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Postcovoid Syndrome: Modern Approaches to Diagnosis and Treatment

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Abstract The article shows the features of the manifestations of prolonged COVID-19. It has been demonstrated that according to the literature there are more than 200 symptoms of this condition. Dysfunctions of organs and body systems after infection were revealed. The modern achievements in the diagnosis and treatment of postcovid syndrome are clearly shown. Priority areas for future experimental and clinical research are outlined.

Keywords Long covid, SARS-CoV-2, Cognitive disorders, Vascular complications, Gastrointestinal tract, Respiratory disorders

1. Introduction

Postcovoid syndrome is a condition that develops after acute respiratory syndrome caused by the SARS-CoV-2 virus. According to the WHO definition, prolonged COVID is a condition in which symptoms last more than 3 months or new symptoms develop 3 months after initial infection, and the duration of these symptoms should not be less than 2 months and should not be caused by causes other than COVID. At least 65 million people worldwide suffer from a prolonged form of COVID, based on a conservative estimate of the incidence of 10% of the more than 651 million reported cases of COVID-19 worldwide. However, this number is probably much higher due to the large number of undocumented cases. It is believed that prolonged COVID occurs in 10-30% of non-hospitalized patients, 50-70% of hospitalized patients and 10-12% of previously vaccinated patients. It occurs in all age groups and does not depend on the severity of the acute phase of the disease. Thus, the highest percentage of morbidity is observed in people aged 36 to 50 years, and most cases occur in patients who have suffered a mild course of acute infection, since this population represents the majority of COVID-19 cases [1].

More than a hundred studies have been conducted to study the clinical picture of prolonged COVID. The results of these studies have shown that the manifestations can be diverse and include symptoms of damage to almost all organs and systems of the body. Moreover, the prolonged course of COVID can lead to the development of new pathological conditions, including cardiovascular, thrombotic and cerebrovascular diseases, type 2 diabetes, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and dysautonomia of the autonomic nervous system, especially postural orthostatic tachycardia syndrome (SPOT). Symptoms can persist for years, and in cases of ME/CFS and SPOT, for life. It is also alarming that, against the background of the lack of highly effective treatment methods, a significant number of patients are unable to return to their previous professional activities, and the scale of disability caused by prolonged COVID in some countries is already contributing to a shortage of labor.

Risk factors for the development of this disease include female sex, type 2 diabetes, reactivation of the Epstein-Barr virus, the presence of specific autoantibodies, connective tissue diseases, attention deficit hyperactivity disorder, chronic urticaria and allergic rhinitis, however, one third of patients with a long course had no previous pathologies. Also, a higher prevalence of prolonged COVID has been recorded among some ethnic groups, including people of Spanish or Latin American origin, and socio-economic risk factors include low income and inability to fully rest and recover in the first weeks after infection with COVID-19.

Regarding the causes of this disease, there are probably many potentially overlapping mechanisms. Several hypotheses have been proposed, including the persistence of the SARS-CoV-2 virus in tissue reservoirs; impaired immune regulation with reactivation of other pathogens (such as herpes viruses, Epstein-Barr), the effect of SARS-CoV-2 on the intestinal microbiota, autoimmune mechanisms, increased microvascular coagulation due to endothelial dysfunction, and impaired signal transmission in the brain stem and/or vagus nerve [2].

The purpose of this work was to study the main scientific achievements in understanding the pathogenetic mechanisms and clinical manifestations of the prolonged course of COVID

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in order to develop new methods of treatment and improve the quality of life of patients with this disease.

2. Materials and Methods of Research

Three electronic databases (PubMed, Web of Science, Cochrane Library) searched for full-text articles on pathogenetic mechanisms, clinical manifestations and the course of prolonged COVID, published before March 2024.

3. Results and Their Discussion

The main violations of prolonged COVID

Immunology and virology

A study of the immune system of patients with long-term COVID, who suffered a mild acute form of COVID-19, revealed depletion of the stock of T cells, a decrease in the number of CD4+ and CD8+ effector memory cells and increased expression of PD1 in central memory cells, persisting for at least 13 months. There is also evidence of high activation of innate immune cells, the absence of naive T and B cells, and increased expression of type I and III interferons (interferon-β (IFNß) and IFNλ1), persisting for at least 8 months after infection. A comprehensive comparison of patients with a long course of COVID with uninfected people and infected people without a long course revealed an increase in the number of non-classical monocytes, activated B cells, twice negative B cells, as well as CD4+ T cells secreting IL-4 and IL-6, a decrease in the number of ordinary dendritic cells and depleted T cellscells, as well as low cortisol levels in patients with long-term COVID, on average 14 months after infection. A link was also found between T cell hyperactivity and the persistence of the virus in the gastrointestinal tract. Additional studies have found elevated levels of cytokines, especially IL-1β, IL-6, TNF and IP10 in patients with cognitive symptoms of prolonged COVID. Numerous studies have revealed elevated levels of autoantibodies in long-term COVID, including autoantibodies to ACE2 (SARS-CoV-2 entry receptor), β2-adrenergic receptors, muscarinic M2 receptors, angiotensin II AT1 receptors and angiotensin 1-7 MAS receptors. High levels of other autoantibodies were found in some patients in the acute phase of COVID-19, including autoantibodies to connective tissue, extracellular matrix components, vascular endothelium, blood clotting factors and platelets, cells of lung tissue, central nervous system, skin and gastrointestinal tract, immunomodulatory proteins (e.g. cytokines, chemokines, complement components and cell surface proteins). However, the presence of autoantibodies is not the main cause of the long-term course of COVID.

Reactivated viruses, including EBV and HHV-6, have been found in patients with long-term COVID. It is known that reactivation of these viruses leads to fragmentation of mitochondria and seriously affects energy metabolism. A recent study has shown that EBV reactivation correlates with increased fatigue and neurocognitive dysfunction in patients with long-term COVID.

The results of several studies have established that low production of antibodies to SARS-CoV-2 or its absence, as well as other signs of a weak immune response in the acute stage of COVID-19, can serve as predictors of the long course of COVID after 6-7 months in both hospitalized and non-hospitalized patients. Signs of a weak immune response are low baseline IgG levels, low levels of receptor-binding domain and spike-specific memory B cells, low levels of IgG nucleocapsid and low spike-specific IgG peaks. In one study, a weak or absent response of CD4+ T cells and CD8+T cells was noted in patients with severe long-term COVID, and another study revealed lower levels of CD8+ T cells expressing CD107a and a decrease in CD8+ T cells producing interferon-γ in patients with long-term the course of COVID compared to infected control groups without a long-term course of COVID. High levels of autoantibodies with prolonged COVID were found to be inversely correlated with protective antibodies to COVID-19, suggesting that patients with high levels of autoantibodies are more susceptible to infection persistence. In support of this hypothesis, it was found that the persistence of the SARS-CoV-2 virus in the intestine is characterized by lower levels and a slowdown in the production of the IgA receptor-binding domain and IgG antibodies. There are serious differences in antibody formation, seroreversion, and antibody titer levels depending on gender: women have a lower probability of seroconversion, a higher probability of seroreversion, lower antibody levels in general, and a rapid decrease in antibodies after vaccination, which partially explains the high susceptibility of women to prolonged COVID.

Thus, the persistence of the virus as a result of immunological disorders is considered as the main cause of the long-term course of COVID. Patients often have viral proteins and/or RNA in the reproductive system, cardiovascular system, brain, muscles, eyes, lymph nodes, appendix, breast tissue, liver, lungs, plasma, feces and urine. In one study, the circulating spike antigen SARS-CoV-2 was detected in 60% of patients with a long-term course of COVID within 12 months after diagnosis, compared with a control group consisting of people who had undergone the acute phase, but did not show symptoms of a long course, which is probably due to the presence of a reservoir of active virus or components of the virus in individuals with a prolonged course. Indeed, the results of studies using a biopsy of the gastrointestinal tract indicate that in some patients the virus may persist in the tissues of the gastrointestinal tract for a long time [3,4].

Vascular disorders and organ damage

Although COVID-19 was initially considered a respiratory disease, it was later found out that SARS-CoV-2 is capable of damaging many other body systems. The damage found in various tissues is mainly due to an immune-mediated reaction and subsequent inflammation, rather than direct damage to cells by the virus. Circulatory disorders are mainly

represented by endothelial dysfunction and its consequences, such as an increased risk of deep vein thrombosis, pulmonary embolism and bleeding. Microthrombs found in both acute and long-term COVID-19 predispose to the development of thrombosis, and long-term changes in the size and stiffness of blood cells can also negatively affect the delivery of oxygen to tissues. A long-term decrease in vascular density, especially small capillaries, was found in patients with long-term COVID compared with the control group 18 months after infection. The study, which found elevated levels of vascular pathology biomarkers in the blood in COVID, also showed that angiogenesis markers ANG1 and P-selectin are predictors of the long-term course of COVID.

An analysis of the U.S. Department of Veterans Affairs database, which includes more than 150,000 people, showed a significantly increased risk of developing various cardiovascular diseases 1 year after infection with SARS-CoV-2, including heart failure, arrhythmias and stroke, regardless of the severity of the initial manifestation of COVID-19. Studies using MRI of the heart revealed cardiac abnormalities in 78% of 100 people who had previously been diagnosed with COVID-19 (on average 71 days after infection) and in 58% of participants with a long course of COVID (12 months after infection), which confirms the persistence of cardiac disorders.

In addition to cardiovascular disorders, numerous studies have revealed damage to other organs. Thus, one prospective study involving people from a low-risk group, examining the heart, lungs, liver, kidneys, pancreas and spleen, showed that 70% of 201 patients had damage to at least one of the organs, and 29% had multiple damage. In a follow—up study lasting one year, conducted by the same research group with 536 participants, the study authors found that 59% of patients had a single organ lesion, and 27% had multiple organ damage. In a study involving more than 89,000 people who had COVID-19, an increased risk of kidney disease was identified. Another analysis, which included more than 181,000 people who had been ill with COVID-19, showed that infection also increases the risk of developing type 2 diabetes. Thus, these studies show that organ damage during the long-term course of COVID is persistent, and the long-term consequences of these injuries remain insufficiently studied [5,6].

Neurological and cognitive disorders

Neurological and cognitive symptoms are the main feature of the long-term course of COVID, which significantly reduces the quality of life of patients. These include sensorimotor symptoms, memory loss, cognitive impairment, paresthesia, dizziness and balance problems, sensitivity to light and noise, loss of sense of smell or taste, and autonomic dysfunction.

According to one meta—analysis, fatigue was found in 32% and cognitive impairment in 22% of patients with COVID-19 12 weeks after infection. The cognitive impairments that develop with COVID are so pronounced that they are equated with a cognitive decline that develops over a 10-year period of natural aging. Moreover, these disorders may worsen over time. So, in one study, cognitive dysfunction was initially detected in 16% of patients 2 months after infection, but after 12 months the number of patients with cognitive symptoms reached 26%. The prevalence of cognitive impairment after COVID may actually be even higher, since some patients may not even suspect that they have cognitive dysfunction. They occur regardless of the presence of emotional disorders such as anxiety and depression, and occur with the same frequency in both hospitalized and non-hospitalized patients. A study of more than 1.3 million people who have had COVID-19 has shown that the symptoms of emotional disorders (anxiety and depression) They may decrease on their own over time, but the increased risk of cognitive impairment, seizures, dementia, psychosis and other neurocognitive disorders persists for at least 2 years.

The mechanisms of cognitive dysfunction development in prolonged COVID have been studied by numerous studies. Their development is closely related to the activation of the kynurenine pathway of glucose metabolism by cells. The severity of cognitive disorders is particularly correlated with the presence of metabolites of quinolinic acid, 3-hydroxyanthranilic acid and kynurenine in the blood. It is believed that the activation of the kynurenine pathway occurs due to an increase in the activity of proinflammatory cytokines, and intermediate metabolites of this pathway are able to penetrate the hemato-encephalic barrier and have pronounced neurotoxic effects, thus leading to damage to neurons. Possible mechanisms also include neuroinflammation, damage to blood vessels due to coagulopathy and endothelial dysfunction, as well as direct damage to neurons by the virus. Studies have also found disorders similar to those in Alzheimer's disease. Peptides that transform into amyloid plaques toxic to neurons have been found in patients with long-term COVID. In addition, the scientists described diffuse inflammation of the nervous tissue, hypometabolism of the brain and brainstem correlating with cognitive symptoms, abnormal parameters of cerebrospinal fluid, abnormal levels of mitochondrial proteins, as well as cellular components of the SARS-CoV-2 virus, tetrahydrobiopterin deficiency and signs of oxidative stress. A recent preprint reported multilinear cellular dysregulation and loss of myelin, with hyperreactivity of microglia similar to that observed with chemotherapy, even in patients who have undergone the acute phase in mild form. In the eyes, with prolonged COVID, there is a loss of small corneal nerve fibers and an increased density of dendritic cells, as well as significantly altered pupil responses to light and impaired retinal microcirculation. Some researchers believe that SARS-CoV-2 can infect and replicate in retinal organoids and enter the brain from there. A British biobank study that used brain imaging in the same patients before and after COVID-19, as well as in controls, showed a decrease in gray matter thickness in the orbitofrontal cortex and parahippocampal gyrus, an overall decrease in brain size and a greater decrease in cognitive function in patients after COVID-19 compared with the control group.

Similar changes in the nervous system were found in animal models of COVID-19. Thus, infection of mice with the SARS-CoV-2 virus led to an increase in microglial reactivity and an increase in CCL11 levels, which correlated with cognitive dysfunction and impaired neurogenesis. In another study, infection in hamsters led to a prolonged inflammatory process in the brain, including activation of T cells and myeloid cells, production of pro-inflammatory cytokines and interferon, which correlated with anxiety and depressive-like behavior in hamsters. Infected primates with a mild form of the disease also had inflammatory reactions in brain tissue, neuron damage and apoptosis, microbleeds in the brain, as well as chronic hypoxemia and hypoxia of the brain.

Recent reports indicate low blood cortisol levels in patients with long-term COVID compared to those in the control group, with symptoms lasting more than 1 year. Low production of cortisol by the adrenal glands is normally compensated by an increase in the production of adrenocorticotropic hormone (ACTH) by the pituitary gland, however, this does not occur with prolonged COVID, which indicates dysfunction of the hypothalamic-pituitary-adrenal axis, which may be a consequence of the neuroinflammatory process [7,8].

The reproductive system

Changes in the reproductive system are often reported during the long course of COVID, although there is still insufficient information to reliably determine the degree of dysfunction of this system. The most common complaint is menstrual irregularities (irregular and rare menstruation), which occur more often in women with prolonged COVID than in women who have had COVID-19, but without a prolonged course. There is also evidence that exacerbation of symptoms of prolonged COVID in women is more likely to occur during menstruation and during the week before menstruation. In addition, there is a decrease in ovarian reserve and changes in the secretion of sex hormones. It is believed that disorders in the reproductive system in women are associated with an abundance of ACE2 receptors in ovarian and endometrial tissue. It is known that these receptors are the entrance gates for the SARS-CoV-2 virus. Individuals with COVID-19 and menstrual cycle changes are more likely to experience fatigue, headache, body pain and shortness of breath than those without menstrual cycle changes. It is worth noting that disorders of the reproductive system are also described in the literature on ME/CFS. For example, there is a link between ME/CFS and premenstrual dysphoric disorder, polycystic ovary syndrome, menstrual disorders, ovarian cysts, early menopause and endometriosis. Pregnancy, postpartum changes, perimenopause and menstrual cycle fluctuations affect the severity of ME/CFS, metabolic and immune changes.

In men, the persistence of the virus in penile tissues has been documented, as well as an increased risk of erectile dysfunction, probably caused by endothelial dysfunction. One study reported abnormalities in sperm count, sperm volume, motility, sperm morphology, and sperm concentration in individuals with long-term COVID compared with individuals from the control group. These changes correlated with elevated cytokine levels and the presence of caspase 8, caspase 9 and caspase 3 in seminal fluid. Thus, disorders in the reproductive system in both women and men are part of the clinical picture of prolonged COVID. Additional research is required in order to better understand the pathophysiology of these disorders [9,10].

Respiratory system

Respiratory symptoms are one of the main manifestations of long-term COVID. Shortness of breath and cough persist for at least 7 months in 40% of patients with long-term COVID. Several imaging studies involving individuals with long-term COVID have demonstrated numerous pulmonary disorders, including so-called "air traps" and impaired lung perfusion. Immunological and proteomic studies of patients 3-6 months after infection revealed apoptosis and epithelial damage in the respiratory tract, and immunological studies revealed a correlation between decreased lung function, systemic inflammation and T cells specific to SARS-CoV-2 [11].

The gastrointestinal system

Long-term gastrointestinal symptoms of COVID include nausea, abdominal pain, loss of appetite, heartburn and constipation. The composition of the intestinal microbiota varies significantly in patients with COVID-19, which is also typical for ME/CFS. Prolonged COVID is characterized by higher levels of Ruminococcus gavus and Bacteroides vulgatus, lower levels of Faecalibacterium prausnitzii, and low levels of butyrate-producing bacteria, which closely correlate with the duration of COVID. A link has been identified between persistent respiratory and neurological symptoms and specific intestinal pathogens. In addition, SARS-CoV-2 RNA is present in stool samples of patients with acute COVID-19, while the virus content decreases as they recover. So, one of the studies showed the persistence of the virus in the feces in 12.7% of patients after 4 months and in 3.8% 7 months after diagnosis. While in most patients with long-term COVID symptoms, the persistence of the antigen in the intestinal mucosa persisted 7 months after infection. Higher levels of fungal translocation from the intestinal and/or lung epithelium into the blood were found in patients with long-term COVID compared with patients without long-term COVID, which may provoke prolonged production of proinflammatory cytokines. Interestingly, the transplantation of intestinal bacteria from patients with long-term COVID to healthy mice leads in mice to impaired cognitive functions and a decrease in protective mechanisms in the lungs, which is partially stopped by treatment with the commensal probiotic bacterium Bifidobacterium longum [12].

Course of the disease and prognosis

The onset and course of the disease vary from person to person and depends on the type of symptoms. For example,

cognitive symptoms often occur after a few weeks or months. Among patients with cognitive symptoms, 43% reported the appearance of these disorders 1 month after infection with COVID-19. Some neurocognitive symptoms worsen over time and tend to persist longer, whereas gastrointestinal and respiratory symptoms are more likely to decrease. In addition, pain in joints, bones, ears, neck and back, as well as paresthesia, hair loss, blurred vision and swelling of legs, arms and feet are more often observed after 1 year. Parosmia occurs on average 3 months after initial infection and unlike other neurocognitive symptoms, the severity of this symptom often decreases over time.

Unfortunately, only a few people with long-term COVID show full recovery. For example, one study showed that 85% of patients who developed symptoms 2 months after initial infection reported symptoms persisting after 1 year [13].

Prolonged COVID in childhood

The prolonged course of COVID is found in children of all ages. One of the first studies to study the clinical picture of prolonged COVID in children showed that symptoms such as fatigue, headache, dizziness, shortness of breath, chest pain, dysosmia, dysgeusia, decreased appetite, difficulty concentrating, memory problems, mental and physical exhaustion and sleep disorders are more common in persons aged 15-19 who had suffered from COVID, compared with a control group of the same age who had never had COVID. Subsequently, similar results were obtained in other randomized controlled trials. For example, a nationwide study conducted in Denmark found that children with a positive result of a PCR test for SARS-CoV-2 have a higher chance that at least one of the above symptoms will persist for more than 2 months. There is evidence indicating that in children who have had COVID, liver damage is subsequently more often recorded, the risk of acute pulmonary embolism, myocarditis and cardiomyopathy, venous thromboembolism, acute renal failure and type 1 diabetes may develop functional and structural changes in the brain and lung tissue similar to changes, observed in adults. And infants born to women who had COVID-19 during pregnancy are more likely to be diagnosed with disorders of the nervous system in the first year after childbirth. Risk factors for the development of long-term COVID in children are attention deficit hyperactivity disorder, chronic urticaria and allergic rhinitis.

More research is needed on the long-term course of COVID in children, although there are difficulties in establishing a proper control group due to testing problems. Several studies have shown that children infected with SARS-CoV-2, compared with adults, are significantly less likely to receive a positive PCR test result, despite seroconversion after a few weeks, as a result of which up to 90% of cases of infection in children remain missed. In addition, children are much less likely to have seroconversion compared to adults, and even if antibodies appear, there is a high probability that a weakening of the immune response will be observed a few months after infection [14].

4. Conclusions

Thus, postcovoid syndrome is a multisystem disease that includes symptoms such as cognitive disorders, vascular disorders, increased blood clotting, gastrointestinal, respiratory and many other disorders. This disease has already negatively affected the quality of life of millions of people around the world, and their number continues to grow. The notion that COVID-19 has only respiratory effects may lead to delayed recognition of the neurological, cardiovascular, and other multisystem effects of COVID-19. Unfortunately, many clinicians still pay more attention to the treatment and rehabilitation of respiratory manifestations, which contributes to the aggravation of neurological, cognitive and other manifestations.

Unfortunately, existing diagnostic and treatment methods are not effective enough [15,16], therefore, numerous additional clinical trials are needed to develop new treatment methods aimed at eliminating possible biological mechanisms of the prolonged course of COVID, including virus persistence, inflammation, excessive blood clotting and autoimmune mechanisms.

REFERENCES

[1] Davis, H. E. et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. // ClinicalMedicine 38, 101019 (2021).

[2] Proal, A. D. & VanElzakker, M. B. Long COVID or post-acute sequelae of COVID-19 (PASC): an overview of biological factors that may contribute to persistent symptoms. // Front. Microbiol. 12, 698169 (2021).

[3] Klein, J. et al. Distinguishing features of Long COVID identified through immune profiling. // Preprint at medRxiv https://doi.org/10.1101/2022.08.09.22278592 (2022).

[4] Phetsouphanh, C. et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. // Nat. Immunol. 23, 210–216 (2022).

[5] Hafke, M. et al. Endothelial dysfunction and altered endothelial biomarkers in patients with post-COVID-19 syndrome and chronic fatigue syndrome (ME/CFS). // J. Transl Med. 20, 138 (2022).

[6] Katsoularis, I. et al. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after covid-19: nationwide self-controlled cases series and matched cohort study. // BMJ 377, e069590 (2022).

[7] Cysique, L. A. et al. Post-acute COVID-19 cognitive impairment and decline uniquely associate with kynurenine pathway activation: a longitudinal observational study. // Preprint at medRxiv https://doi.org/10.1101/2022.06.07.22276020 (2022).

[8] Crivelli, L. et al. Changes in cognitive functioning after COVID-19: a systematic review and meta-analysis. // Alzheimers Dement. 18, 1047–1066 (2022).

[9] Maleki, B. H. & Tartibian, B. COVID-19 and male reproductive

function: a prospective, longitudinal cohort study. // Reproduction 161, 319–331 (2021).

[10] Khan, S. M. et al. SARS-CoV-2 infection and subsequent changes in the menstrual cycle among participants in the Arizona CoVHORT study. // Am. J. Obstet. Gynecol. 226, 270–273 (2022).

[11] Littlefield, K. M. et al. SARS-CoV-2-specific T cells associate with inflammation and reduced lung function in pulmonary post-acute sequalae of SARS-CoV-2. // PLOS Pathog. 18, e1010359 (2022).

[12] Zollner, A. et al. Postacute COVID-19 is characterized by gut viral antigen persistence in inflammatory bowel diseases. // Gastroenterology 163, 495–506.e8 (2022).

[13] Tran, V.-T., Porcher, R., Pane, I. & Ravaud, P. Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. //Nat. Commun. 13, 1812 (2022).

[14] Kompaniyets, L. Post–COVID-19 symptoms and conditions among children and adolescents — United States, March 1, 2020–January 31, 2022. MMWR Morb. Mortal. Wkly Rep. 71, 993–999 (2022).

[15] Ledford, H. Long-COVID treatments: why the world is still waiting. // Nature 608, 258–260 (2022).

[16] Jasim SA, Mahdi RS, Bokov DO, Najm MAA, Sobirova GN, Bafoyeva ZO, Taifi A, Alkadir OKA, Mustafa YF, Mirzaei R, Karampoor S. /The deciphering of the immune cells and marker signature in COVID-19 pathogenesis: An update // J Med Virol. 2022 Jul 14;10.1002/jmv.28000.