Factors affecting the severity of COVID-19 and the development of complications

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ABSTRACT

Due to the prevalence and diversity of both symptoms and outcomes of COVID-19, understanding the factors that determine the risk of the severe course of this disease and its possible complications is of particular importance. In this review, we present the information on the specifics of COVID-19 pathogenesis and give a theoretical justification for the factors that determine the course of this disease in patients of different age groups, patients with chronic pathology, and pregnant women. Particular attention is paid to the post-COVID syndrome.

Keywords: COVID-19, SARS-CoV-2, disease severity, complications, post-COVID syndrome

INTRODUCTION

The coronavirus infectious disease (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has placed an unprecedented burden on various aspects of human activity worldwide since its outbreak in early 2020. First and foremost, the global healthcare system has faced significant challenges in COVID-19 diagnostics, the discovery of new drugs, and the repurposing of existing drugs to mitigate the disease, as well as in developing and testing specific vaccines and antivirals. The main factors that determine the risk of severe disease and potential complications have become clear over the past three years of the ups and downs of the COVID-19 pandemic. These factors include old age, pregnancy, and chronic diseases. The patient’s immune status is increasingly recognized as an essential risk predictor, since more and more data on the immunopathogenesis of COVID-19 are emerging.

Mechanisms of COVID-19 pathogenesis and SARS-CoV-2 as the causative agent

SARS-CoV-2 interacts with the host cell by binding to the angiotensin-converting enzyme 2 (ACE2), a receptor of the viral spike (S) protein. ACE2 expression varies in different tissues and depends on the host’s age, sex, and race. ACE2 is abundantly expressed in lung epithelial cells, heart, kidney, pancreas, spleen, gastrointestinal tract, bladder, eye, blood vessels, and adipose tissue cells. ACE2 is also found in the central and peripheral nervous systems and skeletal muscles [1-3]. Chronic lung
and heart diseases, diabetes mellitus, and tumors are associated with ACE2 overexpression, which increases the risk of COVID-19 disease and mortality [4]. The risk of septic shock in patients with three or more comorbidities is much higher than in those without comorbidities [5]. In addition, SARS-CoV-2 activates the inflammatory response mediated by both innate and adaptive immunity, which can result in cytokine storm and, ultimately, in multiorgan injury [2].

The likelihood of SARS-CoV-2 infection in humans also depends on the genetically determined ACE2 expression. Genetic predisposition to develop severe forms of COVID-19 may result from certain polymorphisms of genes that are involved in the regulation of vascular tone, cell growth, and proliferation [6]. After analyzing genomic studies on the association of renin-angiotensin system (RAS) components with cardiovascular, pulmonary, and other pathologies, Nikitina et al. [6] concluded that specific polymorphisms in the human genes encoding AGTR1, AGTR2, ACE2, and ACE proteins can lead to an imbalance in RAS. The response of pneumocytes, vascular endothelium and smooth muscle fibers during SARS-CoV-2 infection may be much more pronounced in carriers of unfavorable genetic variations due to a shift towards the vasoconstrictor, proliferative, and profibrotic processes.

Children are much less likely to get COVID-19 compared to adults, and they usually develop a milder form of the disease, often asymptomatic. This may be due to age-related characteristics of their immune system and RAS. RAS elements are widely represented in the lungs and actively participate in the inflammatory process. The RAS biochemical cascade is considered to be a key element in the pathogenesis of COVID-19. Nikitina et al. [6] described it from two points of view: ACE2 expression on the cell surface and genetic polymorphisms of the RAS system. First, the transmembrane protein ACE2 serves as a “gateway” for SARS-CoV-2. Second, ACE2 has a regulatory function, converting the proinflammatory vasoconstrictor angiotensin II into the anti-inflammatory angiotensin (1-7) that exhibits vasodilatory activity. Thus, the potential tissue-damaging effect of angiotensin II is determined by the amount of the ACE2 enzyme. Children have higher levels of ACE2 than adults, which seems to promote balance in the RAS system and protect cells and tissues from angiotensin II-induced damage. Consequently, complications associated with COVID-19 are rarely reported in children.

COVID-19 is characterized by complications that affect nearly all organs, regardless of the severity of the disease. The causes can be attributed to the specifics of COVID-19 pathogenesis mechanisms. The clinical presentation of COVID-19 varies greatly among individuals depending on both the direct impact of the virus and the host immune response. The latter may be accompanied by a cytokine storm, oxygen imbalance, hypercoagulation, inflammation of lung tissue, and hypoxic vasoconstriction; the choice of lung ventilation and potential negative outcomes of therapy can further influence the clinical picture [7, 8].

COVID-19 in the pediatric population

COVID-19 is less common in the pediatric population than in adults, with most cases being asymptomatic or presenting mild to moderate symptoms. Severe forms of the disease are more frequently observed in children and adolescents with pathologies, such as immunodeficiency state, cancer, obesity, diabetes, kidney disease, and other conditions [9].

A distinctive feature of COVID-19 with skin involvement in children is the multisystem inflammatory syndrome (MIS-C), or Kawasaki-like syndrome. The pathogenesis of MIS-C is driven by the uncontrolled production of proinflammatory cytokines, manifesting as a systemic inflammatory response along with multiorgan injury. According to Radia et al. [10], a key criterion in determining MIS-C, fever, was reported in all 783 (100%) pediatric patients participated in the study. Gastrointestinal symptoms were reported in 553/785 patients (71%), including abdominal pain (285/783, 36%), diarrhea (214/783, 27%), and vomiting (196/783, 25%). Skin symptoms were found in 330 (42%) children and included erythematous papular rash, foci of erythema, and dense edema of the hands and feet. Respiratory tract symptoms were infrequent: 35 children (4.5%) had cough and 32 had sore throat (4%) [11]. Although lethal outcomes of COVID-19 are rare in children, a severe course of the disease including cases of severe inflammation and nonrespiratory manifestations, is more frequent compared to influenza [4].

COVID-19 in adults

Age structure

Aging is accompanied by immunosenescence: efficiency of the immune system declines with age, which leads to dysregulation of immune function and often to the development of inflammation. In older adults, immune system dysregulation underlies the increased susceptibility to many infectious diseases including COVID-19, as well as the severity of their course [12]. Studies analyzing the causes of severe COVID-19 usually highlight conditions such as obesity, arterial hypertension, and other cardiovascular diseases, particularly among patients aged 60 years and older. Other negative factors include type II
Complicated course of COVID-19

- diabetes mellitus (DM), type I DM, chronic kidney disease, chronic obstructive pulmonary disease (COPD), cancer, and anemia. The impact of these diseases, except for type I DM, is also most pronounced in patients aged 60 years and older [13]. Older patients are more vulnerable to neuropsychiatric and cognitive impairment in COVID-19, and pre-existing disorders of this spectrum including dementia tend to progress after coronavirus infection [14].

**Gender structure**

During the COVID-19 pandemic, most countries recorded higher mortality rates in men than in women [15]. Men, including boys, exhibit a higher frequency and greater severity of COVID-19 infection compared to women. This may be due to the activating effect of androgens on coronavirus replication [4]. Testosterone participates in the regulation of the synthesis of ACE2 and transmembrane serine protease 2 (TMPRSS2) that facilitates the entry of SARS-CoV-2 into target cells. On the other hand, low testosterone levels increase the risk of cardiopulmonary complications. Hypogonadism has been identified as an important factor leading to complications caused by COVID-19 in men [16].

**Pregnancy and childbirth**

Pregnancy is a special state of a woman’s body during which physiological changes occur: heart rate and oxygen consumption increase, lung capacity decreases, and the risk of thromboembolic complications grows. These changes affect maternal morbidity and the functioning and integrity of the placenta, posing inevitable additional risks to the fetus and newborn. Pregnancy itself is a state of natural immunosuppression with reduced activity of cell-mediated immunity. The combination of these biological factors in pregnant women can contribute to the adverse outcome of respiratory diseases such as influenza. However, the absolute risk of severe COVID-19 has been found to be low in pregnant women [17].

Most pregnant women experience COVID-19 in a mild form, but the disease affects the course of pregnancy and delivery. Pregnant women with COVID-19 demonstrate increased rates of pre-eclampsia and preterm birth [18], and the prevalence of cesarean delivery reaches 67.2–94.0% among women who have recovered from COVID-19 [19].

In newborns, no intrauterine vertical transmission of the infection has been shown and complication rates of COVID-19 were not comparable to those in the general population [18]. On the other hand, SARS-CoV-2 RNA can be detected in newborns, indicating the possibility of vertical transmission of the infection. The circulation of SARS-CoV-2 in the mother increases the risk of newborn infection even with full compliance with preventive measures [20–22]. The rate of hospitalization in the intensive care unit (ICU) among newborns born to mothers with COVID-19 is high, reaching about 25% [19].

The highest-risk group for developing severe forms of COVID-19 involves pregnant and postpartum women with physical pathology: chronic lung diseases, including moderate to severe bronchial asthma; cardiovascular diseases, including arterial hypertension; diabetes mellitus; cancer; obesity; chronic kidney disease; liver disease [23, 24]. During the 2020 pandemic, pregnant women with COVID-19 had higher rates of maternal mortality (38.2-fold) and perinatal mortality (1.9-fold) compared to the general population. The risk of maternal mortality in COVID-19 is associated with comorbid factors such as obesity, DM, chronic arterial hypertension, respiratory diseases, anemia, and late initiation of COVID-19 therapy [20–22]. A case of rapid COVID-19 progression in a pregnant woman has been described, with a fatal outcome occurring within only two weeks from symptom onset [25].

Pregnant women can develop various pathologies after COVID-19 infection, including spontaneous miscarriages in the first and second trimesters, preterm births, and fetal-placental insufficiency. In some cases, fetal growth restriction is diagnosed, which is attributed to a decrease in uteroplacental blood flow in COVID-19. In addition, pregnant women who have recovered from COVID-19 may experience manifestations of chronic conditions and postpartum bleeding [23, 24].

**Complications of COVID-19**

**Cardiovascular complications**

SARS-CoV-2 infection was initially considered a disease that predominantly affects the lungs. However, as clinical data have accumulated, it has become evident that this viral infection frequently triggers a robust immune response with overproduction of pro-inflammatory cytokines, or the cytokine storm. Such immune response can involve multiple organs and systems damage, including the heart and blood vessels. A hypercoagulable state, which is characteristic of COVID-19 patients, contributes to the development of pulmonary embolism and myocardial infarction as well. Ruzzenenti et al. [26] reviewed a number of cardiac abnormalities and pathologies observed in patients with COVID-19. They explored potential pathogenetic mechanisms that directly involve the etiological agent, SARS-CoV-2, as well as the indirect damage caused by the COVID-19 pandemic. The latter included the reduction in healthcare services for acute and chronic cardiovascular diseases, leading to higher mortality and morbidity rates among cardiac patients.
Coronary heart disease. Coronary heart disease (CHD) is associated with a severe/critical course of COVID-19, admission to the ICU, disease progression, and mortality. Just six months into the pandemic, Mitran et al. [27], based on a literature analysis, reported that 20–30% of hospitalized COVID-19 patients exhibited signs of myocardial injury. The authors cautioned that recovered patients may still develop cardiomyopathy and cardiac arrhythmia in the future despite the apparent restoration of their cardiac function. Mitran et al. were among the first to characterize this pathology as post-COVID-19 cardiac syndrome.

Myocardial injury in COVID-19 correlates with worse outcomes, and higher levels of troponin are observed in high-risk patients: men, the elderly, and those with co-morbid cardiovascular diseases [26, 28]. Liang et al. [29] performed a meta-analysis of 40 studies that included 22,148 patients with CHD. They showed that CHD is associated with poor COVID-19 prognosis and increased mortality, but the presence of hypertension has a mitigating effect on this association.

In the extensive scientific medical literature published over the past three years, there are multiple reports of myocardial involvement in COVID-19 (see reviews [4, 30, 31]). The causes of myocardial injury are varied and include coronary necrosis and other acute manifestations of both premorbid and comorbid CHD [4]. Nevertheless, the question of whether myocardial involvement is a direct result of the virus affecting the heart and blood vessels or a consequence of the severe progression of the disease including generalized sepsis [26] remains a topic of ongoing discussion.

Arterial hypertension. Specific comorbidities are associated with an increased risk of infection and adverse outcomes including higher mortality rates and more severe lung injury. The most frequent comorbidity in COVID-19 patients is hypertension (27-30%). However, this does not necessarily imply a causal relationship between hypertension and the severity of COVID-19. Arterial hypertension is common among elderly individuals, and this age group is particularly susceptible to a high risk of SARS-CoV-2 infection and severe forms of COVID-19 with subsequent complications. Patients with hypertension often receive ACE inhibitors and angiotensin II receptor blockers (ARBs). ACE inhibitors decrease the formation of angiotensin II, while ARBs block its function by inhibiting AT1 receptors. As a result, these pharmacological agents can help alleviate systemic inflammation, especially in the lungs, heart, and kidneys. Thus, ACE inhibitors and ARBs can reduce the likelihood of developing acute respiratory distress syndrome (ARDS), myocarditis, or acute kidney injury – pathological conditions that are characteristic of patients with COVID-19 [32].

Atrial fibrillation. COVID-19 infection is found to be associated with an increased incidence of atrial fibrillation (AF). Dysfunctional microvascular support by endothelial cells can increase the predisposition to AF via higher levels of myocardial inflammation, fibrosis, increased tissue edema, and interstitial hydrostatic pressure. All of these factors can lead to electrical perturbances at the tissue and cellular levels. Angiotensin, pulmonary hypertension, and regulatory T cells are considered additional factors of AF during COVID-19 infection [33].

Disorders of hematopoiesis. Abnormalities in hematopoiesis, as well as in the morphology and functional state of blood cells, often manifest during COVID-19. Lymphopenia, a common pathology of the hematopoietic system, is frequently observed in severe patients with an unfavorable prognosis. For example, Huang & Pranata [34] carried out a systematic review and meta-analysis of 24 studies involving 3,099 participants to show that patients with a poor COVID-19 outcome have lower lymphocyte counts (561.06 cells/μl on average) than those with a positive outcome. Lymphocyte depletion has also been shown in ARDS survivors who received intensive care and in patients with severe COVID-19. Overall, lymphopenia was associated with a severe course of the disease, and the relationship between lymphocyte count and adverse outcomes was affected by age [34, 35].

Patients with anemia frequently have a medical history of one or multiple comorbidities, and their COVID-19 infection tends to follow a severe course. Most patients in the anemic group present elevated C-reactive protein (CRP), procalcitonin (PCT), and creatinine as well as higher values of erythrocyte sedimentation rate (ESR), D-dimer, myoglobin, T-pro-brain natriuretic peptide (T-proBNP), and urea nitrogen. Moreover, the proportion of patients with dyspnea, elevated CRP, and PCT positively correlates with the severity of anemia [36].

Many studies have found COVID-19 to be associated with an increased risk of thrombosis, which is a key factor contributing to numerous complications of this infection (see reviews [37, 38]). Having analyzed 20 studies enrolling 1,988 patients with COVID-19, Di Minno et al. [39] calculated that the weighted mean prevalence of venous thromboembolism (VTE) was 31.3%, while deep vein thrombosis accounted for 19.8%, and pulmonary embolism – for 18.9%. These pathologies were most often diagnosed in patients with severe COVID-19. Autopsy studies identified deep vein thrombosis in 40-60% of cases, and pulmonary embolism was the direct cause of death in 20-25% of patients with COVID-19 [40].
Cancer and COVID-19

Cancer and COVID-19 lead to an increased risk of thrombosis and exceptionally high levels of D-dimer, while anticoagulant therapy may prove ineffective in some cases. Cancer patients are more susceptible to SARS-CoV-2 infection, and the mortality rate in this cohort is higher than in the general population [41]. Grivas et al. [42] examined 4,966 COVID-19 patients with malignancies. Older age, male sex, cardiovascular and pulmonary diseases, obesity, kidney disease, diabetes mellitus, black race, Hispanic ethnicity, recent cytotoxic chemotherapy, and hematologic malignancy were associated with an increased incidence of COVID-19. Low or high absolute lymphocyte count, high absolute neutrophil count, low platelet count, and abnormal creatinine, troponin, lactate dehydrogenase, or C-reactive protein correlated with higher COVID-19 severity among hospitalized patients. Specific anticancer therapies were associated with high mortality [42]. The numerous symptomatic manifestations seen in COVID-19 and the significant overlap of COVID- and cancer-related symptoms pose challenges for specialists who are responsible for diagnosing and managing oncology patients during the COVID-19 pandemic. Furthermore, clinicians face difficulties in differentiating the cause of certain pathologies, e.g., in distinguishing intoxication in COVID-19 from the side effects of chemotherapy drugs used in oncology treatment [43].

Pneumonia and ARDS

SARS-CoV-2 can affect the lower respiratory tract, leading to the development of viral pneumonia and, in severe cases, ARDS. ARDS can result in a fatal outcome due to multiple organ failure, particularly in elderly patients and individuals with specific comorbidities (DM, obesity, cardiovascular diseases, cancer, etc.) [8]. Pneumonia manifests as extensive involvement of lung parenchyma, diffuse alveolar damage (DAD), thrombotic events, and impairment of ventilation-perfusion relationships in the lungs [44]. DAD was identified as the morphological substrate of pulmonary pathology in ARDS. It is noteworthy that in COVID-19, DAD phases are prolonged and develop asynchronously. This pathology is also characterized by alveolar hemorrhage syndrome and the involvement of pulmonary vasculature [45].

Immune system hyperreactivity plays a major role in the pathogenesis of ARDS - one of the main causes of death in patients with COVID-19. Immunopathogenesis of ARDS is associated with increased levels of proinflammatory cytokines: interleukin (IL) 6, IL1, IL17, and tumor necrosis factor α (TNFα). Their uncontrolled production, known as the cytokine storm, results in a hyperinflammatory response, both local and systemic [46]. Excessive release of cytokines into the bloodstream leads to endothelial damage and thromboembolic complications, which aggravates the patient’s condition. ARDS is diagnosed in approximately 15% of COVID-19 cases [46], and its course has a worse prognosis compared to ARDS in other diseases. The ARDS-associated mortality rate in COVID-19 ranges from 26.0% to 61.5% [45].

During COVID-associated pneumonia and after recovery, patients may develop suppurative diseases of the lungs and pleura. A surgical approach using minimally invasive videothoracoscopy allows for early debridement and sterilization of the pleural and intrapulmonary cavi- ties, ensuring earlier and more effective patient recovery and reduced hospitalization time [47].

Lung pathology and COVID-19

Pneumomediastinum – an accumulation of air in the mediastinum – can occur spontaneously or as a result of various diseases due to well-established etiological factors. In COVID-19 patients who have not received endotracheal intubation and artificial lung ventilation (ALV), pneumomediastinum is classified as spontaneous. Retrosternal pain as a symptom of pneumomediastinum can be the primary clinical manifestation when patients initially seek medical attention. The epithelium of the respiratory tract provides a “gateway” for SARS-CoV-2, the etiological agent of COVID-19. The virus quickly enters its primary target, alveolar cells, and triggers DAD. The subsequent pathological process follows a typical pattern of pneumomediastinum development. The intra-alveolar pressure increases during ALV or even coughing, which can cause alveolar rupture and enable air to leak outside the alveoli. Air spreads from the alveoli to the lung root and mediastinum due to the Macklin effect [48], which results in the typical clinical presentation of pneumomediastinum [49].

The majority of patients with COPD have a long history of smoking or exposure to harmful particles or gases, and their lung defense can remain weakened even years after exposure ceases. Patients with COPD reportedly have increased susceptibility to viral respiratory infections, which is often exacerbated by bacterial co-infections and leads to adverse clinical outcomes. COPD appears to increase both susceptibility to SARS-CoV-2 and the severity of COVID-19 [50].

Dermatologic manifestations of COVID-19

Dermatologic manifestations of COVID-19 are divided into five groups: 1) maculopapular rash (47%); 2) acral erythema with vesicles or pustules, or “COVID toes/fingers” (19%); 3) urticarial rash (19%); 4) varicella-like (papulovesicular) exanthem (9%); 5) livedo, or tissue necrosis (6%) [51]. The analysis of skin biopsies has linked
these dermatological manifestations to thrombotic vasculitis with SARS-CoV-2-associated endothelitis, when the virus is detected within the endothelium. In addition, COVID-19 patients can present lesions of mucous membranes of various organs including eyes and digestive and urogenital systems. The true cause underlying skin involvement in COVID-19 is yet to be determined. However, the following hypotheses are currently being considered: direct damage by the virus, reactive inflammation, thrombosis and vasculitis, toxic and allergic effects of drugs used in COVID-19 treatment, and various iatrogenic factors [4, 51].

**Gastrointestinal manifestations of COVID-19**

Gastrointestinal (GI) symptoms are present in one out of four patients hospitalized with COVID-19 [52]. According to data published by Lin et al. [53], SARS-CoV-2 can affect the digestive system in more than 50% of infected individuals. GI symptoms increase the risk of adverse and life-threatening complications of COVID-19. The most common GI manifestations of COVID-19 are anorexia, diarrhea, nausea, abdominal pain, and vomiting [54, 55]. Erosions and ulcers of the gastrointestinal mucosa can also be observed [56].

Viral components isolated from stool samples of infected patients suggest the fecal-oral transmission route of SARS-CoV-2. Moreover, SARS-CoV-2 RNA can be detected in blood samples of infected patients, which implies hematological dissemination of the virus as a possible route of GI involvement [57]. Abundant expression of ACE2 (SARS-CoV-2 receptor) in glandular cells and enterocytes of the small intestine can explain why the virus replicates in the intestine for an extended period, sometimes for a month or more [58]. Virus replication in the enterocytes can promote an inflammatory response resembling hemorrhagic enterocolitis [46]. Overall, GI symptoms seem to increase the risk of adverse and life-threatening complications of COVID-19.

**Liver pathology and COVID-19**

In COVID-19, nearly half of the severe patients demonstrate laboratory signs of mild hepatocellular insufficiency, while changes in liver enzymes may also be observed in some cases. COVID-related liver damage is multifactorial and occurs due to the direct impact of the virus on hepatocytes and cholangiocytes, immune-mediated inflammation, hypoxia, and treatment with hepatotoxic medications [57, 59].

Based on histopathological studies of 150 autopsies conducted between March 2020 and March 2022 on patients who died of COVID-19, Pestl et al. [60] concluded that endothelial damage is the most frequent, albeit non-specific, liver pathology in COVID-19 cases. Viral RNA and proteins are detected in non-parenchymal liver cells, which indicates the cytotoxic action of SARS-CoV-2 not only in the lungs but also in other organs, including the liver. The occurrence of necrosis/apoptosis and endothelial damage in individuals affected by SARS-CoV-2 infection implies that patients who experienced severe COVID-19 may require an extended period of liver recovery. Therefore, close monitoring is recommended during their post-COVID phase.

The mortality rate in patients with liver cirrhosis and other chronic liver diseases reaches 40% in COVID-19 cases. Several factors can aggravate the progression of COVID-19 in these patients: immune-mediated damage to liver cells, direct toxicity resulting from the virus replicating in hepatocytes, hypoxia, drug-induced liver injury, and the recurrence of latent liver diseases such as hepatitis B or C [61]. Cases of autoimmune hepatitis following COVID-19 have been reported in recently recovered patients. High titers of anti-SARS-CoV-2 IgG antibody were observed in these cases [62].

**Urinary system pathology and COVID-19**

Independently of baseline kidney function, acute kidney injury (AKI) is a common complication of COVID-19, associated with increased morbidity and mortality. COVID-19 most frequently causes acute tubular necrosis. However, focal segmental glomerulosclerosis and direct renal damage by the virus have also been reported in some cases. Even a mild renal dysfunction can be an independent risk factor for COVID-19 infection, hospitalization, and mortality. Dialysis patients also carry an increased risk of other severe COVID-related complications including arrhythmias, shock, ARDS, and acute heart failure [63]. Vaccination programs hold great promise for improving outcomes in patients with kidney disease [64].

AKI, being secondary to COVID-19, is a multifunctional process. Kidney injury can arise either directly from the virus entering renal cells or secondarily as a consequence of immune, ischemic, and coagulation disorders [65]. Renal failure often develops in COVID-19 patients during prolonged stays in the ICU, and its treatment is challenging as it requires extracorporeal dialysis systems [46]. A study by Chebotareva et al. [66] involved 1,280 patients with COVID-19. Mild to moderate proteinuria (from 0.3 g/l to 3 g/l) was diagnosed in 648 participants (50.6%), hematuria – in 77 (6.0%), leukocyturia – in 282 (22.0%), while 571 patients (28.9%) developed AKI. In most cases, the disease was halted at the first stage, and only 10 patients (2.7%) required hemodialysis. Age over 65 years, elevated levels of inflammatory markers (CRP and ferritin), increased D-dimer levels, and prolonged
activated partial thromboplastin time were identified as independent risk factors for AKI. The presence of AKI was significantly associated with an increased risk of mortality.

The role of SARS-CoV-2 in the development of lower urinary tract symptoms (LUTS), which manifest as urinary urgency, dysuria, and nocturia, is not fully understood. It is suggested that the development of LUTS involves virus-stimulated activation of ACE2 expression, cytokines, Toll-like receptor 4 (TLR4), and other molecular pathways. In the literature, elevated levels of cytokines, which are released into the urine and/or expressed in the bladder along with LUTS in patients with COVID-19, have been referred to as “de novo urinary symptoms” or “COVID-19-associated cystitis” (CAC). This pathology develops in the absence of any bacterial pathogens in the urine [67].

Patients who experienced the onset of acute pyelonephritis after recovering from COVID-19 are more likely to develop suppurative pyelonephritis and more severe damage to the kidney interstitium and tubules [68]. Additionally, hyperfiltration, hyposthenuria, and higher levels of fibrinogen, CRP, procalcitonin, and urinary neutrophil gelatinase-associated lipocalin 2 were observed more frequently. Nearly 50% of patients with acute pyelonephritis and a history of COVID-19 exhibit persistent urinary syndrome during examination 3-4 months after the onset of the disease.

**Diabetes mellitus and COVID-19**

Diabetes is one of the most common comorbidities in patients with COVID-19, and its prevalence varies from 7 to 30%. Diabetic patients infected with SARS-CoV-2 exhibit higher rates of hospitalization, severe pneumonia, and mortality compared to non-diabetic patients. Chronic hyperglycemia compromises both innate and adaptive humoral immunity. Diabetes is associated with a mild chronic inflammatory state, which contributes to the development of a stronger inflammatory response and, consequently, ARDS. SARS-CoV-2 has been shown to damage the pancreas, thus worsening hyperglycemia or even triggering the onset of diabetes in previously non-diabetic individuals [69]. In addition to inducing diabetes, SARS-CoV-2 can cause acute pancreatitis either through direct infection of pancreatic tissue by the virus or as a result of multiple organ dysfunction syndrome, accompanied by increased levels of amylase and lipase [70].

Patients with COVID-19 and type 2 DM demonstrate pronounced persistent hyperglycemia, although a third of them can have episodes of hypoglycemia. Dexamethasone treatment results in the most pronounced hyperglycemia without any episodes of hypoglycemia. Even if a patient with comorbidities is stable after completing glucocorticoid treatment, it is advisable to recommend blood glucose testing at least 5-6 times a day, including mandatory monitoring during nighttime [71].

Patients with DM have been shown to have a 21.8% higher incidence of COVID-19 compared to those without the disease. DM patients develop more severe viral pneumonia and its prevalence is three times higher compared to non-DM individuals. During clinical observation, a 2.2-fold increase has been found in the proportion of individuals developing extensive lung damage (>50%) [72]. Patients with DM and COVID-19-induced pneumonia are more likely to be hospitalized (+8.0%), intubated (+8.1%), and admitted to the ICU (+4.5%) compared to patients without DM. The analysis of laboratory data has shown elevated levels of CRP, creatinine, and fibrinogen. It takes longer for the markers of hypercoagulability, such as antithrombin III, fibrinogen, and D-dimer, to return to normal levels. Overall, the presence of concomitant DM in COVID-19 is associated with severe pneumonia, persistent reduction in oxygen levels, increased hyperglycemia, accelerated renal dysfunction, systemic inflammatory disorders, and hypercoagulation [72, 73].

The mortality rate among type 2 DM patients with COVID-pneumonia is estimated to be around 15%, and it is significantly higher in male patients and individuals receiving insulin therapy. The lethality of COVID is significantly lower in patients under the age of 65 as well as in those receiving metformin, overall antihypertensive therapy, beta-blockers, diuretics, and RAS blockers. [74].

**Obesity and COVID-19**

Given that ACE2 expression is higher in adipose tissue compared to lung tissue, it is reasonable to hypothesize that adipose tissue may be susceptible to infection by SARS-CoV-2. Obesity has been identified as a risk factor associated with adverse outcomes and a more severe course of COVID-19, including respiratory failure, the need for ALV, and increased mortality [3].

**Nervous system injury in COVID-19**

**Neurological disorders**

COVID-19 affects the nervous system in about one-third of cases. Patients with COVID-19 complain of headaches and manifest altered consciousness, ataxia, acute cerebrovascular events, seizures, hyposmia/anosmia, hypogeusia/dysgeusia, and neuralgia [42]. Notably, headaches and abnormalities in the sense of smell and taste often manifest early in COVID-19, serving as the primary symptoms in up to 90% of cases and sometimes persisting as the sole manifestations of the disease [4]. A review
by Chukhlovina [75] analyzed the incidence of smell and taste changes depending on the patient’s age and the severity of COVID-19. Patients with hyposmia and hyposgesia were found to be younger, and they generally experienced a milder course of the disease.

In COVID-19, the inflammatory process starts predominantly in the nasopharynx, the “gateway” of SARS-CoV-2. The anatomical structure and aerodynamics of the nasal cavity facilitate the entry of pathogens into the olfactory epithelium. By interacting with the membrane protein ACE2, SARS-CoV-2 enters the cell and then replicates. Affecting one cell after another, this process results in an impaired sense of smell. Yet, this is a simplified description of SARS-CoV-2-induced dysosmia, and its comprehensive understanding is still lacking. For example, it was shown that SARS-CoV-2 can enter host cells through interaction not only with ACE2 but also with the CD147 receptor. Wang et al. showed that meplazumab – a humanized antibody against CD147 – effectively prevents SARS-CoV-2 from penetrating host cells in vitro [76]. Furthermore, the interaction between CD147 and the S protein of SARS-CoV-2 was confirmed in biochemical and immunochemical experiments (Kd=1.85×10^{-7} M), as well as by colocalization of these two proteins in Vero E6 cells [76]. CD147 is known to be involved in the regulation of cellular activity in the central nervous system (CNS). Even before the COVID-19 pandemic, there was extensive discussion about utilizing this cell receptor as a target for pharmacotherapy of CNS diseases, including neurodegeneration (for review see [77]).

When discussing various types of nervous system disorders caused by COVID-19, the following mechanisms are being considered: direct cytotoxic effects of SARS-CoV-2, systemic inflammatory response and cytokine storm, autoimmune injury, hypoxia resulting from respiratory and cardiovascular pathology, thrombotic and thromboembolic complications, direct endothelial involvement of the microvasculature, and the potential for direct brain injury [4, 78, 79].

Patients with severe systemic manifestations of COVID-19 have more frequent neurological symptoms than those with a mild course. The most commonly diagnosed conditions include neuromuscular disorders (53.7%), cerebrovascular pathology (27.3%), acute encephalopathy (19.4%), seizures (7.8%), and various other conditions (11.6%), such as hiccups, myoclonic tremor, Horner’s syndrome, and transverse myelitis. COVID-19-associated cases of acute hemorrhagic necrotizing encephalopathy and Guillain-Barré syndrome with predominant cranial nerve damage have also been reported [80-82].

A growing body of evidence suggests a potential link between COVID-19 and ischemic stroke. The occurrence of COVID-stroke spans various age groups, with a higher prevalence observed in males. Research indicates a higher proportion of ischemic strokes among COVID-19 patients compared to age-matched individuals with other medical conditions. Notably, a rise in the incidence of ischemic strokes among younger individuals has been reported. However, whether this trend will persist after the end of the pandemic remains unclear [83].

COVID-stroke occurs either simultaneously with the onset of pulmonary symptoms or up to 40 days later. Clinical manifestations of COVID-19 are often mild or even absent. Most patients with COVID-stroke achieve complete or partial recovery; however, about 25% of cases face a fatal outcome. The pathophysiological mechanisms contributing to stroke in COVID-19 are rooted in the established Virchow’s triad that includes hypercoagulability, impaired hemodynamics, and vascular endothelial injury/dysfunction (angiopathy).

COVID-stroke is a multifactorial condition, predominantly embolic, and it is more frequently attributed to cardiovascular risk factors rather than coagulopathy. Through interaction with host cells, SARS-CoV-2 depletes ACE2, a critical component of the RAS, thus promoting endothelial dysfunction and the development of in situ thrombi. Patients with COVID-19 exhibit an imbalance in biochemical markers, specifically in the ACE1/antithrombin II ratio, which is accompanied by elevated blood pressure, cytokine hyperproduction, and increased vascular permeability. Atherothrombotic and embolic ischemic strokes are common in individuals with COVID-19. Another distinctive feature of COVID-19-related CNS pathology is a substantial cumulative cerebral involvement [84, 85].

Thus, COVID-19 can be especially threatening to individuals with pre-existing neurological and genetic disorders. Moreover, patients with syndromic pathologies are particularly susceptible to an elevated risk of COVID-19 complications [86, 87].

**Mental disorders**

Neuropsychiatric symptoms of COVID-19 are most frequently associated with multiple biological and social factors, including electrolyte imbalance, liver inflammation, impaired renal function, impaired oxygenation, hyperinflammation, and social isolation. The significant neurotropism exhibited by SARS-CoV-2 can contribute to the emergence of psychiatric disorders in COVID-19. This particular coronavirus demonstrates the ability to invade neurons and glial cells of the CNS, where it
actively reproduces. Consequently, apoptotic pathways are triggered, inducing a cascade of reactive inflammation within the brain. According to Nakamura et al. [88], the virus-induced inflammatory response may lead to dysfunction of the blood-brain barrier (BBB), resulting in immune cell infiltration and subsequent damage to CNS tissues. The direct viral invasion of the CNS is infrequent, even among patients experiencing severe symptoms. Additionally, the development or exacerbation of mental disorders can be facilitated by SARS-CoV-2-induced coagulopathy [88, 89].

Mental disorders can manifest during the acute phase of COVID-19 or following the alleviation of its primary symptoms. Furthermore, COVID-19 can trigger the exacerbation of pre-existing psychiatric pathology [89]. Experts in mental disorders have concluded that within the first year of the pandemic, there was a surge of 27.6% in severe depressive disorders worldwide, while anxiety disorders increased by 25.6% [84]. Numerous factors contribute to the emergence of depressive states, either directly or indirectly associated with COVID-19. These factors may include the neurotropic nature of SARS-CoV-2, the neurotoxic effects resulting from coronavirus infection, adverse reactions to pharmacological interventions, exposure to psychologically distressing information, social isolation, uncertainty about the future, the bereavement of loved ones, etc.

Decades of extensive research on trauma demonstrate that for the majority of individuals, negative life events such as significant loss or natural disasters typically lead to either resilience (minimal impact on anxiety and/or depression symptoms) or recovery (initial short-term exacerbation of anxiety and/or depression symptoms) followed by healing. This pattern is consistent with the outcomes that have been observed in comprehensive studies conducted during the COVID-19 pandemic. A meta-analysis of longitudinal cohort studies has identified a notable increase in psychological symptoms during the early stages of the pandemic, and a gradual decline has been observed over time [90].

Anxiety, depression, panic attacks, and sleep disturbances are frequently encountered as prevailing affective disorders among patients and individuals in the recovery phase of COVID-19 [91]. Alongside the aforementioned conditions, Mazza et al. [92] have documented cases of post-traumatic stress disorder and symptoms of obsessive-compulsive disorder during the pandemic. A meta-analysis by Deng et al. [93] demonstrated that 45% of COVID-19 patients experience depression, 47% experience anxiety, and sleep disturbances affect 34% of individuals.

Pathology of the peripheral nervous system
Considering the peripheral nervous system, patients with COVID-19 may exhibit neuralgia and skeletal muscle damage, Guillain-Barré syndrome, polynuereitis, neuromuscular junction disorders, neuro-opthalmic disorders, and neurosensory hearing loss [94].

The SARS-CoV-2 receptor, ACE2, is expressed in cells of the peripheral nervous system and skeletal muscles, mediating musculoskeletal involvement during COVID-19. Pathological processes affecting muscles include edema, necrosis, atrophy, denervation, and diaphragm dysfunction. Cases of synovitis have also been identified, along with hematomas in soft tissues. Additionally, severe manifestations such as gangrene, “COVID toes/fingers,” atypical bedsores, osteoporosis, and osteonecrosis have been documented [2].

Ophthalmological manifestations
According to published data, the frequency of ophthalmological manifestations of COVID-19 ranges from 0.8% to 31.6% [95]. Proteins associated with the renin-angiotensin-aldosterone system, which play a crucial role in the pathogenesis of COVID-19, are widely present in the eye tissues such as the retinal pigment epithelium, retina, and aqueous humor. The S protein of SARS-CoV-2 can interact with ACE2 receptors in the conjunctiva and cornea, as it does in cells of other organs [1]. Ophthalmic pathologies have been detected in both outpatient and hospitalized COVID-19 patients with a frequency of 11.4%. Conjunctivitis is the most prevalent manifestation characterized by eye hyperemia, eye pain, and follicular conjunctivitis [96]. Conjunctival hyperemia has been reported to precede the development of pneumonia [97].

Post-COVID syndrome
COVID-19 symptoms can persist for a long time after recovery, significantly affecting patients’ quality of life and ability to work. This condition, known as the “post-COVID syndrome” (PCS), is raising growing concerns among healthcare professionals globally. PCS has rapidly emerged as a clinically and socially significant pathological state that requires continuous monitoring of COVID-19 survivors and the implementation of rehabilitation programs [98]. PCS refers to the consequences of COVID-19, characterized by the continued presence of clinical symptoms in survivors for a minimum of 12 weeks following the acute phase of the disease [99].

Neurologically, the following manifestations can be highlighted within the multitude of PCS symptoms: memory and attention decline, dizziness, headaches, irritability, and anxiety. Respiratory symptoms include
shortness of breath, cough, and chest pain. Gastrointestinal symptoms involve anorexia, abdominal pain, dyspepsia, and diarrhea. COVID-19 survivors may also experience long-lasting or newly developed skin conditions such as itching, hives, hair loss, and fibromyalgia [84, 91]. A meta-analysis by Alkodaymi et al. [100] revealed substantial heterogeneity among studies regarding the prevalence of all documented symptoms.

CNS involvement can persist for a long time after recovering from COVID-19. It is potentially linked to the immune-mediated response of glial cells which can secrete pro-inflammatory cytokines IL6, IL12, IL15, and TNFα for an extended duration [101]. Following the resolution of acute COVID-19, many individuals experience long-term fatigue and/or cognitive impairments. The frequency and debilitating nature of these symptoms prompts the exploration of the underlying neurobiological mechanisms and the development of optimal treatment strategies.

Cognitive and emotional disorders are frequently observed in individuals with PCS and can stem from various factors. In numerous studies conducted throughout the three-year pandemic (see review [102]), patients with COVID-19 have shown disruptions in brain structure and metabolism, such as hypometabolism in regions associated with motivation. These structural and functional CNS impairments are associated with certain COVID-19 consequences, including endothelial dysfunction, hyperinflammation, autoimmunity, and multiorgan pathology. A causal link has been established between specific pro-inflammatory cytokines, rapid mood changes, and cognitive decline. Additionally, indirect effects related to psychological and social factors such as isolation and prolonged artificial ventilation or sedation have also been documented [84, 102].

The manifestations of PCS can be linked to prolonged hospitalization and severe cases of COVID-19. PCS is observed more frequently in younger individuals (18-50 years old), despite the higher risk of fatal outcomes and complications among elderly patients [103, 104]. Comorbidities are present in over one-third of PCS patients, with arterial hypertension, cardiovascular diseases, diabetes, lung diseases, and obesity being the most prevalent. The diagnosis of PCS presents a complex challenge due to the lack of clear diagnostic criteria and limited understanding of its underlying pathogenesis. This multifactorial process is influenced significantly by chronic inflammation and hypoxia [99].

Post-COVID-19 complications can act as triggers for autoimmune disorders. Certain conditions, such as systemic lupus erythematosus, hemolytic anemia, thrombocytopenia, Guillain-Barré syndrome, vasculitis, and multiple sclerosis, have been reported in some patients after recovering from COVID-19 [62]. Furthermore, individuals who have had COVID-19 may be diagnosed with ophthalmological pathologies, including conjunctivitis, anterior uveitis, choroiditis with retinal detachment, optic neuritis, and retinal vasculitis [97].

Recovered COVID-19 patients can experience the following cardiovascular complications: myocardial damage resulting from the cytokine storm, predominantly leading to myocarditis; generalized endothelial injury in various vascular locations; cardiotoxic effects caused by specific medications; and progression of pre-existing cardiovascular conditions [83]. Cardiovascular system damage was diagnosed 3 months after recovery from COVID-19 in 71% of patients with a light course of the disease, and in 93% and 95% of patients with a medium and severe course of the disease, respectively. Diagnostic assessments reveal left ventricular dysfunction, signs of prior pericarditis, and various arrhythmias [105]. Moreover, SARS-CoV-2 infection can lead to left atrial myocardial remodeling in the form of diffuse fibrosis. In patients recovering from COVID-19, the arrhythmogenic substrate may extend beyond the pulmonary vein ostia to involve other areas of the left atrium [106].

Three months following recovery from COVID-19 pneumonia, individuals can exhibit concealed right ventricular systolic dysfunction [107]. Compared to three months post-discharge, a higher prevalence of cardiovascular diseases was observed one year after recovery, which is driven primarily by the development of arterial hypertension and chronic heart failure. Echocardiography reveals changes in ventricular geometry accompanied by a decline in diastolic and systolic function of the left ventricle (LV), including reduced global longitudinal strain and deformation in the apical myocardium and partially the mid myocardial segments [108]. In the long term, patients recovered from the COVID-pneumonia can develop alterations in the right heart chambers. Echocardiography demonstrates an enlargement of the right heart chambers, an increased tricuspid regurgitation gradient, elevated systolic and mean pulmonary artery pressures, and pulmonary vascular resistance [109]. Additionally, the electrocardiogram can show a prolonged PQ interval, reflecting the time taken for the electrical impulse to travel from the sinoatrial node to the ventricles.

Myocarditis can develop in the long term after COVID-19. There are two main clinical variants of post-COVID myocarditis. Arrhythmic myocarditis is characterized by the emergence of new extrasystoles and atrial fibrillation without systolic dysfunction, whereas decompensated myocarditis is associated with systolic...
dysfunction and biventricular heart failure [110]. Distinctive features of myocarditis in COVID-19 include coronary arteritis and the possibility of myocarditis occurring alongside lymphocytic endo- and pericarditis [111].

Hydropericardium should be considered a specific manifestation of SARS-CoV-2 infection and taken into account when assessing symptoms of post-COVID syndrome. Exudative changes in the pericardium are 12 times more frequent in individuals who recovered from COVID-19 than in a similar group of patients before the pandemic. The significant occurrence of exudative pericarditis, irrespective of the COVID-19 severity, highlights the necessity of regular echocardiographic monitoring for a minimum of two months following the recovery from the disease [112].

COVID-19 survivors may also develop or continue to experience gastrointestinal symptoms, including dyspepsia, dysbiosis, elevated liver enzyme levels, and altered or reduced taste perception (dysgeusia and hyposgesia, respectively) [113]. Irritable bowel syndrome is another post-COVID manifestation that can persist for up to six months after recovering from the disease.

CONCLUSION

COVID-19 is a very complex and severe disease. Its causative agent, SARS-CoV-2, remains a major focus of research conducted by virologists, molecular biologists, and immunologists. Despite circulating in the human population for three years, COVID-19 continues to challenge global health and perplex health professionals with its diverse clinical symptoms and consequences. At the onset of the pandemic, the pathogenesis and treatment strategies for this novel viral disease were not understood at all. Consequently, researchers were urgently exploring the possibilities of repurposing existing medications and searching for novel therapeutic options. Over the past three years, substantial progress has been achieved. Scientists and clinical researchers have gained insights into the key factors contributing to the severe course and adverse outcomes of COVID-19. As a result, new therapeutic and preventive drugs as well as rehabilitation strategies for recovering individuals have been developed. A variety of medications is now available, including antiviral drugs (e.g., molnupiravir, paxlovid, remdesivir), monoclonal antibodies targeting SARS-CoV-2 (e.g., bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab, bebtelovimab), anti-inflammatory drugs (dexamethasone), and immunomodulators (e.g., baricitinib and tocilizumab) (https://www.ncbi.nlm.nih.gov/books/NBK554776/). The rapid development of vaccines has played a crucial role in saving numerous lives. COVID-19 vaccination has proven to be an effective measure in reducing not only the risk of SARS-CoV-2 infection, but also the likelihood of severe illness, hospitalization, and mortality associated with COVID-19.

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