

## REVIEW

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# SARS-CoV2 Infection and Comorbidities, Role in Oncogenesis

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### Abstract

The widespread infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) significantly impacts major human diseases. It is undoubtedly evident that cancer patients are more susceptible to the infection and at a higher risk of severe COVID-19 than the general population. Moreover, the rise in cancers incidence is waiting in the Globe as a long-term effect of post-COVID-19 complications. Multiple mostly unknown mechanisms participate and determine the oncogenic impact of virus-induced transformation. Imbalance in oncogenesis is considered critical in cancer development. Modified immunogenicity and metabolic features emerge as pivotal in COVID-19 pathogenesis and the organism system's response. The molecular mechanisms of the onset of the metabolic disorder have not yet been fully elucidated. The pathology is complicated, multifactorial, and emerging in various processes. Preventive anticancer therapy taking into account the change in metabolic processes, helps them respond better to anti-COVID-19 treatment than relying only on antiviral drugs. The modified therapeutic algorithm was provided to reduce the likelihood of post-acute complications in patients with preexisting pathologies and the onset of other chronic pathologies and cancers.

**Keywords:** COVID-19- virus-induced disorders- SARS-CoV2- cancers

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### Introduction

Coronavirus disease 2019 (COVID-19) has an essential burden on the social health and economic situation. Comorbidities determine both the complications development and patient survival. The hemostasis disorders and distress syndrome initiation become the most known origins of the unfavorable prognosis (Kamyshnyi et al., 2020). Preexisting pulmonary, cardiovascular, and metabolic diseases are the main ones (Reynolds et al., 2020). The percent of incidence varies from 32 to 46-50 % (Shi et al., 2020). An unfavorable outcome in patients has a level of 67%. Despite the intensive efforts in SARS-CoV2 (severe acute respiratory syndrome) research, there is no predictive marker associated with the prognosis of COVID-19 (Aras et al., 2020). Patients with organ transplants and people with Down syndrome (trisomy 21) have the highest risk for hospitalization after SARS-CoV2 infection (Koppe et al., 2021).

The global SARS-CoV2 spreading since 2019 has grown into a pandemic, which impacts the world health system is enormous. The high mortality rate associated with the deterioration of the underlying disease against the infection background is well known. In turn, existing chronic diseases can change their course, worsening the

condition of patients.

In addition, a global inflammatory response occurs involving multiorgan lesions. In particular, cardiovascular system disorders have long been the hallmarks of an unfavorable disease course. Moreover, it is essential to consider the new insights for supporting therapy COVID-19 in patients with comorbidities (Kang et al., 2020).

Up-to-date, several mechanisms have been postulated for COVID-19-associated cardiovascular damage, including SARS-CoV-2 receptor angiotensin-converting enzyme 2 (ACE2) activation, cytokine storm, hypoxemia, stress, and cardiotoxicity of antiviral drugs (Wu et al., 2020).

The first host receptor identified for the virus invasion was angiotensin-converting enzyme two receptors (ACE2). In addition, ACE2 is a significant component of the renin-angiotensin system. ACE2 deteriorates angiotensin II, a peptide that is responsible for the promotion of stroke. The downregulation of ACE2 further activates an immunological cascade. Human ACE2 expression level and pattern in various tissues might be decisive for the vulnerability, symptoms, and treatment outcomes of the SARS-CoV-2 infection. The COVID-19 pandemic has affected people with various preexisting

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diseases, including ischemic stroke (Kaushik et al., 2020). Moreover, recent data established the oncogenic effect of the SARS-CoV2 virus impacted the rise in tumors incidence.

#### *Preexisting Pathology and COVID-19*

It is believed that the course of diseases of the bronchopulmonary system, in particular interstitial pneumonia, significantly worsens in the presence of concomitant pathology: hypertension, obesity, cardiovascular diseases, or diabetes mellitus (Kamyshnyi et al., 2020). According to Kamyshnyi (2020), most patients suffer from one or more concurrent infections. Poor survival occurs among older people with a high SOFA (Sequential Organ Failure Assessment), combined with a high level of D-dimer (more than 1 µg / ml), which is used to assess organ failure, the risk of mortality, and sepsis in patients in the intensive care unit and intensive care unit (Zhou et al., 2020).

Diabetes and prognosis of COVID-19. The management of chronic endocrine disorders during the pandemic proved particularly challenging, as they require close physician-patient contact for proper long-term management. In addition, acute endocrinologic conditions presented during the COVID-19 period required timely management in an unusual clinical setting, which provided clinicians with ongoing challenges (Martino et al., 2021). Metabolic disorders are found to have the most pronounced effect on SARS-CoV2 patients. Virus-related complications are often associated with hyperglycemia and obesity, resulting in increased fibrosis risk in lungs and vascular disorders. DM was associated with mortality, severe COVID-19, ARDS, and disease progression in patients with COVID-19 (Huang et al., 2020). In patients with diabetes mellitus (DM) and obesity, baseline increases the risk of molecular and biological peculiarities involved in pathological processes in cells and tissues. Unfavorable outcomes follow intensive inflammation in infected patients and severe post-diseases complications (Nouri et al., 2021). In common, DM in SARS-CoV2 patients is considered the factor of intense COVID-19 course due to preexisting and revealed cardio-metabolic and immunological disorders (Magdy et al., 2021).

High glucose level is the basal laboratory test widely used for indicating the risk of poor outcomes (Ortega et al. 2021). Impaired Fasting Glucose and diabetes at admission were associated with higher risks of adverse effects among patients with COVID-19 (Zhang et al., 2020).

Well-controlled blood glucose (BG) level was associated with markedly lower mortality than individuals with poorly controlled glucose levels. These findings have found clinical evidence correlating improved glycemic control with better outcomes in patients with COVID-19 and preexisting type 2 diabetes mellitus (Zhu et al., 2020; Gianchandani et al., 2020). Patients with severe COVID-19 should be monitored closely to develop lactic acidosis, acidosis, and decreased kidney function (Yang et al., 2021). Hyperglycemia and obesity in SARS-CoV2 patients impact the course and outcome of the infection, requiring further intensive study at the molecular level-effective therapy based on the COVID-19 follow-up.

Obesity and prognosis of COVID-19. Obesity is a risk factor for COVID-19, but the underlying mechanisms are unclear. The rise in Adiponectin/Leptin, due to increased adiponectin and reduced leptin, is a compensatory response to systemic inflammation. This mechanism might be blunted in patients with worse cardiometabolic health (diabetes, hypertension), possibly contributing to higher mortality (Filippo et al., 2021).

The impact of SARS-CoV-2 diseases on metabolic outcomes in these patients is more significant than it could be predicted before. Infectious diseases can result in a catabolic state, prolonged inflammation, and possibly trigger an acute metabolic decompensation in inborn and acquired errors of metabolism. Studies regarding the course of SARS-CoV-2 infections in patients with impaired metabolism are generally limited to case reports. However, patients with metabolism disorders should be considered a virus-sensitive population for COVID-19 and have a significant risk of developing post-COVID-19 lesions (Zubarioglu et al., 2021).

#### *COVID-19 and Post-Diseases Complications*

Follow-up patients, including those with post-acute COVID-19 syndrome, display a spectrum of multiple persistent biochemical pathophysiologicals. The metabolic phenotyping approach may be applied for multisystem functional assessment of individual post-acute COVID-19 patients (Holmes et al., 2021).

COVID-19 affects the respiratory system and causes multi-organic damage. Hepatitis is among the main extrapulmonary COVID-19 complication. Liver injury is defined as any liver damage occurring during the treatment of COVID-19 in patients with or without preexisting liver disease. It appears in approximately one in five patients. Mechanisms linking COVID-19 to liver damage are multiple. The patients with preexisting liver disease, such as metabolic dysfunction with fatty liver disease, chronic liver disease due to viral or autoimmune disease, liver transplant carriers, or cirrhosis, have a higher risk of adverse outcomes (Gracia-Ramos et al., 2021)

The neurological manifestations of COVID-19 are found following a pathophysiology-based approach using standardized pre-defined case definitions to yield more specific and comparable data (Leven et al., 2021).

Myocardial damage is accompanied by ischemia symptoms, myocarditis, and myocardial infarction. The mechanism of cardiotoxicity is linked to the virus's direct action on angiotensin-converting enzyme 2 (ACE2) and hypoxia initiation, a systemic inflammatory reaction with a cytokine storm. Besides, the drugs used in the COVID-19 treatment may have side effects. It was revealed that the risk of cardiovascular diseases developing increases after a previous infection, which is possible, both against the background of a preexisting clinical pathology that does not manifest itself and with a heart muscle lesion that develops during infection (Shaw et al., 2019).

Coagulation system disorders are the leading pathogenetic syndrome associated with complications. COVID-19 is often accompanied by microthrombi formation, even if patients received anticoagulation therapy (Menter et al., 2021) and thrombosis, contributing

to an unfavorable outcome (Janssen et al., 2020). It is believed the molecular mechanisms associated with the development of acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation play an essential role in shaping the outcomes of COVID-19, including determining the spectrum of long-term consequences (Ponti et al., 2021).

Myocardial inflammation and myocarditis, as well as cardiac arrhythmias, have been described following SARS-CoV-2 infection. In patients with severe acute COVID-19 and thromboembolic disease, myocardial damage has been described, determined by a troponin increased level. The increase in heart failure as a significant consequence of COVID-19 is of concern, which could have implications for the elderly population with multiple comorbidities and younger, previously healthy patients, including athletes (del Rio et al., 2020).

Many studies have reported an association between acute pancreatitis (AP) and COVID-19. We showed that pancreatic injury could occur in some COVID-19 patients (Liu et al., 2020). Direct pancreatic damage in SARS-CoV2 infected patients is a crucial disease-related complication. The angiotensin-converting-enzyme two receptor proteins found in the pancreas are the entrance for virus and cause of metabolic disorders induction. Moreover, AP may be a secondary indicator of cytokine storms and altered inflammatory responses (Jabłońska et al., 2021).

The long-term health effects of COVID-19 remain largely unclear. Sporadic reports examine patients' health effects with COVID-19 discharged from the hospital and associated risk factors, particularly the severity of the disease. Huang et al., (2021) established that patients had neurological symptoms six months after recovery. Today, the most common symptom is a violation of the nervous system: headache, dizziness, and chemosensors dysfunction. However, stroke is severe and a rare consequence of acute COVID-19. Encephalitis, seizures, and other conditions such as sudden mood swings and "blurred consciousness" have been reported within 2-3 months after the disease's onset: anxiety, fatigue, post-traumatic stress disorder, and more rare neuropsychiatric syndromes (Rogers et al. 2020). In common, short-term and long-term effects of SARS-CoV2 infection determine the severity of metabolic disorders.

#### *SARS-COV2 and Cancers, Interplay*

Cancers are regarded as one of the leading causes of death and result in a high health burden worldwide. The origin of cancer at the molecular and cellular levels is not well understood. The primary cause of the origin of cancer is genomic instability or impaired metabolism (Poljsak et al., 2019). Early reports of SARS-CoV2 complications and comorbidities, including cardiovascular, pulmonary, and neurological conditions, have raised concerns about the long-term effects of COVID-19 (Derosa et al., 2020).

It is becoming increasingly evident that cancer patients are more susceptible to the infection and are at a higher risk of severe COVID-19 than the general population (Wang et al., 2020). The immunosuppressed status of

some cancer patients increases their risk of infection compared with the general population (Al-Quteimat et al., 2020). The susceptibility of patients with cancer to SARS-CoV-2 infection is reflected in the morbidity and mortality, and it differs depending on the cancer type, staging, and therapeutics. Different common types of cancer have other effects on COVID-19 severity (Zong et al., 2021).

Currently, carcinogenesis in SARS-CoV2 post-disease long-term effect is considered the future perspective. Nevertheless, whether long COVID-19 increases cancer risk in those with no prior malignancies remains unclear (Saini et al., 2021). The significant steps are the direct oncogenic action and indirect impact on the metabolism and immune system. Firstly, the increased predicted risk of malignancies is also associated with fibrosis due to the flu, indicating a Ground Glass Opacity (GGO). GGOs have been observed in COVID-19 patients with severe symptoms, including pneumonia in both lungs. It is essential to reflect that GGO may indicate high-risk subjects for developing lung cancer (Sadhukhan et al., 2020).

There isolated single facts that SARS-CoV-2 may induce cancers due to carcinogenic effects of this coronavirus. Newly found data indicate that SARS-CoV-2 may directly impair pRb and p53, critical gatekeepers with tumor suppressor functions (Stingi et al., 2021). We observed an immunological profile of severe COVID-19 patients characterized by upregulated cytokines, interferon-induced proteins, and pronounced T cell lymphopenia, supporting findings by previous studies. We identified several host immune targets, including PERK, PKR, TNF, NF- $\kappa$ B, and other essential genes that modulate the significant pathways and genes identified in COVID-19 patients. Finally, it is identified genes modulated by COVID-19 infection implicated in oncogenesis. They include E2F transcription factors and RB1, suggesting a mechanism by which SARS-CoV-2 infection may contribute to oncogenesis (Policard et al., 2021).

Additionally, COVID-19 features a preeminent inflammatory response with significant oxidative stress, acting as an initiator and promoter of carcinogenesis. Another mechanism that may lead to carcinogenesis is oxidative stress (Alpalhão et al., 2020). There were molecular similarities between cancer and COVID-19 and summarized the four major signaling pathways at the intersection of COVID-19 and cancer: cytokine, type I interferon (IFN-I), androgen receptor (AR), and immune checkpoint signaling. In addition, we discuss the advantages and disadvantages of repurposing anticancer treatment for the treatment of COVID-19 (Zong et al., 2021). The MMR deficiency is found to be a factor of prolonged persistence of the virus in the host cells (Haque et al., 2021)

Many scientists identified a dangerous interaction of SARS-CoV-2 infection with the host's metabolic health (Lonardo et al., 2020). The increased risk of cancer is known in cases of associated metabolic disorders. The long-term post COVID consequences are breast, prostate cancers, and other hormone-dependent tumors.



Growing data become evident and show the association of metabolic syndrome (MetS) or its components with cancer development and cancer-related mortality (Pothiwala et al., 2009).

Although every component of MetS is known to be associated with cancer development, it is still debated whether the effects of these components are additive or synergistic (Cantiello et al., 2014). On the other hand, in the association between MetS and cancer (Dong et al., 2021). The components of MetS include diabetes mellitus, obesity, and hypertension (Cantiello et al., 2014). The cancer-causing mechanisms in diabetes are complex, including excessive ROS-formation, destruction of essential biomolecules, chronic inflammation. Epithelial-to-mesenchymal transition (EMT) and endothelial-to-mesenchymal transition contribute to cancer-associated fibroblast formation in tumors, allowing the epithelium and endothelium to enable tumor cell extravasation (Srivastava et al., 2020).

The present understanding and management of post-COVID-19 long-term consequences focused on the metabolic corrections. The clinicians concluded that cellular metabolism is the foundation of all biological activities [Haque F, 2021]. During the commitment to cell proliferation, extensive metabolic rewiring must occur for cells to acquire sufficient nutrients such as glucose, amino acids, lipids, and nucleotides (Zhu et al., 2019).

A clear understanding of the origins of post-COVID cancer is the basis of successful strategies for effective cancer prevention and management. It is postulated that an insulin-sensitizing agent, metformin, has cancer-preventing effects on diabetic patients (Uzunlulu et al., 2016; Kowall et al., 2015). Antidiabetic drugs such as sulfonylureas, biguanides, and thiazolidinediones showed beneficial and repurposing actions in cancer management. Thus, the activities of these drugs against cancer are attributed to some of the metabolic links between the two disorders, including hyperglycemia, hyperinsulinemia, inflammation, oxidative stress, and obesity (Olatunde et al., 2021). Therefore, antidiabetic drugs, which are involved in insulin secretion and sensitivity, may benefit cancer treatment (Shafiei-Irannejad et al., 2017). Flavonoids improve GLUT-4 expression and translocation to the plasma membrane by activation of insulin-sensitive PI3K/Akt signaling and insulin-independent AMPK, SIRT-1, and MOR activation pathways for regulation of glucose homeostasis, and improve fat oxidation and reduce lipid synthesis by regulation of related genes for lipid homeostasis in the body of obese diabetic animals (Dinda et al., 2020; Dong et al., 2021).

#### *Molecular Mechanisms of Virus-Induced Disorders*

Moreover, metabolic disorders are considered the main predictors of the COVID-10 patients' outcomes. Hyperglycemia and dyslipidemia are the primary metabolic disorders accompanied by the SARS-CoV-2 infection. COVID-19 infection involves a paramount pathological pathway. Previously, the release of pro-inflammatory cytokines and a "cytokine storm" initiation were considered an important event in the

pathogenesis of SARS-CoV2 related complications (Qin et al., 2020). However, at present, there are several more significant pathogenetic mechanisms, including endothelial dysfunction. The hypercoagulability and pathological angiogenesis determine the severity of the clinical manifestations of infection. The pathogenesis of such phenomena is complex, multi-stage, involving various molecular and biological factors, modifying the clinical signs and laboratory indicators, and affecting the patients' course and outcome with COVID-19 (Norooznejhad et al., 2021).

The pathogenesis of such phenomena is complex, multi-stage, involving various molecular and biological factors, modifying the clinical signs and laboratory indicators, and affecting the patients' course and outcome with COVID-19 (Norooznejhad et al., 2021). Thus, the infection spreading results in altered microcirculation, hypercoagulation, followed by multiorgan damage. We showed that pancreatic injury could occur in some COVID-19 patients (Chen et al., 2020). The association between acute pancreatitis and COVID-19 is plausible as SARS-CoV-2 receptors are expressed in the pancreas, and endothelial damage can occur (de-Madaria et al., 2021). Additionally, a high proportion of critically unwell patients with COVID-19 have raised serum amylase levels; this does not necessarily reflect acute pancreatitis or a clinically crucial pancreatic injury (Stephens et al., 2021).

Yang et al., (2010) reported that patients infected with SARS-CoV suffered from hyperglycemia, which might be caused by SARS-CoV damaging the pancreatic islets through ACE2. As patients with Middle east infection, most people did not show signs of necrotizing pancreatitis; the consequences of the pancreatic injury can be potentially severe. The pathological conditions such as aggravating systemic inflammation accelerate acute respiratory distress syndrome (Zhou et al., 2010) and even develop into chronic pancreatitis, severely impacting patients' health and quality of life.

Pancreatitis is considered to be the most urgent COVID-19 complication. It impacts the patients' prognosis and manifests in virus-induced multiorgan damage. The failure in respiration and ARDS (acute respiratory distress syndrome) is an essential point in disease's spreading. The ARDS is a critical event that determines the course of the disease. It is believed that ACE2 has a protective effect, reducing the severity of inflammatory reactions and the development of multiorgan pathologies. These data may be necessary not only for disease verification. It is also promising in treatment algorithms modification and future vaccine design (Cheng et al., 2020).

Potential pathogenetic links between COVID-19 and diabetes are understandable. The multiple processes maintaining the DM pathogenesis become more intensive and aggravating. The decisive step in SARS-CoV2 infection with DM includes inflammation, glucose homeostasis effects, immunogenicity, and activation of the renin-angiotensin-aldosterone system (RAS) (Bilka et al., 2021).

The receptors for ACE2 present in the gastrointestinal

tract cell, particularly in the liver, cause pathological reactions in these organs. Liver damage also refers to the direct effects of the virus. An unbalanced immune response, sepsis, and, very often, side effects of the use of antiviral agents have a significant impact on the death of hepatocytes (Wu et al., 2020; Huang et al., 2021).

During the previous SARS epidemic, around 60% of patients developed various degrees of liver damage. In the current pandemic, hepatic dysfunction has been seen in 14-53% of patients with COVID-19, particularly those with severe disease. Cases of acute liver injury have been revealed and are associated with higher mortality (Wu et al., 2020).

Hepatitis is known as a wide-spreading complication in COVID-19 patients. The patient's outcome depends on the severity of liver damage in SARS-Cov2 infection. The molecular and biological features resulting in direct and indirect liver damage remain unknown. Recent studies have made some explorations and investigations. Liver damage due to the progression of preexisting liver disease is a crucial mechanism of infection. At the same time, direct damage to the liver by the virus, including cell death during active systemic inflammation and due to side effects of drugs, makes a significant contribution to the manifestation of complications, determining the severity of the disease (Huang et al., 2021). Consequently, liver damage is currently considered as evidence of multiple organ actions of the SARS-CoV2 virus.

Adipose cells are responsible for producing a series of substances that silently cause irreparable damage to our bodies. Adiponectin, IL-6, tumor necrosis factor-alpha (TNF-alpha), resistin, leptin, angiotensinogen, and plasminogen activator inhibitor-1 (PAI-1) are the most well-known. Adiponectin is reduced in obese patients, and its levels are inversely correlated with insulin resistance (Grund, 2016; Leisegang et al., 2019).

IL-6 and TNF-alpha are pro-inflammatory cytokines that contribute to insulin resistance and, mainly responsible for the complications found in patients with metabolic syndromes, such as diabetes, atherosclerosis, hypertension, and chronic kidney disease.

Therefore, in patients with metabolic syndrome, there is a constant and sustained inflammatory state that is probably exacerbated with SARS-CoV-2, worsening the clinical scenario of COVID-19. As we know, the greater severity of the SARS-CoV-2 is due to increased systemic inflammation, particularly pulmonary, which is demonstrated by a significant elevation of cytokines and intensive immune response initiation (Chocair et al., 2020).

The impaired metabolism and virus-related metabolic disorders in the COVID-19 pandemic require further research. The multiple mechanisms manifest in the organ damage, including acute inflammation, deterioration of extra-lungs organs, and short-term and long-term complications. There is a question about the origin of metabolic disorders. The direct viral action on ACE2 receptors independent tissues is a single way. The side effect of anti-COVID-19 therapy on metabolic diseases, chronic pathology, and even oncogenesis is noted.

In conclusion, COVID-19 has re-established the

significance of analyzing the organism through a metabolic perspective to uncover the dynamic interconnections within the biological systems. The role of metabolic health emerges as pivotal in COVID-19 pathogenesis and the immune system's response and oncogenesis.

Metabolic disruption, proceeding from modifiable factors, has been proposed as a significant risk factor accounting for infection susceptibility, disease severity, and risk for post-COVID complications. At present, there is a clear understanding of the metabolic disorders accompanying the infectious disease, as triggers of the disease and markers of the post-disease disorders, etc. Hyperglycemia and dyslipidemia influence the patient's outcome and the onset of the complications in SARS-CoV2.

It is unknown about the mechanisms behind such metabolic changes. It is believed that the inflammatory reaction against the background of existing pathologies, including diabetes mellitus, obesity, and cardiovascular diseases, can be aggravated.

At the same time, the mechanism of development of post-COVID disorders and metabolic features in previously healthy patients is the most complex and multifaceted. It is believed that microcirculation disorders can form conditions for necrosis and subsequent inflammation. It results in organ inflammation and a lack of functions. Impaired lipids metabolism may result from both direct infection and therapeutic side effects.

Recently, the oncogenic effect of SARS-CoV2 infection results in oncosuppressor disruptions and oncogenic signaling pathway activation. The impaired metabolism is a powerful mechanism underlying the susceptibility of cancer patients to the disease. Additionally, metabolic-induced cancers are considered to be the trigger of tumors initiation. Little is known about the interlink in the SARS-CoV2 effect on health, but the rise in chronic pathology worldwide is a perspective in Globe. Modification of the health management system, diagnostic algorithms is prominent nowadays.

## Author Contribution Statement

Liudmila V. Spirina, planning and supervising; Nadezhda V. Masunova, Vladimir N. Masunov, writing; Victoria V. Makova, editing; Yumzhana S. Dagbaeva, -analysis of data; Irina V. Kovaleva, writing;

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### Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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