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CORONAVIRUS SARS-COV-2 MODIFIES ANTITUMOR REDOX STATUS OF BLOOD AND INTERCELLULAR MATRIX IN METASTATIC COLORECTAL CANCER PATIENTS (A PILOT STUDY)

Background. The current studies demonstrate that SARS-CoV-2 infection results in increasing complications incidence and the total risk of death in cancer patients. SARS-CoV-2 infection triggers oxidative stress representing one of the major factors of the inflammation contributing to the complicated course of the diseases including cancer. **Aim.** To assess the effect of hypoxia caused by SARS-CoV-2 infection on the redox status of blood in patients with metastatic colorectal cancer (mCRC). **Materials and Methods.** 10 patients with SARS-CoV-2, 11 mCRC patients with metachronous liver disease, and 14 mCRC patients with preceding SARS-CoV-2 infection were included in the study. The data on blood biochemistry (C-reactive protein, ferritin, transferrin, and free iron) were analyzed. The levels of superoxide radicals (ROS) in blood cells were determined by electron paramagnetic resonance (EPR) using the spin trap technique. The metalloproteinase activity was measured by polyacrylamide gel zymography with the addition of gelatin as a substrate. **Results.** In mCRC patients with prior SARS-CoV-2 infection, a 1.26-fold increase in ROS-generating activity of blood neutrophils was observed compared to mCRC patients with no history of SARS-CoV-2 infection. The blood content of C-reactive protein, transferrin, and free iron in mCRC patients with prior SARS-CoV-2 infection increased by 2, 6, and 1.4 times, respectively. The total activity of gelatinases in platelets and neutrophils in the blood of mCRC patients with prior SARS-CoV-2 infection was 1.4 and 1.2 times higher

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compared to mCRC patients with no history of SARS-CoV-2 infection. **Conclusion.** mCRC patients with prior COVID-19 have a higher risk of exacerbation of inflammatory reactions. SARS-CoV-2 infection results in redox disbalance, which may contribute to the unfavorable course of the disease.

Keywords: SARS-CoV-2, redox state, metastatic colorectal cancer.

Coronavirus-caused pneumonia (SARS-CoV-2) is an extraordinary situation for healthcare due to its contagiousness and mortality. SARS-CoV-2 infection commonly starts as a respiratory disease and can escalate to pneumonia, severe acute respiratory syndrome, and multiple organ failure [1]. The risk of COVID-19 severe cases increases further with age. The studies show that SARS-CoV-2 increases the complications and overall risk of death in cancer patients. Compared with the general population, cancer patients have a 3-fold increased vulnerability to lethal outcomes due to SARS-CoV-2, as their immune system may be weakened by the disease itself and its treatment [2].

The extracellular matrix supports the tissue structure and modulation of cellular functions, including differentiation, migration, proliferation, metastasis, and survival. The redox state of tissues is largely determined by the redox state of blood and the composition and functional activity of blood cells. SARS-CoV-2-induced pneumonia with respiratory failure is characterized by increased fibrosis and remodeling of the extracellular matrix. In tumors of epithelial origin (lungs, colon, breast, pancreas, etc.), the loss of stability of the extracellular matrix due to changes in its redox state initiates tumor progression.

The aim of the pilot study was to evaluate the effect of coronavirus SARS-CoV-2-induced hypoxia on the redox blood status and metastasis in patients with metastatic colorectal cancer (mCRC).

Materials and Methods

The study included 10 patients with SARS-CoV-2, 11 mCRC patients with metachronous liver disease, and 14 mCRC patients who before treatment at the oncology clinic had received treatment for SARS-CoV-2. COVID patients without any oncological pathology were observed at the Kyiv Clinical Hospital No. 10. mCRC patients were treated at the National Cancer Institute, Kyiv, Ukraine. All patients agreed to allow the use of their clinical data in the depersonalized form for scientific purposes. The study was approved by the Ethics Committees of the R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the NAS of Ukraine and the National Cancer Institute, Kyiv, Ukraine.

The data on the levels of ferritin and C-reactive protein (CRP) in the blood of all groups of patients as well as the data of PCR test for SARS-CoV-2 were obtained from the laboratory studies performed in the Synevo medical company (Kyiv, Ukraine).

At the time of the study, SARS-CoV-2 patients were considered healthy according to the negative PCR test. The levels of transferrin, "free iron" (FI) in the blood were determined by EPR at a temperature of 77 K, for which samples were formed using a special mold, frozen in liquid nitrogen, and then electron paramagnetic resonance (EPR) spectra were recorded [3]. The levels of superoxide radicals (ROS) in neutrophils were determined by EPR using the spin trap technique and spin traps [4, 5]. The activity of matrix metalloproteinases MMP-2 and -9 was determined in neutrophil and platelet samples by polyacrylamide gel zymography (with the addition of gelatin as a substrate) based on SDS-electrophoresis of proteins [1]. After washing the gel, the active forms of MMP-2 and -9 were visualized as discolored stripes on a blue background, the location of which was determined by molecular weight standards (Sigma, USA) and corresponded to the molecular weight of

either of the enzymes (72 and 92 kDa, respectively). The proteolytic activity was evaluated by measuring the area of the lysis zone, using for comparison the standard kit of MMP-2 and MMP-9 (Sigma, USA) and expressed in the conditional units (CU) as the activity per 1 g of the original sample [6]. The results were assessed by TotalLab 1.01. software. Statistical analysis was performed using the application licensing program Origin 7.0. Student's *t*-test was used to evaluate the reliability of the differences between the studied groups. The experimental results are presented as M ± m. They were considered significant at $p < 0.05$.

Results and Discussion

SARS-CoV-2 infection causes multisystem inflammatory disorders. This disease is characterized by acute respiratory distress syndrome, cytokine-induced hyperinflammation, and modulation of the leucocytic formula and total leukocytosis. In this connection, the neutrophils were considered important effector cells in SARS-CoV-2 development. The pathophysiology of COVID-19 is characterized by changes not only in the blood count of neutrophils but also in their function. In SARS-CoV-2 infection, elevated neutrophil counts are observed in the nasopharyngeal epithelium [7] and later in the distal lungs [8], and signs of neutrophil activation are an important feature of blood transcriptome in severe cases [9]. The data on neutrophil counts and ROS-generating activity in the groups of patients under study are given in Table 1.

We demonstrated a significant increase in blood neutrophil count in the mCRC patients with preceding SARS-CoV-2 infection compared to the healthy donors. Only an insignificant trend of such an increase was observed in the SARS-CoV-2 patients without oncological pathology and mCRC patients who were not affected by COVID-19. The rate of ROS generation in blood neutrophils in all studied groups exceeds manifold that in healthy donors (13.4-fold in SARS-CoV-2 patients without oncological pathology, 15.6-fold in mCRC patients, and 19.6-fold in mCRR patients with preceding SARS-CoV-2 infection). Moreover, in mCRC patients with preceding SARS-CoV-2 infection, ROS activity in blood neutrophils is significantly higher compared to mCRC patients without SARS-CoV-2 infection and SARS-CoV-2 patients without oncological pathology. Therefore, SARS-CoV-2 infection contributes to the increasing oxidative potential of neutrophils in mCRC patients and this may affect the redox state of the intercellular matrix of the tumor. Our data and the data presented in the study [8] indicate the key role of neutrophil-induced tissue damage in SARS-CoV-2 pathology. Several studies have reported that the neutrophil-to-lymphocyte ratio (NLR)

Table 1. **Neutrophil counts and ROS-generating activity**

Groups	Neutrophil count, 10^9 cells/l	ROS, nmol/10^6 cells•min
Donors	2.2 ± 0.9	0.5 ± 0.2
Patients: SARS-CoV-2	3.5 ± 1.4	6.7 ± 0.3*
mCRC	3.9 ± 1.6	7.8 ± 0.5*
mCRC + SARS-CoV-2	6.2 ± 2.3#	9.8 ± 0.6**

Notes: * $p < 0.01$ compared to donors; ** $p < 0.05$ compared to SARS-CoV-2, and mCRC; # $p < 0.05$ compared to donors.

Table 2. **Platelet counts and ROS-generating activity**

Groups	Neutrophil count, 10^9 cells/l	ROS, nmol/10^6 cells•min
Donors	4.05 ± 2.25	1.3 ± 0.3
Patients: SARS-CoV-2	4.15 ± 1.49	6.7 ± 0.2#
mCRC	3.65 ± 1.20	8.3 ± 0.5*,#
mCRC + SARS-CoV-2	6.20 ± 2.32	11.3 ± 0.6**,#

Notes: #$p < 0.01$ compared to donors; *$p < 0.01$ compared to SARS-CoV-2; **$p < 0.01$ compared to SARS-CoV-2 and mCRC.

is a clinical biomarker of inflammation in the early stages of SARS-CoV-2 infection, which is a predictive marker of the severity of the disease [8—11]. Thus, the presence of a pro-inflammatory microenvironment due to the increase in superoxide-generating activity of neutrophils may contribute to the reactivation (awakening) of tumor cells, increasing the risk of metastasis. However, raising awareness of the potential risks to cancer patients with SARS-CoV-2 may lead to improved treatment strategies to prevent metastasis.

Platelets are critical for both hemostasis and inflammation. To promote inflammation, platelets produce inflammatory cytokines, which activate the migration of neutrophils into tissues. Thrombocytopenia was found in 42% of patients with SARS-CoV-2 and varied depending on the severity of the disease [12]. The number and superoxide-generating activity of platelets was analyzed. The results of these studies are given in Table 2.

Platelet counts were the highest in mCRC patients with preceding SARS-CoV-2 infection although this trend was insignificant. Nevertheless, the differences in the rate of ROS generation in patients of all groups compared to healthy donors were significantly higher (5.2—8.7-fold). At the same time, in the mCRC + SARS-CoV-2 group, this activity was higher than in mCRC patients without preceding SARS-CoV-2 infection or SARS-CoV-2 patients without oncological pathology. One may suggest that SARS-CoV-2 infection contributes to the increasing rate of generation of superoxide radicals in platelets of mCRC patients.

Cancer patients may be more prone to SARS-CoV-2 infection and have severe disease consequences and high mortality associated with platelet hyperactivity, systemic inflammation, thrombotic complications, and coagulopathy [13, 14]. As known, platelets also promote the growth of tumor cells, their survival in the blood, and angiogenesis in distant metastatic loci [15]. The

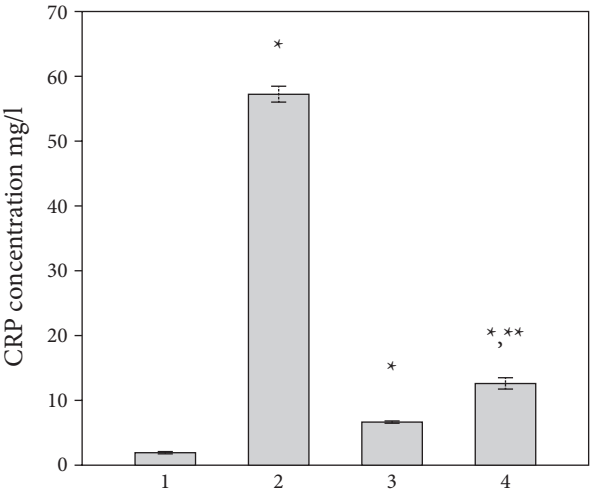

Fig. 1. CRP concentration: 1 — donors; 2 — patients with SARS-CoV-2; 3 — mCRC patients; 4 — mCRC patients who had prior SARS-CoV-2 infection: * $p < 0.05$ compared to donors; ** $p < 0.05$ compared to mCRC patients without prior SARS-CoV-2 infection

anomalous platelet reactivity may promote hypercoagulation during the SARS-CoV-2 infection itself, as well as aggravate such phenomena in cancer patients. Summarizing our observations and literature data, we may suggest that modified platelet physiology in SARS-CoV-2-infected cancer patients can promote tumor progression and dissemination.

C-reactive protein (CRP) is an important marker of endothelial dysfunction during inflammation caused by infection. We analyzed the CRP levels in the groups of patients under study (Fig. 1).

Literature data suggest that patients with metastatic malignancies are particularly susceptible to SARS-CoV-2 infection, so CRP may be a predictor for the severity of SARS-CoV-2 in mCR patients. Patients with SARS-CoV-2 and patients with CRC and prior SARS-CoV-2 had elevated CRP levels in their blood as compared to normal values in donors ($p = 0.01$ and $p = 0.014$, respectively). Our data and the results of other authors show that in patients with SARS-CoV-2, the ROS-generating activity of neutrophils and

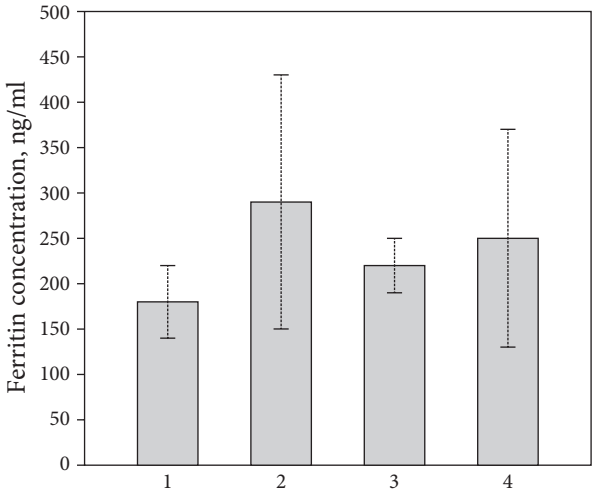

Fig. 2. The ferritin level: 1 — donors; 2 — patients with SARS-CoV-2; 3 — mCRC patients; 4 — mCRC patients who had prior SARS-CoV-2 infection

platelets, as well as CRP levels, were higher compared to the other groups. In patients with mCRC along with SARS-CoV-2, a significant increase in ROS-generating neutrophil activity and CRP level indicates a negative course of the disease and an adverse clinical outcome [16]. The CRP level may be particularly useful in predicting disease progression in patients with SARS-CoV-2-positive mCRC. CRP level > 10 mg/l significantly correlated with higher chances of death from SARS-CoV-2 in patients with leukemia, myeloma, and lymphoma [17]. Therefore, CRP should be considered a prognostic marker in cancer patients with SARS-CoV-2 during their treatment.

The pathogenesis of hyperferritinemia syndrome is extremely complex and variable. Genetic mutations, infections, and immunosuppression can lead to hyperferritinemia (> 500 ng/ml) and hyperinflammation [18, 19], so an elevated ferritin level is likely to be needed to support the inflammatory process. Recent studies have shown a direct role of the H-chain of ferritin in activating macrophages to increase the secretion of inflammatory cytokines [20]. An elevated serum ferritin level is associated with a poor prognosis, and an increase in it can be expected to worsen the outcome of patients with SARS-CoV-2. Nevertheless, in our study, we have not managed to demonstrate significant changes in the ferritin levels in all study groups possibly due to the large fluctuations of individual data (Fig. 2).

In humans, ferritin binds "free iron" (FI) and stores it in a biologically available form to carry out important cellular processes and thus protects proteins, lipids, and DNA from oxidative damage. Ferritin and its subunits are known to exert immunomodulatory effects. A sharp increase in the blood ferritin level as a part of the systemic response to inflammation (hyperferritinemia response) significantly affects the mortality rate in patients with SARS-CoV-2 [21]. The main modulator of ferritin level is an increase in FI level. Our data and the data of other authors [22] suggest that even though the total amount of circulating iron in the blood is much higher than the control value, the iron-binding capacity of ferritin in such patients is lower than in healthy people.

The increase in FI levels in COVID-19 can be one of the factors contributing to its pathogenesis. Indeed, the manifestations of COVID-19, such as inflammation, hypercoagulation, hyperferritinemia, and immune dysfunction, are accompanied by iron overload. FI, which results from dysregulation and iron overload, is highly reactive and potentially toxic due to its role in ROS formation. Moreover, iron-catalyzed lipid damage has a direct causal effect on the recently discovered non-apoptotic cell death known as ferroptosis.

We found an increase in the FI levels in the blood of patients of all studied groups relative to the control (Fig. 3). FI level in mCRC patients who had prior SARS-CoV-2 infection was significantly higher than in mCRC patients without such infection.

Lung damage in patients with COVID-19 occurs due to endothelial activation and destruc-

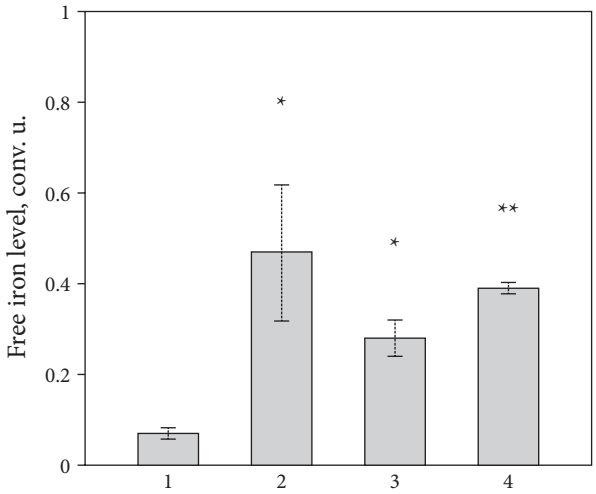

Fig. 3. The level of free iron (FI): 1 — donors; 2 — patients with SARS-CoV-2; 3 — mCRC patients; 4 — mCRC patients who had SARS-CoV-2 infection before: * $p < 0.05$ compared to donors; ** $p < 0.05$ compared to mCRC patients and donors

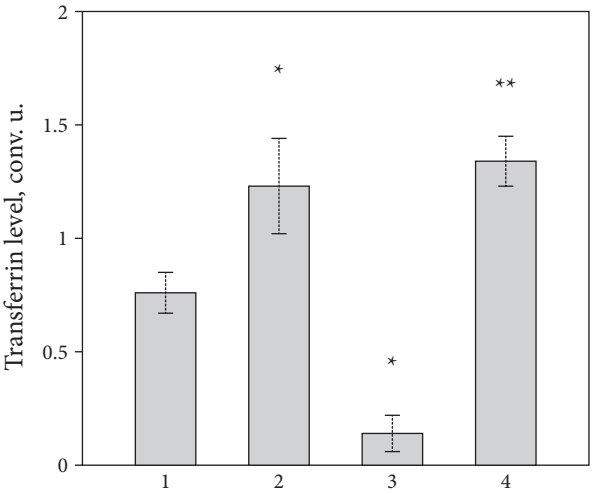

Fig. 4. The level of transferrin: 1 — donors; 2 — patients with SARS-CoV-2; 3 — mCRC patients; 4 — mCRC patients who had SARS-CoV-2 infection before: *$p < 0.05$ compared to donors; ** $p < 0.05$ compared to patients with mCRC patients without prior SARS-CoV-2 infection

tion of capillary membranes by oxygen radicals [23]. Elevated FI levels were found in the fluid secreted from the lungs of patients with COVID-19, and high levels of transferrin, ferritin, and lactoferrin were found in the cells, indicating impaired iron homeostasis in the lungs of patients [24]. The authors [25] found levels of FI in the blood, which contribute to the non-enzymatic formation of parafibrin. Parafibrin is an insoluble biomaterial, similar to fibrin, which can cause inflammatory reactions in the arteries, formed by the oxidation of fibrinogen by oxygen radicals. In addition, blood clotting is a major problem in the pathogenesis of COVID-19. In the context of iron cell overload, coagulopathy is a sign of iron toxicity. Oxidized iron accelerates blood coagulation by interacting with proteins of the coagulation cascade. Mitochondrial dysfunction, inflammation in the walls of blood vessels, platelet activation, and MMP-9 can be drivers of thrombosis [26, 27].

Transferrin is a glycosylated transport protein with a molecular weight of 79.6 kDa, which can bind two iron ions (Fe^{3+}) and transport them from the gastrointestinal tract to storage organs (liver) and organs that use iron ions. In our study, blood transferrin levels were elevated in patients with SARS-CoV-2 and patients with mCRC and prior SARS-CoV-2 (Fig. 4). In the mCRC patients, we found decreased transferrin levels compared to the donors and patients not infected with SARS-CoV-2.

The proteomic analysis of the infected cells demonstrated transferrin upregulation due to SARS-CoV-2. No interaction of transferrin with SARS-CoV-2 proteins was detected, indicating that upregulation is a response to infection [28]. Most importantly, transferrin not only functions as a protein that transports iron but also inhibits antithrombin and potentiates the effects of thrombin and coagulation factor FXIIa through iron-independent mechanisms. These phenomena can be considered a cause of hypercoagulation in SARS-CoV-2 patients [28, 29]. Transferrin procoagulant expression has been shown to be higher in men, increasing with age, and increasing in severe acute respiratory

SARS-CoV-2 syndrome. There is evidence that the expression level of the transferrin antagonist antithrombin does not increase with age and is similar in women and men. The authors believe that an increased transferrin/antithrombin ratio may be a marker of the development of coagulopathy associated with COVID-19 [28].

19% of surveyed donors and 11% of patients with mCRC did not show MMP-2 and/or MMP-9 activities in platelets, while in the other donors and patients, the total activity of gelatinases (MMP-2 and -9) in platelets (TGAP) varied from 33 to 316 CU. The mean TGAP for the mCRC group of patients with SARS-CoV-2 in anamnesis was 3.2-fold higher than in donors and almost 1.5-fold higher than in SARS-CoV-2 or mCRC patients. At the same time, the highest TGAP values characterizing patients with prior SARS-CoV-2 were associated with the highest values of platelet count and ROS platelet activity among the studied groups of patients (Table 3).

The total gelatinase activity (MMP-2 and -9) value in neutrophils (TGAN) in the examined donors and patients ranged from 63 CU up to 478 CU. The mean TGAN value for the mCRC group of patients with SARS-CoV-2 in anamnesis was 2.9-fold higher than in donors and 1.2-fold higher than in mCRC patients. In addition, the highest TGAN scores for mCRC patients who had SARS-CoV-2 before were associated with the highest neutrophil count and SR generation rate among the study groups (Table 4).

High levels of TGAP and TGAN in the blood of patient groups compared to donors, especially mCRC patients with SARS-CoV-2 in anamnesis, are a consequence and evidence of activation of the redox factors, profound hypoxia, and global inflammation not only in the blood but also in the body of patients. The data obtained show that this condition is characteristic of both patients with mCRC alone and mCRC patients with prior SARS-CoV-2 but the latter have significantly worse redox values compared to mCRC patients free of SARS-CoV-2. It is known that platelet gelatinases, due to their proteolytic effect on a number of receptors, in addition to their participation in thrombosis, also play an important role in the formation of so-called platelet clusters with disseminated tumor cells, thereby helping them avoid the immune response, increasing their survival in the vascular bed and the efficiency of the metastasis process [6, 30, 31]. High levels of MMP activity in both platelets and neutrophils, through proteolytic modification of cellular receptors, enhance the release and/or activation of a number of proinflammatory and parafibrin factors, cytokines and chemokines, which also promote tumor progression [32]. Thus, SARS-CoV-2 infection may pose a certain risk to mCRC patients [33], which should be further studied.

To sum up, cancer patients who previously had COVID-19 have a higher risk of exacerbation of inflammatory reactions, and oxidative stress can be one of the major factors contribu-

Table 3. **Indices of gelatinase (MMP-2 and -9) activity in platelets of donors and patients**

Patients	MMP-2 and -9 activity (total), CU
Donors	66 ± 21
SARS-CoV-2	134 ± 17$^{\#}$
mCRC	147 ± 22$^{\#}$
mCRC+SARS-CoV-2	212 ± 28$^{\#,\star}$

Notes: #$p < 0.05$ compared to donors; *$p < 0.05$ compared to patients with SARS-CoV-2 or mCRC patients.

Table 4. **Indices of gelatinases (MMP-2 and -9) activity in neutrophils of donors and patients**

Patients	MMP-2 and -9 activity (total), CU
Donors	112 ± 25
SARS-CoV-2	297 ± 26$^{\#}$
mCRC	268 ± 33$^{\#}$
mCRC+SARS-CoV-2	327 ± 24$^{\#,\star}$

Notes: #$p < 0.05$ compared to donors; *$p < 0.05$ compared to mCRC patients.

ting to the complications of the disease. Analysis of the presented results suggests that ROS-generating activity of neutrophils and platelets, levels of ROS, FI, ferritin, transferrin, and MMP-2, -9 activities may be early biological markers of SARS-CoV-2-induced thromboembolic complications and remodeling of the extracellular matrix in healthy people, as well as the risk of adverse CRC course. Redox changes in the blood of COVID-19 patients enhance the metastatic potential of tumors and may be considered a new target for therapy.

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КОРОНАВІРУС SARS-COV-2 МОДИФІКУЄ ПРОТИПУХЛИННИЙ ОКИСНО-ВІДНОВЛЮВАЛЬНИЙ СТАТУС В КРОВІ ТА МІЖКЛІТИННОМУ МАТРИКСІ У ХВОРИХ НА МЕТАСТАТИЧНИЙ КОЛОРЕКТАЛЬНИЙ РАК (ПІЛОТНЕ ДОСЛІДЖЕННЯ)

Стан питання. Сучасні дослідження показують, що SARS-CoV-2 збільшує ускладнення та загальний ризик смерті хворих на рак. Окисно-відновний стан тканин значною мірою відображується на окисно-відновному стані крові щодо її кількісного складу і функціональної активності клітин. Окислювальний стрес є одним із основних явищ запальної реакції та основним фактором, що сприяє ускладненню захворювання, тож посилення редокс-дисбалансу в організмі хворого на рак може сприяти прогресуванню пухлини. **Мета.** Оцінити вплив гіпоксії, викликаної коронавірусом SARS-CoV-2, на окисно-відновний статус крові у пацієнтів з метастатичним колоректальним раком (мКРР). **Матеріали та методи.** Використано методи ЕПР при температурі 77 K із астосуванням Spin Trap технології та зимографії на поліакриламідному гелі на основі SDS-електрофорезу білків. **Результати.** Визначено, що у хворих на мКРР, які перенесли SARS-CoV-2, супероксид утворююча активність нейтрофілів крові у 1,26 рази, рівні С-реактивного білка — майже у 2 рази, трансферину — майже у 6 разів, вільного заліза в крові — у 1,4 рази, сумарна активність желатиназ тромбоцитів у 1,4 рази, нейтрофілів — у 1,2 рази достовірно вищі, а рівні ферритину дещо вищі, але недостовірно, порівняно з пацієнтами з мКРР, які не хворіли на SARS-CoV-2. **Висновок.** Досліджені показники є перспективними маркерами несприятливого перебігу мКРР. Фактори окислювально-відновних змін у крові пацієнтів з мКРР, які перехворіли на SARS-CoV-2, можуть посилювати метастатичний потенціал пухлин і стати новими мішенями для терапії.

Ключові слова: SARS-Cov-2, окісно-відновний стан, метастатичний колоректальний рак.