ISSN 2313-7347 (print)
ISSN 2500-3194 (online)

АКУШЕРСТВО ГИНЕКОЛОГИЯ РЕПРОДУКЦИЯ

Включен в перечень ведущих рецензируемых журналов и изданий ВАК

2021 • том 15 • № 6

OBSTETRICS, GYNECOLOGY AND REPRODUCTION

2021 Vol. 15 No 6

www.gynecology.su

ISSN 2313-7347 (print)
ISSN 2500-3194 (online)

Научный обзор | Review article

https://doi.org/10.17749/2313-7347/ob.gyn.rep.2021.249

Features of the novel coronavirus infection in cancer patients

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Abstract

A novel coronavirus (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) is largely associated with various coagulopathies, which can lead to either bleeding and thrombocytopenia or hypercoagulation and thrombosis. Thrombohemorrhagic complications also could accompany the development of cancer process. In addition, circulating inflammatory biomarkers such as fibrin, D-dimer, P-selectin and von Willebrand factor (vWF) typical to both coronavirus infection and malignancy process are of special interest. In this review, we discuss potential interplay between COVID-19 and cancer related to endothelial dysfunction, platelets, and systemic inflammatory response syndrome. Most importantly, patients should be treated in early stage of the disease process when elevated levels of fibrinogen, D-dimer, vWF, and P-selectin are observed. The level of these markers will rise rapidly upon disease progression, followed by a cytokine storm, would evidence about a poor prognosis.

Keywords: novel coronavirus infection, COVID-19, cancer, hemostasis disorders, systemic inflammatory response syndrome

For citation: Makatsariya A.D., Elalamy I., Brenner B., Vorobev A.V., Ashrafyan L.A., Maslenkova E.V., Bitsadze V.O., Khizroeva J.Kh., Shkoda A.S., Solopova A.G., Galkin V.N., Gris J.-C. Features of the novel coronavirus infection in cancer patients. *Akusherstvo, Ginekologia i Reprodukcia = Obstetrics, Gynecology and Reproduction*. 2021;15(6):726–737. https://doi.org/10.17749/2313-7347/ob.gyn.rep.2021.249.

Особенности течения новой коронавирусной инфекции у онкологических больных

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Obstetrics, Gynecology and Reproduction

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Резюме

Новый коронавирус (SARS-CoV-2), вызывающий коронавирусную инфекцию 2019 (COVID-19), в значительной степени ассоциируется с возможным развитием коагулопатий, которые могут привести либо к кровотечению и тромбоцитопении, либо к гиперкоагуляции и тромбозу. Тромбогеморрагические осложнения также могут сопровождать и развитие онкологического процесса. Особый интерес представляют циркулирующие биомаркеры воспаления, характерные и для коронавирусной инфекции и для развития злокачественного новообразования, такие как фибрин, Д-димер, P-селектин и фактор фон Виллебранда (vWF). В данном обзоре обсуждаются потенциальные точки взаимодействия COVID-19 и онкологического процесса, связанные с дисфункцией эндотелия, тромбоцитов, синдромом системного воспалительного ответа. Наиболее важной проблемой является своевременная терапия пациентов на ранних стадиях развития заболевания, когда присутствуют повышенные уровни фибриногена, Д-димера, vWF и P-селектина. Стремительный рост уровня этих маркеров, за которым последует «цитокиновый шторм», будет свидетельствовать о плохом прогнозе.

Ключевые слова: новая коронавирусная инфекция, COVID-19, онкологические заболевания, нарушения гемостаза, синдром системного воспалительного ответа

Для цитирования: Макацария А.Д., Элалами И., Бреннер Б., Воробьев А.В., Ашрафян Л.А., Маслёнкова Е.В., Бицадзе В.О., Хизроева Д.Х., Шкода А.С., Солопова А.Г., Галкин В.Н., Гри Ж.-К. Особенности течения новой коронавирусной инфекции у онкологических больных. *Акушерство, Гинекология и Репродукция.* 2021;15(6):726–737. https://doi.org/10.17749/2313-7347/ob.gyn.rep.2021.249.

Introduction / Введение

Since the beginning of the pandemic, the epidemiological characteristics of the novel coronavirus infection COVID-19 have been constantly changing. The total number of global cases exceeds 260 million people, the infection was most widespread in the USA, India, Brazil, Great Britain, Russia, and Turkey [1]. The main source of infection is a sick person, including those in the disease incubation period. The incubation period for COVID-19 is approximately two weeks, with most infected people displaying symptoms five days after exposure. The magnitude of the disease ranges from mild to extremely severe. In about 80 % of cases, the disease is asymptomatic or has mild symptoms, in 15 % – a severe course and 5 % – an extremely severe course [2]. Owing to tests and quarantine restrictions, the actual case fatality ratio (CFR) for COVID-19 is challenging to determine, but it ranges from 1 to 3 % [1, 2].

Two ways for virus penetration into host cells have been suggested: the binding on the receptor for angiotensin-converting enzyme 2 (ACE2) or to the transmembrane glycoprotein CD147. The interaction of COVID-19 with the renin-angiotensin-aldosterone system via ACE2

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Highlights

What is already known about this subject?

- The International Center for Disease Control and Prevention has identified high risk factors for severe COVID-19 and related death, one of which is concomitant cancer, especially during anticancer treatment.
- The "cytokine storm" characteristic of coronavirus infection is a life-threatening systemic inflammatory response syndrome caused by elevated levels of circulating cytokines and hyperactivated immune cells.

What are the new findings?

- We summarize the data on the specifics of COVID-19 pathogenesis in cancer patients, namely higher levels of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), as well as biomarkers such as procalcitonin and C-reactive protein.
- Proinflammatory cytokines, which expression is induced by COVID-19 and tumor tissue, contribute mainly to thrombogenesis.
- Taking into account developing systemic inflammatory response syndrome typical for both cancer and COVID-19 patients, heparin-induced thrombocytopenia represents an additional risk factor for thrombocytopenia.

How might it impact on clinical practice in the foreseeable future?

- Suppression of IL-6 production may be a positive therapeutic effect both in cancer treatment preventing malignant progression and to attenuate the "cytokine storm" in COVID-19.
- Investigating an association of thrombotic complications in cancer patients with COVID-19 bearing antiphospholipid antibodies is promising, and accordingly, coagulopathy should be evaluated and treated as immune-mediated rather than classical antiphospholipid syndrome.

Основные моменты

Что уже известно об этой теме?

- Международный Центр по борьбе с COVID-19 определил факторы высокого риска тяжелого течения и смерти от заболевания, одним из которых является наличие онкологического заболевания, особенно во время противоопухолевого лечения.
- Характерный для коронавирусной инфекции «цитокиновый шторм» представляет собой угрожающий жизни синдром системного воспалительного ответа (ССВО), обусловленный повышенным уровнем циркулирующих цитокинов и гиперактивацией иммунных клеток.

Что нового дает статья?

- Обобщены данные об особенностях патогенеза COVID-19 у онкологических больных, а именно, более высокие уровни провоспалительных цитокинов, в том числе фактора некроза опухоли альфа (TNF-α) и интерлейкина-6 (IL-6), а также такие биомаркеры, как прокальцитонин и С-реактивный белок.
- Провоспалительные цитокины, экспрессия которых вызвана COVID-19 и опухолевой тканью, вносят основной вклад в развитие тромбоза.
- С учетом развития ССВО, характерного как для онкологических больных, так и для больных COVID-19, дополнительным фактором риска развития тромбоцитопении является гепарин-индуцированная тромбоцитопения.

Как это может повлиять на клиническую практику в обозримом будущем?

- Подавление выработки IL-6 может являться положительным терапевтическим эффектом как в лечении рака, предотвращая злокачественное прогрессирование, так и для ослабления «цитокинового шторма» при COVID-19.
- Перспективными являются исследования ассоциации тромботических осложнений у онкологических пациентов с COVID-19 с наличием антифосфолипидных антител, и соответственно, коагулопатию следует оценивать и лечить как иммуноопосредованную, а не как классический антифосфолипидный синдром.

is a key factor in the pathological features. ACE2 physiologically counteracts RAAS activation of renin-angiotensin-aldosterone system and serves as a receptor for SARS-CoV-2 [3, 4]. Penetration through ACE2 is carried out because the viral S-protein in its structure mimics ACE2, due to which viral particles successfully bind to ACE2 receptors, which are expressed by cells of lung tissue (type 2 alveolocytes), intestines, kidneys, blood vessels, as well as the oral mucosa cavity (**Fig. 1**) [3, 4]. The affinity of the SARS-CoV-2 S-protein for the ACE2 receptor is 10–20 times higher than that of SARS-CoV-1, which accounts for its greater contagiousness. The mechanism of entry into a cell using the CD147 receptor is similar to that of for penetration via ACE2 [4].

The International Center for the Fight against COVID-19 (Center for Disease Control and Prevention, CDC) has identified high-risk factors for severe disease and death from the disease, such as age over 65, obesity – body mass index (BMI) ≥ 35, the presence of comorbid con-

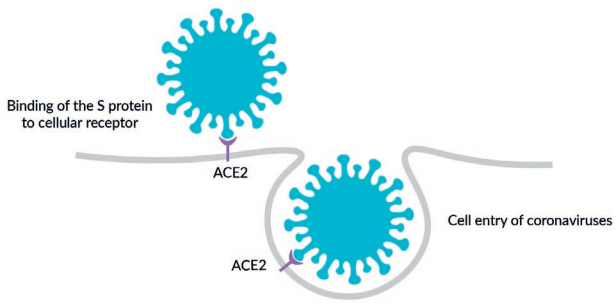

Figure 1. The mechanism of COVID-19 virus penetration into the cell [drawn by authors].

Note: *ACE2 – angiotensin-converting enzyme 2.*

Рисунок 1. Механизм проникновения вируса COVID-19 в клетку [рисунок авторов].

Примечание: *ACE2 – ангиотензинпревращающий фермент 2.*

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ditions: diabetes mellitus, chronic diseases of the heart, kidneys or liver [5–9]. This group also included patients with cancer, especially those receiving anticancer treatment. Cancer patients are most susceptible to infectious diseases due to systemic immunosuppression caused by malignant neoplasms and anticancer therapy [10].

Groups of high risk of infection and development of severe COVID-19-related complications have been identified among patients with cancer in the recommendations of the European Society for Medical Oncology (ESMO) [11]:

– patients receiving or who received chemotherapy within the last three months;

– patients receiving radiation therapy;

– patients who have undergone bone marrow transplantation in the last six months, as well as those receiving immunosuppressive therapy;

– patients with oncohematological diseases, even if they are not undergoing treatment.

Thus, these patients may have an increased risk of severe COVID-19 and a correspondingly poorer prognosis.

Coronavirus infection in cancer patients / Коронавирусная инфекция у онкологических больных

According to a study by W. Liang et al., among the first 1590 cases of coronavirus infection, 18 (1.0 %) patients suffered from cancer [12]. Lung cancer was the most common (28.0 %), with four patients underwent antitumor treatment during the last month, whereas the remaining patients had previously undergone radical surgical treatment. Compared to others, cancer patients were older, smoked more often, had tachypnea, and more pronounced changes according to CT scan. No significant differences in gender distribution as well as in severity of concomitant diseases and baseline changes were found on radiographs. Cancer patients were characterized by a higher incidence of severe course (7 out of 18 patients) requiring stay in the intensive care unit, mechanical ventilation, or resulting in death (124 out of 1572 patients; p = 0.0003) [12]. In addition, chemotherapy or surgery in the last month (in 3 out of 4 patients) was associated with a higher risk of complications compared to those who received no chemotherapy or surgery (6 out of 14 patients). When conducting regression analysis and excluding other risk factors: age of patients, smoking intensity, presence of concomitant diseases, such risks were confirmed (risk ratio (RR) = 5.34; p = 0.0026). In cancer patients, only old age was an additional risk factor for severe events (RR = 1.43; p = 0.072). Lung cancer patients had no higher likelihood of severe events compared with other cancer patients (1 out of 5 lung cancer patients versus 8 out of 13 patients with other malignant neoplasms; p = 0.294). Regression analysis also revealed that cancer patients are characterized by a more rapid development of severe events than other patients: the mean time to severe events was 13 days vs. 43 days (RR = 3.56; p < 0.0001) [12].

While comparing the biochemical parameters of COVID-19 in patients with/without cancer, higher levels of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), were found. Infection-related biomarkers procalcitonin and C-reactive protein were also higher in patients with malignant neoplasms [13]. In addition, patients with cancer had more cases of multiple organ damage compared to other patients. Cancer patients had higher neutrophil count as well as transaminase and lactate levels, whereas eosinophils, albumin, globulin, and total protein were reduced. In addition, parameters associated with coagulation, such as decreased platelet count as well as prolonged prothrombin time (PT) and activated partial thromboplastin time, were also more prominent in patients with cancer [13].

According to the study conducted in three hospitals in Wuhan, China, 28 cancer patients were registered out of 1276 patients (2.2 %) admitted between January 13, 2020, and February 26, 2020 [14]. The average age was 65.0 years; and males comprised 17 (60.7 %) among them. Lung cancer was most common (n = 7; 25.0 %) in this cohort, followed by esophageal cancer (n = 4; 14.3 %) and breast cancer (n = 3; 10.7 %). Stage IV cancer was diagnosed in 10 patients (35.7 %). All patients received anticancer therapy. Within 14 days after the diagnosis of COVID-19, 6 (21.4 %) patients received at least one type of anticancer therapy, such as chemotherapy (n = 3; 10.7 %), targeted therapy (n = 2; 7.1 %), radiation therapy (n = 1; 3.6 %) or immunotherapy (n = 1; 3.6 %). As of February 26, 2020, 15 (53.6 %) patients developed severe clinical events, 6 (21.4 %) patients were admitted to the intensive care unit, 10 (35.7 %) patients had life-threatening complications, and 8 (28.6 %) of patients died. Out of 10 patients with stage IV cancer, 7 (70.0 %) developed severe complications. Among 6 cancer patients who received anticancer treatment within 14 days after COVID-19 diagnosis, 5 (83.0 %) of them developed severe complications. In addition, 84.6 % of patients (11 of 13) with consolidation foci on CT on admission developed severe complications. The most common complication was acute respiratory distress syndrome (n = 8; 28.6 %), followed by septic shock (n = 1; 3.6 %) and acute myocardial infarction (n = 1; 3.6 %). Two patients (7.1 %) were suspected of pulmonary embolism [14].

In total, from March 18, 2020 to April 8, 2020, 218 patients diagnosed with COVID-19 were identified. In this group 61 (28.0 %) patients died from COVID-19 with a case-fatality rate (CFR) of 37.0 % (20 of 54) and 25.0 % (41 of 164) among patients with oncohematological diseases and solid malignant neoplasms, respectively,

whereas 6 out of 11 (55.0 %) patients with lung cancer died. Increased mortality was associated with older age, multiple comorbidities, required intensive care, and elevated D-dimer levels. Evidence showing a significantly increased mortality from COVID-19 among cancer patients points at the need for active strategies to reduce the likelihood of infection and improve its early detection in this group of patients [15].

Patients with malignant neoplasms associated with severe immunodeficiency (lymphomas, leukemias, and multiple myelomas) are likely to be at peak risk for COVID-19 infection. The most severe coronavirus infection was in patients with myelosuppression as well as after hematopoietic cell transplantation. Risk factors included age over 50 years, graft versus host disease, corticosteroid use, neutropenia, lymphopenia, and hypoalbuminemia [15].

The COVID-19 and Cancer Registry (CCC19) has published data from a large cohort study of 928 patients from the United States, Canada, and Spain [13]. The mortality rate of cancer patients was analyzed within 30 days after verifying COVID-19. The average age of the patients was 66 years (57–76). The disease was most often associated with breast (21.0 %) and prostate (16.0 %) cancers. Independent risk factors associated with 30-day mortality included age (RR = 1.84; 95 % confidence interval (CI) = 1.53–2.21), smoking status (RR = 1.60; 95% CI = 1.03–2.47), male gender (RR = 1.63; 95% CI = 1.07–2.48), number of concomitant diseases (more than one disease: RR = 4.50; 95% CI = 1.33–15.28), active oncological process (RR = 5.20; 95% CI = 2.77–9.77). It should be noted that obesity, the type of tumor, and the anticancer therapy used did not affect the mortality rate [16].

Systemic inflammatory response syndrome / Синдром системного воспалительного ответа

In the pathogenesis of COVID-19, activation of the endothelium and its interaction with various inflammation biomarkers, as well as with the virus, may be critical. SARS-CoV-2 initiates the development of the systemic inflammatory response syndrome, which results in inhibited thromboresistant properties of the vascular endothelium and upregulated expression of tissue factor (TF). A similar pathogenesis is typical for the development of malignant neoplasms, thus the procoagulant effect of the virus and tumor cells has a synergistic effect and much more often leads to the development of disseminated intravascular coagulation (DIC) [17].

All three components of the Virchow triad are relevant for both cancer patients and patients with COVID-19. In these diseases, damage to the endothelium occurs, which leads to the activation of proinflammatory stimuli. Stasis is realized upon prolonged hospitalization and immobilization, especially in patients on mechanical ventilation and admitted to the intensive care unit. The expression of proinflammatory cytokines caused by COVID-19 and tumor tissue mainly contribute to thrombogenesis in both cases [18]. The tumor also secretes multiple cytokines found in patients with SARS-CoV-2 infection. TNF-α and IL-1 may contribute to thrombosis by inducing expression of TF and von Willebrand factor (vWF) on vascular endothelial cells, increasing the level of plasminogen, and weakening anticoagulant effects by suppressing thrombomodulin expression [19].

Tissue factor plays a decisive role in ensuring coagulation and angiogenesis in both solid neoplasms and lymphoproliferative diseases. SARS-CoV-2 promotes the induction of endothelins in multiple organs as a direct consequence of viral injury and host inflammatory response. Tissue factor is also expressed by mononuclear cells and macrophages in response to proinflammatory cytokines [20]. Coagulation mainly depends on TF-expressing inflammatory monocytes recruited by activated endothelial cells [21].

Likewise, cancer-related neutrophil extracellular traps (NETs), a DNA-linked network of proteases and histones derived from neutrophils, can promote the activation of host cells, contributing to developing thrombosis [22]. For instance, NETs can serve as a platform for direct platelet adhesion and aggregation. Moreover, NETs-associated histones can indirectly increase platelet aggregation by increasing the level of vWF released from activated endothelial cells.

The "cytokine storm" characteristic of coronavirus infection is a life-threatening systemic inflammatory response syndrome resulting from increased level of circulating cytokines and hyperactived immune cells [23]. While cytokine storm develops, DIC with occlusion of large and small vessels and hemorrhagic syndrome proceeds relatively quickly due to pulmonary embolism, shortness of breath, hypoxemia, and hypotension may develop. Many patients develop respiratory symptoms, including cough and tachypnea, which may progress to acute respiratory distress syndrome, requiring mechanical ventilation to compensate hypoxemia. The nonspecific markers of inflammation, such as C-reactive protein, will be elevated correlating with the disease severity. IL-6 is one of the most multi-faceted cytokines, as it is expressed and acts on both immune and non-immune cells in many organs and systems. Its activation leads to systemic hyperinflammatory reaction with secretion of monocyte chemoattractant protein type-1 (MCP-1), IL-8, additional expression of IL-6, as well as an increase in the production of vascular endothelial growth factor (VEGF), which contribute to increased vascular permeability and direct pulmonary dysfunction [24]. TNF-α, expressed both in COVID-19 and tumor, is a potent pro-inflammatory cytokine that enhances systemic inflammation and, in turn, induces IL-6 production [25]. TNF-α

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can induce cell apoptosis, and in mouse models it has been shown that during developing toxic shock, it was a cytokine driver that triggers and intensifies the "cytokine storm". Plasma proteins, such as complement components and other inflammatory mediators, can contribute to developing "cytokine storm" [26].

On the other hand, cytokines can also increase the production of complement proteins. Thus, the complement system being partially pre-activated in cancer patients can cause additional damage in the presence of coronavirus infection [27]. Elevated serum cytokine levels in COVID-19 patients include IL-1β, IL-6, TNF-α, interferon-γ, macrophage inflammatory protein (MIP) 1α and 1β, and VEGF [28].

Over the past 10 years, the role of IL-6 in oncogenesis and anti-apoptosis signaling as well as assessing cancer prognosis has been demonstrated [29].

"Cytokine storm" can also develop due to CAR (chimeric antigen receptor) T-cell therapy, which is used for chemoresistant hematological malignancies and some solid tumors [30]. Given the critical role of IL-6 in both COVID-19 and cancer, research into the effects of COVID-19 in cancer patients will be indispensable whether it plays a synergistic role in tumor progression. For instance, if a cancer patient becomes infected with SARS-CoV-2, will the tumor cells be susceptible to IL-6 release known to be associated with malignant progression, and lead to worse outcomes? Therefore, are anti-IL-6 receptor monoclonal antibodies a drug of choice in cancer patients, since downmodulated IL-6 production can be a positive therapeutic effect both in cancer treatment and alleviating the "cytokine storm" caused by COVID-19? In May 2020, a phase II clinical trial (NCT04370834) was launched to evaluate the effectiveness of tocilizumab use in patients with COVID-19 and malignant neoplasms, but in January 2021 the study was interrupted and its results have not yet been published (https://clinicaltrials.gov/ct2/show/study/NCT04370834).

In addition, the question is whether IL-6 release due to COVID-19 can activate oncogenesis still remains. One scenario is that treating COVID-19 patients with IL-6 therapies can prevent malignant progression, and that patients with documented IL-6-mediated malignancies and COVID-19 may be eligible for specific therapy. While clinical trials are exploring multiple ways to reduce IL-6 production, the question remains: Which COVID-19 patients would benefit most from IL-6 suppression, and what parameters should be used assess it?

SARS-CoV-2 influencing hemostasis / Влияние SARS-CoV-2 на систему гемостаза

The severe course of COVID-19 infection is usually associated with the development of DIC and coagulopathy, as well as pulmonary embolism [31–33]. Developing as a hypocoagulant septic coagulopathy, disseminated intravascular coagulation syndrome can lead to significant complications. The effect of SARS-CoV-2 infection on the hemostatic system is mediated by proinflammatory cytokines such as IL-1β, TNF-α, with IL-6 being especially pronounced [31]. The endothelial cell dysfunction resulting from infection contributes to the excessive thrombin formation and suppressed fibrinolysis, i.e., a hypercoagulable state. Hypoxia occurring in severe pneumonia can be both a consequence and a cause of microvascular thrombosis.

Although both low and high levels of fibrinogen have been reported in COVID-19 (normal levels range within 2–4 mg/ml) [32], the main factor behind high fibrinogen levels is the increased blood coagulation potential. Fibrinogen, D-dimer, vWF, and P-selectin play a central role in the development of coagulopathy in both COVID-19 and cancer patients [33]. In a cohort study of 201 patients with confirmed COVID-19 pneumonia, risk factors associated with acute respiratory distress syndrome development and the transition from acute respiratory distress syndrome to death included particularly hemostatic dysfunction [34]. D-dimer was within the normal range or slightly increased at the onset of the disease, but while it proceeded, D-dimer increased significantly, as in the case of developing oncological process. It was also found that DIC-syndrome in COVID-19 is accompanied by significantly decreased level of fibrinogen and noticeably increased formation of fibrin degradation products and D-dimer. An increase in the level of fibrin degradation products and D-dimer is a characteristic feature for DIC-syndrome with hyperfibrinolysis, whereas DIC caused by infection is accompanied by released inhibitor of plasminogen-1 activator (PAI-1) and suppressed fibrinolysis [34].

The processes of thrombogenesis and inflammation are closely interrelated. Regardless of the etiology of pneumonia, coagulopathy is recorded in many patients with severe course. However, are there any features of the coagulopathy pathogenesis in patients with pneumonia associated with COVID-19 compared with same severity pneumonia caused by other infection? In a retrospective study, S. Yin et al. was one of the first to describe the features of the hemostasis system functioning in patients with severe pneumonia caused by SARS-CoV-2 (COVID-19 group) and non-SARS-CoV-2 (non-COVID-19 group) [35], in particular, the effectiveness of anticoagulant therapy in patients with elevated D-dimer levels was evaluated. The study included 449 patients with COVID-19 and 104 patients with pneumonia of a different etiology. There was a double mortality in the COVID-19 group compared to the non-COVID group (29.8 % vs. 15.4 %, respectively; p = 0.003). However, it was noted that in the COVID-19 group, on average, pa-

tients were older (65.1 ± 12.0 years vs. 58.4 ± 18.0 years, respectively; $p < 0.001$). The authors concluded that an increased level of D-dimer due to coronavirus infection was associated with a poor prognosis in patients with severe course.

Fibrinogen receptors are of particular importance because the binding of their ligands causes the activation of various inflammatory signaling pathways. These pathways are essential for healthy physiological processes but play a critical role in pathophysiology, including the "cytokine storm" in COVID-19 and cancer. Poor outcomes in COVID-19 correlate with clinical and laboratory signs of systemic inflammatory response syndrome and elevated D-dimer levels. However, in the presence of a "cytokine storm", bleeding predominates, and a low survival rate is noted. In other words, at an early stage of COVID-19, patients with normal or slightly elevated D-dimer levels, had increased levels of fibrinogen, vWF and P-selectin and activated platelets, if not treated, the clinical picture changes to a rapid increase in D-dimer, and even more significant increases in fibrinogen, vWF and P-selectin levels and platelet hyperactivation. This corresponds to the state of hypercoagulation and thrombosis. Then, during the development of coronavirus infection, the levels of D-dimer and P-selectin further increase, and the levels of fibrinogen and vWF decrease, as these molecules are depleted either from the circulation or from damaged endothelial cells and hyperactivated platelets [35].

Experts from the International Society of Thrombosis and Haemostasis (ISTH) consider a 3–4-fold increase in D-dimer level as an independent indication in favor for hospitalization of patients with COVID-19 [36]. In addition, coronavirus pneumonia is significantly more often accompanied by thrombocytosis, compared with the group without COVID-19: 215 ± 100×10^9/L vs. 188 ± 98×10^9/L ($p = 0.015$). According to the study, this may be due to a more severe inflammatory reaction development and is associated with a greater risk of development [37].

At the beginning of the infectious process caused by SARS-CoV-2, a moderate increase in the content of fibrinogen and D-dimer is observed, then, as the disease progresses and respiratory failure aggravates, a condition, which experts call pre-DIC-syndrome develops. At the same time, there is a significant increase (3–4 times) in the level of D-dimer and prolonged prothrombin time. The activation of the hemostasis system occurs through inflammatory mediators (IL-6, TNF-α), both by damaging and activating the endothelium (due to TF production) and stimulating platelets, resulting in triggered the external coagulation pathway. The pathogenesis of disseminated intravascular coagulation is also enabled by reducing the activity of natural anticoagulants and disrupting the mechanisms of platelet disaggregation. As disseminated intravascular coagulation proceeds, there is a markedly prolonged prothrombin time and decreased platelet count. Thus, hypercoagulation develops already at early stages, partly predetermining the severe course of the infection being associated with increased risk of developing disseminated intravascular coagulation and thromboembolism [38].

In a number of other studies, it was confirmed that an increase in the levels of D-dimer and fibrinogen, a prolonged prothrombin time is also associated with a severe course of COVID-19. N. Tang et al. found that a significant increase in the level of D-dimer is one of the predictors for increased mortality. In particular, it was noted that in the deceased subjects, the D-dimer content averaged 2.12 (0.77–5.27) μg/ml, while the survivors had it at level of 0.61 (0.35–1.29) μg/ml at a rate of less than 0.5 μg/ml [39].

It is still unknown whether thrombosis caused by COVID-19 can be associated with concomitant antiphospholipid antibodies (APAs). One study found that the development of thrombosis in the three COVID-19 patients was associated with anticardiolipin antibodies (aCL) and antibodies to β_2-glycoprotein 1 ($a\beta_2$-GP1) [40]. In another study, 50 patients with COVID-19 were tested for lupus anticoagulant (LA) and other antiphospholipid antibodies, among which 25 subjects were LA-positive, and only three had aCL and $a\beta_2$-GP1 [41]. Most likely, COVID-19 coagulopathy should be assessed and treated as an immune-mediated rather than classical antiphospholipid syndrome (APS). Finding positive antiphospholipid antibodies in some patients infected with COVID-19 is not sufficient to suggest that these antibodies are directly involved in thrombosis associated with COVID-19. However, life-threatening microthrombosis and DIC in COVID-19 share clinical and laboratory features with catastrophic APS [42].

Indications to use anticoagulant therapy / Особенности применения антикоагулянтной терапии

Low molecular weight heparin (LMWH), in addition to the direct anticoagulant effect, also has anti-inflammatory properties, reducing IL-6 biological activity and serum levels. A retrospective study involved 449 patients with severe COVID-19, of whom 99 subjects received heparin (mainly LMWH). The results show that the heparin-treated group had lower mortality rates among patients with increased coagulopathy and D-dimer levels [43]. Another retrospective study enrolled 42 patients with COVID-19 and analyzed the effectiveness of LMWH in retarding the inflammatory response: 21 patients treated with LMWH had significantly lower IL-6 levels, higher lymphocyte levels, and less severe coagulopathy compared with 21 patients who did not receive LMWH. However, no dif-

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ference in the length of hospital stay between the two groups was observed [44].

Heparin inhibits the binding of von Willebrand factor to platelet glycoprotein (vWF-GP1b), and the reason for this is that heparin overlaps the binding site in the A1 domain of vWF, thereby inhibiting platelet activation. In the late stages of COVID-19, a decrease in vWF levels suggests its depletion, which is associated with massive endothelial damage and endotheliopathy [45].

A factor that can limit the use of anticoagulant therapy in cancer patients with coronavirus infection is thrombocytopenia, which occurs in about half of cases. A meta-analysis of 9 studies showed that platelet counts were significantly lower in patients with more severe COVID-19 infection, and thrombocytopenia is a factor of the unfavorable prognosis [46]. One of the reasons for decreased platelet count may be due to elevated circulating biomarkers such as fibrinogen, D-dimer, P-selectin, and vWF, which can directly bind to platelet receptors, followed by platelet hyperactivation and aggregation. The number of platelets declines during such hyperactivation since the hyperactivated and aggregated platelets are part of the microthrombi. Considering the development of systemic inflammatory response syndrome characteristic of both cancer patients and patients with COVID-19, heparin-induced thrombocytopenia (HIT) is an additional risk factor for thrombocytopenia [46].

X. Liu et al. suggested that antibodies against heparin–PF4 (platelet factor 4) complex are induced in critically ill patients with COVID-19, leading to HIT (**Fig. 2**). During inflammation, activated platelets release PF4 in response to pathogen activity. PF4 promotes neutrophil recruitment and exocytosis resulting in released myeloperoxidase and lysozyme. After the invasion by the respiratory virus, PF4 can stimulate antigen-presenting cells (APCs) to induce lymphocyte proliferation and NK-cell (natural killer cells) cytotoxic activity. PF4 plays a critical role in virus elimination [47]. Since HIT is an immune disease, the risk of its development in systemic inflammatory response syndrome increases significantly. In a retrospective cohort analysis of 652 hospitalized COVID-19 patients at Beth Israel Deaconess Medical Center, 88 patients with severe thrombocytopenia were recruited and received unfractionated heparin (UFH) at least for 5 days. Eight patients were suspected of HIT, and in 5 patients the enzyme immunoassay test was positive for HIT. All 5 patients were treated with direct thrombin inhibitors after an anti-HIT antibody test (four with argatroban, one with bivalirudin). Whereas three patients developed severe hemorrhagic complications with fatal outcomes, one patient suffered from acute cerebrovascular infarction and extensive areas of splenic infarction [48]. High levels of antibodies against heparin–PF4 complex were observed in the majority of patients with thrombocytopenia.

R.R. Riker et al. reported cases of thrombocytopenia with detected antibodies against PF4 in 16 intubated COVID-19 patients together with acute respiratory distress syndrome [49]. All three patients had signs of thrombosis (pulmonary embolism, venous thrombosis of the upper extremities, and skin necrosis). One case was confirmed as a HIT serotonin release assay.

In addition, anticoagulants are used for potential coagulation dysfunction in COVID-19, and other medical procedures also require the heparin use. For critically ill COVID-19 patients, extracorporeal membrane oxygenation (ECMO) is used to replace lung and heart function, and unfractionated heparin is often administered during the procedure to prevent coagulation. It also poses severely or critically ill patients at high risk for HIT. In a study of patients with severe heart failure, 29 patients (50 %) of 57 adult patients who underwent ECMO for at least 5 days were positive for PF4-specific antibodies. HIT was suspected in two patients due to ECMO circuit dysfunction (recurrent clots or fibrin deposition with dramatic decrease in plasma fibrinogen levels) and an unexpected decrease in platelet count after day 5. These two patients also had high levels of PF4-specific IgG. Ultimately, HIT was confirmed in both individuals using a serotonin release assay [50].

Thus, a severe COVID-19 cases if coupled to platelet count decline by more than 50 % from the baseline having signs of arteriovenous thrombosis after heparin administration should be screened for HIT. Patients with COVID-19 using ECMO support are advised to be monitored for HIT. If the ECMO circuitry is abnormal and platelets gradually decrease along with high level of PF4-specific IgG antibodies, then it should be considered that HIT might be suspected to develop [51].

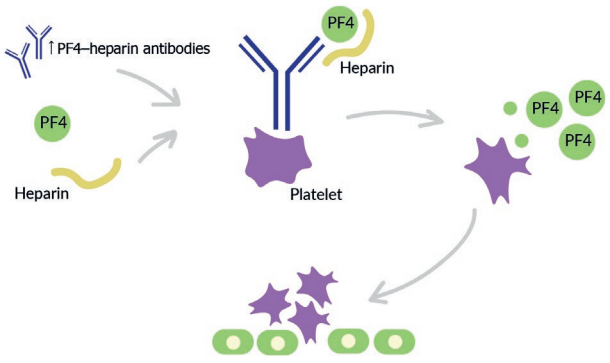

Figure 2. The mechanism of heparin-induced thrombocytopenia development [drawn by authors].

Note: *PF4 – platelet factor 4.*

Рисунок 2. Механизм развития гепарин-индуцированной тромбоцитопении [рисунок авторов].

Примечание: *PF4 – фактор 4 тромбоцитов.*

In COVID-19 patients, serum HIT antibody concentrations correlate significantly with C3a levels, which are elevated in cancer patients. Since complement activation can trigger the release of heparin from mast cells, spontaneous HIT in COVID-19 may be associated with complement activation as it was reported for IgM [52].

Conclusion / Заключение

The data obtained confirm the vulnerability of cancer patients during the COVID-19 pandemic. Thus, it can be concluded that cancer patients have a more severe course of COVID-19, which is associated with the need for inpatient treatment and they have a high risk of developing severe complications. Also, patients with COVID-19 have a higher mortality rate if they suffer from oncology diseases compared to other comorbid conditions. It should be taken into account that COVID-19 is a lung disease combined with a vascular pathology, a dysfunction of the hemostasis system associated with the immune response against viral infection, so that its pathogenesis mimics oncological processes.

Based on these studies, the American Association for Cancer Research (AACR) notes a high likelihood of a more severe course of COVID-19 in cancer patients and recommends a delay in adjuvant chemotherapy or elective surgery if cancer course is stable.

Because patients with COVID-19 often experience coagulation abnormalities, clinical use of heparin to prevent it can lead to HIT, so the symptoms and clinical signs of HIT should be monitored, especially in cancer patients prone to developing this condition.

The higher risk of severe COVID-19 in patients with cancer prompts the development of unique approaches for the treatment of new coronavirus infection in such patients.

ARTICLE INFORMATION	ИНФОРМАЦИЯ О СТАТЬЕ
Received: 26.08.2021. **Revision received:** 03.12.2021.	**Поступила:** 26.08.2021. **В доработанном виде:** 03.12.2021.
Accepted: 06.12.2021. **Published:** 30.12.2021.	**Принята к печати:** 06.12.2021. **Опубликована** 30.12.2021.
Author's contribution	**Вклад авторов**
Makatsariya A.D., Elalamy I., Brenner B., Ashrafyan L.A., Shkoda A.S., Galkin V.N., Gris J.-C. – expert data assessment, text editing; Bitsadze V.O., Khizroeva J.Kh., Solopova A.G. – review of publications; Vorobev A.V. – text writing and editing; Maslenkova E.V. – creating pictures, text editing.	Макацария А.Д., Элалами И., Бреннер Б., Ашрафян Л.А., Шкода А.С., Галкин В.Н., Гри Ж.-К. – экспертная оценка данных, редактирование текста рукописи; Бицадзе В.О., Хизроева Д.Х., Солопова А.Г. – обзор публикаций по теме статьи; Воробьев А.В. – написание и редактирование текста рукописи; Маслёнкова Е.В. – создание рисунков, редактирование текста рукописи.
All authors have read and approved the final version of the manuscript.	Все авторы прочитали и утвердили окончательный вариант рукописи.
Conflict of interests	**Конфликт интересов**
The authors declare no conflict of interests.	Авторы заявляют об отсутствии конфликта интересов.
Funding	**Финансирование**
The review was funded by RFBR, project number 20-04-60274.	Обзор выполнен при финансовой поддержке РФФИ в рамках научного проекта РФФИ №20-04-60274.
Provenance and peer review	**Происхождение статьи и рецензирование**
Not commissioned; externally peer reviewed.	Журнал не заказывал статью; внешнее рецензирование.

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2021 • Vol. 15 • № 6
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