Maria V. Tretyakova – MD, PhD, Obstetrician-Gynecologist, Department of Gynecology, «Medical Center» LLC, Moscow, Russia. ORCID: https://orcid.org/0000-0002-3628-0804.

Andrey S. Shkoda – MD, Dr Sci Med, Professor, Chief Physician, Vorokhobov City Clinical Hospital № 67, Moscow, Russia. ORCID: https://orcid.org/0000-0002-9783-1796.

Svetlana V. Akinshina – MD, PhD, Obstetrician-Gynecologist, Hematologist, «Medical Centre for Women» LLC, Moscow, Russia. ORCID: http://orcid.org/0000-0002-1388-5827.

Nataliya A. Makatsariya – MD, PhD, Associate Professor, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0002-2541-3843. Researcher ID: F-8406-2017.

Valentina I. Tsibizova – MD, PhD, Obstetrician-Gynecologist, Research Laboratory of Operative Gynecology, Institute of Perinatology and Pediatrics; Physician, Department of Functional and Ultrasound Diagnostics, Almazov National Medical Research Centre, Saint Petersburg, Russia. ORCID: https://orcid.org/0000-0001-5888-0774.

Jean-Christophe Gris – MD, Dr Sci Med, Professor, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia; University of Montpellier, Montpellier, France. ORCID: https://orcid.org/0000-0002-9899-9910. Researcher ID: AAA-2923-2019.

Ismail Elalamy – MD, Dr Sci Med, Professor, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia; Professor, Medicine Sorbonne University, Paris, France; Director of Hematology, Department of Thrombosis Center, Hospital Tenon, Paris, France. ORCID: https://orcid.org/0000-0002-9576-1368. Scopus Author ID: 7003652413. Researcher ID: AAC-9695-2019.

Cihan Ay – MD, PhD, Professor, Department of Medicine I, Clinical Division of Haematology and Haemostaseology, Medical University of Vienna, Vienna, Austria. ORCID: https://orcid.org/0000-0003-2607-9717. Scopus Author ID: 55356863800.

Elvira Grandone – Dr Sci Med, Professor, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia; Head of the Department of Thrombosis and Hemostasis, Research Center «Casa Sollievo della Sofferenza», San Giovanni Rotondo, Italia. ORCID: https://orcid.org/0000-0002-8980-9783. Scopus Author ID: 7006391091. Researcher ID: M-1127-2019.

Сведения об авторах:

Макацария Александр Давидович – д.м.н., профессор, академик РАН, зав. кафедрой акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский Университет), Москва, Россия. ORCID: https://orcid.org/0000-0001-7415-4633. Scopus Author ID: 57222220144. Researcher ID: M-5660-2016.

Слуханчук Екатерина Викторовна – к.м.н., доцент кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский Университет), Москва,

Россия; врач акушер-гинеколог отделения абдоминальной хирургии и онкологии 2, ФГБНУ «Российский научный центр хирургии имени академика Б.В. Петровского», Москва, Россия. E-mail: beloborodova@rambler.ru. ORCID: https://orcid.org/0000-0001-7441-2778.

Бицадзе Виктория Омаровна – д.м.н., профессор РАН, профессор кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский Университет), Москва, Россия. ORCID: https://orcid.org/0000-0001-8404-1042. Scopus Author ID: 6506003478. Researcher ID: F-8409-2017.

Хизроева Джамиля Хизриевна – д.м.н., профессор кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский университет), Москва, Россия. ORCID: https://orcid.org/0000-0002-0725-9686. Scopus Author ID: 57194547147. Researcher ID: F-8384-2017.

Третьякова Мария Владимировна – к.м.н., врач акушер-гинеколог отделения гинекологии ООО «Лечебный Центр», Москва, Россия. ORCID: https://orcid.org/0000-0002-3628-0804.

Шкода Андрей Сергеевич – д.м.н., профессор, главный врач ГБУЗ «Городская клиническая больница № 67 имени Л.А. Ворохобова Департамента здравоохранения города Москвы», Москва, Россия. ORCID: https://orcid.org/0000-0002-9783-1796.

Акиньшина Светлана Владимировна – к.м.н., врач акушер-гинеколог, гематолог, ООО «Медицинский женский центр», Москва, Россия. ORCID: http://orcid.org/0000-0002-1388-5827.

Макацария Наталия Александровна – к.м.н., доцент кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский университет), Москва, Россия. ORCID: https://orcid.org/0000-0002-2541-3843. Researcher ID: F-8406-2017.

Цибизова Валентина Ивановна – к.м.н., акушер-гинеколог НИЛ оперативной гинекологии Института перинатологии и педиатрии; врач отделения функциональной и ультразвуковой диагностики ФГБУ «Национальный медицинский исследовательский центр имени В.А. Алмазова» Министерства здравоохранения Российской Федерации, Санкт-Петербург, Россия. ORCID: https://orcid.org/0000-0001-5888-0774.

Гри Жан-Кристоф – д.м.н., профессор кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский

государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский университет), Москва, Россия; профессор гематологии, университет Монпелье, Монпелье, Франция. ORCID: https://orcid.org/0000-0002-9899-9910. Researcher ID: AAA-2923-2019.

Элалами Исмаил – д.м.н., профессор кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский университет), Москва, Россия; профессор медицинского Университета Сорбонны, Париж, Франция; директор гематологии Центра Тромбозов, Госпиталь Тенон, Париж, Франция. ORCID: https://orcid.org/0000-0002-9576-1368. Scopus Author ID: 7003652413. Researcher ID: AAC-9695-2019.

Ай Цихан – д.м.н., профессор, клиническое подразделение гематологии и гемостазиологии, медицинское отделение I, Венский университет, Вена, Австрия. ORCID: https://orcid.org/0000-0003-2607-9717. Scopus Author ID: 55356863800.

Грандоне Эльвира – д.м.н., профессор кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский университет), Москва, Россия; руководитель отделения тромбозов и гемостаза исследовательского центра «Casa Sollievo della Sofferenza», Сан-Джованни-Ротондо, Италия. ORCID: https://orcid.org/0000-0002-8980-9783. Scopus Author ID: 7006391091. Researcher ID: M-1127-2019.