Journal of Biosciences and Medicines, 2023, 11, 90-113
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Long COVID: A Molecular, Cellular and Histopathology Overview

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How to cite this paper: da Silva Barros, B.R., de Oliveira Cruz, L.C., de Sousa, G.F., Souza-Silva, G.A., de Lima, M.R.C.F., Oliveira, E.G., Silva, A.J.D., Macêdo, L.S., Leal, L.R.S., Marcos, B.F.S., Elsztein, C., da Conceição V. Invenção, M., de Freitas, A.C. and Moutinho-Melo, C. (2023) Long COVID: A Molecular, Cellular and Histopathology Overview. *Journal of Biosciences and Medicines*, **11**, 90-113.
https://doi.org/10.4236/jbm.2023.119009

Received: August 2, 2023
Accepted: September 3, 2023
Published: September 6, 2023

Abstract

Long COVID has been studied as different sequelae that some individuals can develop after the acute phase of the disease. Persistent symptoms such as dry cough, fatigue, and dyspnea can remain after six months of COVID-19 cure. Others such as lung fibrosis, kidney injury, and thrombotic risk also are observed. Here, a deep review of each human organ and system infected by the virus was performed aiming to show how molecules expression and cell signaling can induce the organism cure or injuries and, subsequently sequelae. The review also suggests the importance of public health surveillance for these cases including a more comprehensive analysis of molecular biology tools that can clarify and assist in the prognosis, treatment, and preventive methods for potentially more serious disorders in post-COVID-19 patients.

Keywords

Long COVID, COVID-19, Sequelae, Public Health, Surveillance

1. Introduction

The COVID-19 pandemic caused significant impacts on global economies, with the worst performances on stock exchanges since 2008 [1]. In addition to the high mortality rate, it is estimated that the world economy has shrunk by 6%,

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resulting in around 300 million unemployed [2]. Populations of low socioeconomic status, such as in India, Pakistan and Bangladesh, faced greater risks due to the shortage of health services, affecting economic sectors [3].

Socioeconomic and demographic factors indicate that the pandemic has not uniformly affected all groups [4]. In addition, the economic shock driven by COVID-19, including shutdowns, layoffs and company closures, resulted in supply disruptions that triggered shifts in demand in the healthcare sectors as well [5] [6].

Therefore, the COVID-19 pandemic has led to the publication of countless studies, increasingly offering a better understanding of the acute phase of the disease, in addition to the development and improvement of its treatment [7] [8] [9]. On the other hand, even in those patients recovered from the acute phase, there is a series of signs and symptoms that persist from weeks to months, promoting health restriction and limitations in the resumption of daily activities, being thus defined as Long COVID or long COVID [10].

Evidence available to date suggests wide variations in the Long COVID prevalence and incidence estimates due to differences in the populations studied, recruitment methods, follow-up periods, and sample sizes. Furthermore, in most analyses, there is a concentration of symptoms associated with Long COVID instead of dysfunctions presented by each organ separately, in addition to the absence of a control group, thus allowing inferences with dubious outcomes [11].

A comprehensive understanding of patient care needs beyond the acute phase of illness will help in the development of clinical and hospital infrastructure with regard to multispecialty care in the outpatient setting [11] [12]. In view of this, the main aim of this study is to examine the molecular and cellular effects in the acute phase of COVID-19 and the major sequelae developed by individuals who survived the disease enabling advances in the prognosis, treatment, and prevention.

2. The Viral Tropism of SARS-COV-2 in the Host Organism

Viruses, through cell tropism, have the ability to infect different types of tissues or cells in order to carry out their infection mechanisms. Even though the respiratory system is the main target of infection by SARS-CoV-2, it was observed that other organs such as the brain, pancreas, small intestine, heart, and kidneys are also affected [13].

One of the factors that can explain the broad viral tropism is the differential expression of key host proteins involved in the virus-cell interaction. This hypothesis is supported by several studies that, using the RNA-seq methodology, profiled the expression of ACE2 in human organs and showed that the respiratory, gastrointestinal, cardiovascular, urinary, and nervous systems are the most vulnerable [13] [14] [15]. In addition, viral RNA has also been detected in lymph nodes, blood samples, and lymphocytes in the tracheal submucosa of patients, suggesting that the virus may also be transported by lymphocytes in the blood-

stream [16].

Studies have been showing that likewise ACE2 and TMPRSS2, other proteins such as neuropilin-1 (NRP1), CD147, and dipeptidyl peptidase-4 (DPP4), as well as accessory proteases such as cathepsins B and L (CTSL and CTSB) and furin (FURIN) can interact with S protein of virus and mediate the entry of SARS-CoV-2 into host cells [17] [18]. In fact, showed that interaction between CD147 in erythrocytes surface with RBD of Spike protein may induce an adhesive phenotype in the cell membrane and lead to varying degrees of hypoxemia and myocardial damage from abnormal interaction with the vascular endothelium [19].

In the cardiovascular system, ACE2 expression is present, especially in endothelial cells and cardiomyocytes. However, in the latter, SARS-CoV-2 uses the cathepsin B and L proteases in the infection process [20] [21]. Furthermore, studies show that, in patients with heart disease, ACE2 expression is increased during COVID-19 [22].

Into the gastrointestinal system, SARS-CoV-2 infects intestinal epithelial cells, especially in the jejunum and ileum through ACE2, TMPRSS2, and DPP4 cell receptors [23]. Although the tropism in this system is not fully understood, the spread of the virus is wide, and the viral RNA could be detected in esophageal, gastric, duodenal, rectal, and feces biopsies [24].

Another important target for SARS-CoV-2 is the kidneys, where the infection can progress to acute kidney injury [25]. In this organ, ACE2 receptors are mainly in the proximal tubule [26]. Furthermore, virus-like particles were also detected in the renal tubular epithelium and podocytes [27].

Cells of the central nervous system, such as neurons, astrocytes, and oligodendrocytes have high expression of ACE2, CD147, furin, and cathepsin B, and the virus infection in the nervous system can lead to neurodegenerative diseases [21].

3. The Pathophysiology of COVID-19 in Different Organs and Molecules Involved in Infection and Disease Sequelae

The surface protein of SARS-CoV-2 can interact with the ACE2 receptor that is present in several cells. Thus, COVID-19 can affect several organs in the long term, changing the expression patterns of multiple genes associated with the functioning of different systems, such as the respiratory, cardiovascular, gastrointestinal, renal, and nervous systems (**Figure 1**).

3.1. Respiratory System

Airways (nasal mucosa and oropharynx) are the main route of SARS-CoV-2 infection in human organism. The virus through ACE2, TMPRSS2, cathepsin L, and furin present in the host-cell receptors, can infect upper airways, bronchiolar glands, submucosal epithelia, type I and II pneumocytes, alveolar macrophages, and hyaline membranes in the lungs [28]. The infection can be mild to severe

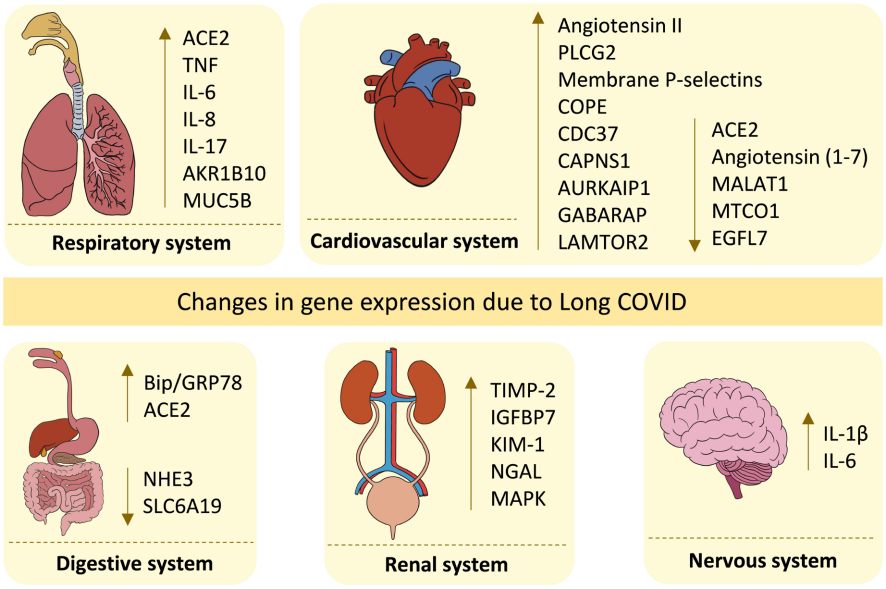

Figure 1. Possible changes in gene expression in different systems of patients with COVID in both acute (initial dysregulation) and convalescent phases (recovery and Long COVID symptoms). In each organ, the genes that can be altered by the disease were mentioned in this review. Up arrows indicate upregulation and down arrows indicate downregulation.

and, in most cases, the disease damage occurs mainly in the lower respiratory tract due to tissue edema, hyaline membranes, and fibrin matrix development, leading to respiratory failure [29]. Moreover, severe disease is triggered to local inflammatory process which can promote apoptosis, vascular leakage, and pro-inflammatory proteins release [28].

From the molecular point of view, in the lungs, the expression of ACE2 is limited mainly to a small fraction of type II alveolar epithelial cells, which act in the defense, and maintenance of alveolar integrity. Thus, is the cellular damage triggered by inflammatory responses, which promotes respiratory impairment. In this inflammatory microenvironment immunological agent, especially cytokines such as IL-1, IL-6, IL-8, IL-17, IL-21, INF-γ, TNF-β, MCP-1, and TGF-β, promotes changes in the lung cells receptors (increase of ACE2), lymphocytes recruitment, and vascular changes. Furthermore, TNF-α and IL-6 can induce upregulation of ACE2 expression and also trigger an increase in ANGII/AT1R axis, exacerbating inflammation [30] [31]. High IL-8 and IL-17 expression in the lungs in severe COVID-19 also promotes higher neutrophil recruitment and NETs release in the respiratory epithelium. The NETosis contributes to the blood clots formation, as evidenced by and Cesta *et al.* (2023) and can lead to breathing difficulties and lung failure [31] [32].

Reinforcing those findings, a study based on transcriptomic data performed by Chabert *et al.* (2022) revealed an increase in the expression of the gene encoding the Aldo-Keto Reductase 1B10 (AKR1B10), a key enzyme involved in the expression of pro-inflammatory cytokines, in lung samples from COVID-19 de-

ceased patients. Moreover, the AKR1B10 sera levels of hospitalized COVID-19 patients were also associated with disease severity and one of the mechanisms that trigger the cytokine storm. The authors still demonstrated that AKR1B10 can be secreted and transferred via extracellular vesicles between different cell types, suggesting that this protein may also contribute to the multi-organ systemic impact of COVID-19 [33].

The MUC5B is one of the main genes associated with mucin production in the respiratory tract and during SARS-CoV-2 infection, that gene is upregulated in the lungs. Due to inflammatory mediators' action (EGFR and IL-1R signaling) and MUC5B upregulation in the bronchial epithelium occurs a mucus accumulation (in a specific lung lobe or segment) with an opaque appearance on imaging exams, such as a chest computed tomography (CT), known as ground-glass opacity [34].

The disease can also evolute to Severe Acute Respiratory Syndrome (SARS) due to the accumulation of mucus and proteins in the pulmonary and alveolar interstitium, resulting in a decrease of lung surface tension and hypoxemia. Aiming the repair, fibroblasts, immunological cells, and inflammatory mediators trigger mechanisms that are able to rebuild the damaged alveolar epithelium promoting the accumulation of collagen and extracellular matrix components [35]. Thus, radiological aspects of lung lesions show the presence of bilateral subpleural ground-glass opacity, indicating lesions and thickening of the alveolar epithelium and indefinite margins predominantly in the lower lobes, as well as the predisposition to develop pulmonary fibrosis at varying levels [36] [37].

The respiratory sequelae after post-discharge are more associated with patients who required hospitalization and invasive mechanical ventilation in the ICU, showing prolonged cough and dyspnea, as well as respiratory impairment and lung structural abnormalities such as fibrosis [38]. However, some patients who developed mild and moderate diseases also present sequelae such as reduced exercise capacity, fatigue, and dyspnea until 12 months after the first manifestations of the disease [39].

Regarding the proposed drug therapies, the use of inhaled corticosteroids can contribute to the recovery from cough and bronchiolitis and an analysis of the administration of prednisolone in thirty symptomatic survivors showed respiratory and tomographic improvements [40] [41].

3.2. Cardiovascular System

Clinical observations of patients affected by COVID-19 have shown that previous cardiovascular illnesses or comorbidities are, beyond risk factors, one of the main causes of mortality. ACE2 is widely expressed in the cardiomyocytes and associated with cytokine storm, respiratory dysfunction, and hypoxemia can trigger damage in the cardiomyocytes and lead to the critical state of the disease [13] [42].

Hypertensive patients usually have increased levels of angiotensin II, which, in turn, causes dysregulation of the RAAS system (renin-angiotensin-aldosterone

system) and an increase in inflammation due to cytokine release. In addition, patients already affected by arterial disease are at high risk of developing acute coronary syndrome, as well as acute cardiac injury, arrhythmia, pericarditis, vasculitis, myocarditis and heart failure during the course of the disease, due to the high myocardial demand and high levels of cytokines [43] [44] [45].

In a physiological context, the renin-angiotensin system, through angiotensin II via the type I angiotensin receptor (ACE-Ang II-AT1R), has the function of promoting vasoconstriction and increasing blood pressure. This process is in dynamic equilibrium with the ACE2-Angiotensin axis (1-7), which induces the opposite effect, protecting the heart. However, in patients affected by COVID-19 occurs the downregulation of ACE2 expression, decreases the angiotensin (1-7) levels and consequent accumulation of angiotensin II. In this scenario, cardioprotective effects are reduced, triggering vasoconstriction, inflammatory reaction, and cardiac damage [46].

According to Xu *et al.* (2023), the differential expression of several genes may be related to cardiovascular and endothelial damage during COVID-19. For example, the downregulation of MALAT1 and MTCO1 genes may be related to the absence of vascular repair, reduced proliferation of cardiomyocytes, production of reactive oxygen species, and an increased risk of atherosclerosis and coronary artery disease. Likewise, the downregulation of the EGFL7 gene, although little discussed, may be related to the development of atherosclerosis, cardiac dysfunction, fibrosis, and severe vascular defects. In addition to these, the upregulation of the PLCG2 gene in cardiomyocytes also may be linked to myocarditis [47].

Patients with severe COVID-19 usually have increased platelets. The increased expression of membrane P-selectins can promote a thrombotic formation and should be considered to a molecular tool for diagnosis [48]. Furthermore, *in silico* studies, also suggested that changes in the expression of genes associated with calcium degranulation, transport activities, and ATP burn such as COPE, CDC37, CAPNS1, AURKAIP1, GABARAP, and LAMTOR2, may be linked to the increase in thrombotic and inflammation risk [49]. In general, the origin of those damage can be structured in tissue hypoxia, electrolyte imbalance, or the high inflammatory state (rich in cytokines such as IL-6, IL-1, and TNF-α) which can alter the ion channels, the ventricular potential and lengthen its depolarization and repolarization time (QT interval) [50] [51].

Serological findings are important tools during acute disease. In relation to cardiac damage promoted by COVID-19, the clinical follow-up of patients through biochemical tests can avoid further sequelae. Lu *et al.* (2022) investigated 5896 patients with COVID-19 and showed that 9% of them developed an acute cardiac injury with altered levels of troponin, lactate dehydrogenase, natriuretic peptides, creatinine, glomerular filtration rate, and liver proteins (SGOT, SGPT) [52]. Another study that analyzed 637 patients hospitalized with COVID-19 showed that 19.2% of them had arrhythmia and were 3 times more likely to die [53]. In addition, patients with COVID-19 have elevated levels of

D-dimer, associated with increased prothrombin time and endothelial activation via tissue factor with consequent platelet activation. This profile leads to the activation of coagulation pathways and fibrin deposition that results in a procoagulant and antifibrinolytic state that increases the risk of inflammatory stress, thrombotic risk, and myocardial infarction [51] [54].

In Long COVID, the most common symptoms are chest pain, arrhythmias, tachycardias, increased risk for the development and persistence of thrombotic events, heart failure, myocardial infarction, and right ventricular dysfunction [55]. A study performed by Zheng *et al.* (2020), showed that of 25 patients who recovered from COVID-19, 44% had abnormalities in the cardiovascular system, 68% had dyslipidemia, and 60% had glucose metabolism disorders [56].

Although molecular treatments such as ACE2 inhibitor drugs, as well as RAAS blockers, have not shown any effects on the virus infection [57]. Drugs that promote the reduction of angiotensin II levels such as ACE inhibitors and angiotensin receptor blockers (ARBs) can control the inflammatory process and cytokines release [58].

3.3. Digestive System

The involvement of the gastrointestinal tract in COVID-19 covers a wide spectrum of symptoms, from the most common, such as nausea and diarrhea, to the most severe, such as small bowel ischemia and gastrointestinal bleeding [59]. Those symptoms can be observed before and during the respiratory manifestations [60].

The study carried out by Balasubramaniam *et al.* (2023) pointed out that diarrhea related to SARS-CoV-2 infection may be associated with infection of enterocytes and stress on the endoplasmic reticulum, increasing the expression of genes responsible for the stress response, such as BiP/GRP78, and the release of DAMPs. Thus occurs the vasoactive intestinal peptide (VIP) expression and release by neuronal cells which can promote the restriction of fluid reabsorption and downregulating of sodium/hydrogen exchangers (NHE3) expression. The fluid accumulation and increased intestinal motility, consequently, stimulate the onset of diarrhea [61].

Regarding viral infection, ischemia is one of the most serious digestive complications and, although the mechanisms that lead to its development are still unclear, studies suggest that it may be related to intense viral infiltration, via ACE2, in enterocytes and endothelial cells, leading to the appearance of inflammation points and thrombosis in small vessels. It is important to emphasize, however, that the occurrence of ischemic injury in the gastrointestinal tract may not be directly related to the patient's thrombotic history [62].

As ACE2 expression is widely distributed throughout the gastrointestinal tract, viral attack and the exacerbated immune response generate an increase in the secretion of pro-inflammatory cytokines with the potential to induce severe tissue damage [15] [63]. The ACE2 receptor, expressed in intestinal cells, in ad-

dition to mediating viral invasion, also regulates the process of amino acid absorption, therefore, changes in its expression influence the establishment of dysbiosis and inflammatory processes [64]. The SLC6A19 gene, which encodes an amino acid transporter that is important for absorption by the small intestine, may have its expression reduced during SARS-CoV-2 infection, affecting gastrointestinal function, and contributing to weight loss and malnutrition in patients with COVID-19 [65]. Damage to the intestinal wall alters the absorption capacity, which, in addition to loss of taste, common in individuals affected by COVID-19, can alter dietary patterns, causing nutritional deficiencies in the short or medium term. In this sense, it has been proposed that nutritional status can influence the recovery of patients with COVID-19 [66].

In the retrospective study carried out by Wei *et al.* (2020), with patients suffering from SARS-CoV-2 pneumonia, for example, it was observed that about a third of them had prolonged infection, in addition to diarrhea with viral particles found in fecal material, even after negative results in samples of the nasopharynx, including the possibility of fecal-oral transmission, due to viral findings in fecal samples from sick individuals, recorded by other research groups [67] [68].

From another perspective, studies show that part of the damage caused to the digestive system is due to the imbalance in the composition of the host microbiota, whose regulation is influenced by the expression of ACE2 [69] [70]. Changes in the intestinal microbiota involve changes in the taxonomic composition, such as species of the genus *Bifidobacterium* and *Lactobacillus*, associated with an increase in microorganisms typical of opportunistic infections, such as *Actinomyces* and *Streptococcus*, and limitation in the diversity of commensal species, leading to dysbiosis [15] [71]. The combined effects of this loss of balance generate systemic and mucosal immune dysregulation with consequent delay in the elimination of SARS-CoV-2 [12] [71].

In COVID-19 occurs bidirectional regulatory interactions between the microbiomes of the respiratory and intestinal tracts, a phenomenon observed in severe respiratory infections, as reviewed by Oliveira *et al.* (2021). In addition, the administration of antibiotics can also cause dysbiosis and potentiate the consequences of the microbiota imbalance caused by the infection [71] [72].

Associated with microbiological investigation the imaging of the abdominal region can also offer a particularly important tool for monitoring the infection. In fact, patients with gastrointestinal symptoms are more prone to chronic liver disease and, therefore, more susceptible to complications from SARS [73] [74]. In the retrospective cross-sectional study carried out by Bhayana *et al.* (2020), the main morphological observations were abnormalities in the intestinal wall, such as thickening of the small intestine, colon, and rectum, being more common in patients admitted to the ICU [73].

Other data show the possible development of irritable bowel syndrome and post-infection dyspepsia especially whether have pre-existing digestive diseases

such as inflammatory bowel disease [75]. The identification of calprotectin and occult blood in fecal samples from patients hospitalized with COVID-19 also are tools to indicate inflammation and tissue damage existence [76] [77]. Although different damage could be observed in the acute phase of the disease, to date no studies published the persistence of gastrointestinal manifestations post-acute phase of COVID-19.

3.4. Renal System

Studies have shown that in the kidneys, SARS-CoV-2 is able to infect several cell types, with podocytes, proximal tubule cells, and $CD31^+$ endothelial cells being the main targets [78]. This infection profile is possibly due to the fact that the aforementioned renal cells express ACE2 and CD147 receptors, in addition to TMPRSS2 and Furin, which play a crucial role in urinary filtration, absorption, and excretion [79]. Cytokine storm, tissue hypoxia, secondary infections, and pharmacological nephrotoxicity also may contribute to the kidney damage [80].

Published studies claim that renal failure is common in patients who have developed the severe phase of COVID-19. An analysis performed by Feng *et al.* (2021) showed that of 17,134 individuals with COVID-19, about 19% had acute kidney injury and 7% required renal replacement therapy [81]. A similar profile was found by Oweis *et al.* (2022) in a cohort conducted in Jordan with 1044 patients, of whom 25.3% developed acute kidney injury and 1.8% were referred for renal replacement therapy [82].

The cardiovascular and renal systems are directly affected by an imbalance in the RAAS. Thus myocardial, endothelial, and coagulation lesions can lead to renal damage ranging from tubular and cortical necrosis to the presence of microinfarcts [83]. In addition, invasive ventilation increases intrathoracic pressure triggering to followed damage such as decreased renal perfusion, low glomerular filtration rate, and increases in the acute kidney injury [84].

In this context, the presence of inflammatory infiltrates of macrophages ($CD68^+$ cells) in the interstitial tube and in regions of tubular necrosis, the accumulation of complement system proteins (5b-9) in the proximal and distal tubules, in addition to the formation of NETs, has promoted damage in renal tissues [85]. As a result, glomerulopathies that collapse into acute necrosis, thromboembolic dysfunction with microvascular obstruction, and renal microinfarctions are observed, among other nephropathies that compromise system function [80] [86].

At the molecular level, serum levels of several biochemical markers are able to predict kidney tissue inflammation, including markers of damage and alteration in function such as TIMP-2 and IGFBP7, damage to proximal and distal tubules such as KIM-1 and NGAL, respectively, and loss of renal function due to the C Cystatin [87] [88]. High levels of creatinine and uric acid, associated with the evaluation of the presence or absence of proteinuria, albumin, and alpha-1-microglobulin also indicate a worse prognosis of the disease, as well as a higher rate of mortality [89]. In addition, Zhang *et al.* (2023), through bioinformatics analy-

sis of RNA-seq and microarray data, showed that the MAPK signaling pathway, the structural pathway of IL-1, and the Toll-like receptor pathway, which are important pathways of systemic pathology and organ inflammation, were dysregulated in COVID-19 [90].

With regard to post-COVID-19, it is already known that the glomerular filtration rate can remain reduced for up to 6 months, regardless of kidney damage during the disease. And it is known that myocarditis can be an effect of acute kidney injury and that the presence of a cardiovascular diagnosis is an obstacle to recovery [91] [92]. Thus, Sinha *et al.* (2022), when monitoring patients about 3 months after hospital discharge, indicated that the progression to chronic kidney disease is high, a condition also showed by Jansen *et al.* (2022) when related to the fibrotic processes promoted by SARS-CoV-2. Those findings and others show that kidney problems developed in COVID-19 go far beyond the symptoms of the acute phase of the disease [93] [94].

In clinical medicine, some drug proposals have shown apparent efficacy, but with adverse effects on the liver and kidneys, as is the case with the antiviral favipiravir [95]. Another nephrotoxic drug is azithromycin, a broad-spectrum antibiotic that is capable of inducing acute interstitial nephritis [96]. Other antiretrovirals, such as ritonavir/lopinavir, also largely unused, culminating in poor renal outcomes. And the application of the retroviral remdesivir, approved for the treatment of COVID-19 by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), is also associated with acute renal failure [97] [98].

3.5. Nervous System

Several mechanisms have been proposed to explain the damage caused by SARS-CoV-2 infection in the nervous system such as the neurotoxicity of the virus, glial changes, hemodynamic changes (coagulopathies, ischemia, and hypoxia) that may involve the incidence of stroke, the severe inflammatory response and/or the combination of all these factors [14] [99] [100] [101]. Among the most commonly described manifestations are demyelinating polyneuropathy, headache, anxiety, fatigue, dysgeusia, anosmia, diffuse myalgia, as well as cerebrovascular disorders, sleep difficulties, depressive symptoms, cognitive deficits, and post-traumatic stress disorder [102] [103] [104] [105].

Neuronal damage in COVID-19 can culminate in functional impairment and behavioral changes, with duration (acute or chronic) and reversibility depending on the degree of nervous system involvement [106]. In addition, environmental stress associated with fear of death, social isolation, and insecurity due to the pandemic also strongly contributed to the triggering of neuropsychiatric diseases [107] [108].

Other symptoms such as loss of smell and memory deficit (promoted by inflammatory mediators such as cytokines and inflammasome) as well as anxiety were also one of the most reported neurological symptoms in the acute phase and remained for months characterizing the psychic face of the Long COVID

[109] [110] [111].

An area of the central nervous system essential for understanding the neuropath physiology of COVID-19 is the dentate gyrus, which is an area of the hippocampus that is involved in many important functions associated with memory, learning, cognition, spatial memory, and essential executive functions [112] [113]. These skills depend on neurogenesis, which consists of the formation of new neurons originating from neural stem cells in the subgranular zone of the dentate gyrus, preventing neurological and psychiatric disorders [114] [115].

Inflammatory processes in these regions have been the main indication of neurological changes presented by patients after the acute phase of COVID-19. It turns out that microglia monitor the brain environment and, when activated, can become neurotoxic, resulting in neuroinflammation, including the production of reactive oxygen species (ROS) and oxidative stress [116]. This disrupts hippocampal neurons, leading to memory problems and neuronal death, which may be related to the effects of SARS-CoV-2 in the brain, where elevated cytokines such as IL-1β and IL-6 have anti-neurogenic effects in the hippocampus, contributing to small brain lesions [117].

In this context, Soung *et al.* (2022) showed that COVID-19 deceased patients exhibit microglial activation and expression of IL-1β and IL-6, especially in the hippocampus and medulla oblongata. Reduced neuroblasts and immature neurons are observed in the dentate gyrus of the hippocampus in humans with COVID-19. Prolonged inflammation, blood-brain barrier disruption, and microglial activation may result in changes in neurotransmission, neurogenesis, and neuronal damage, explaining neuropsychiatric presentations such as deficits in learning, memory, and executive functions in patients with COVID-19 [115].

Long COVID phase is evidenced by cognitive decline marked by difficulty concentrating, low attention, and short-term memory [118].

A cohort that analyzed 1733 COVID-19 survivors in China 6 months after admission showed that a variety of neural symptoms were observed months later or persistently (depression and anxiety 23%, sleep difficulty 26%, fatigue or weakness muscle 63%, smell disorder 11%, and taste difficulty 7%) [119]. Microstructural and volumetric brain changes, caused by neuroinflammation, remyelination, and neurogenesis processes also were detected in recovery patients [103].

4. Final Appointments about Long COVID and Future Perspectives

Understanding the molecular mechanisms behind the sequelae of COVID-19 is critical and may help to develop effective therapies and prevent future complications. For example, the cardiovascular system presents post-COVID symptomatology similar to the respiratory one, including chest pain, arrhythmias, tachycardia, and recurrent palpitations, which are associated with the increase in cardiometabolic demand, promoted during the acute phase of the disease [120] [121]. Cardiovascular damage is severe enough for the establishment of myocar-

dial fibrosis and divisive scars, and this is due to the increase in angiotensin II levels, especially in hypertensive patients, since there is a dysregulation of the renin-angiotensin system directly associated with the promotion of cardiac hypercytokinemia, thus promoting lesions in the cardiac tissue and establishing sequelae [122].

The renal sequelae of post-COVID patients are linked to the events of acute renal failure manifested in the acute phase of the disease, including the reduction in the glomerular filtration rate that extends in most affected patients, months after hospital discharge [13] [123]. As previously mentioned, the hyperinflammation promoted by immune cells (especially neutrophils) and cytokines is the major promoter of all systems disorders and, in the kidneys, associated with some drugs (such as metformin used in the first line in patients with type II diabetes and obesity) can induce glomerular renal dysfunction [124] [125].

The neurological findings mentioned here from fatigue, myalgia, and headache to depression and post-traumatic stress disorders also could be viewed in other coronaviruses. Patients who recovered from SARS-CoV-1 and MERS also presented neuropsychiatric complications such as delirium, depression, anxiety, insomnia, pressured speech, euphoria, and psychosis as well as immunological dysregulation, inflammation, microvascular thrombosis, and iatrogenic effects of drugs used in the clinic (corticosteroids) [126].

Other systems also have common sequelae in the post-COVID-19 clinic, such as the endocrine system, whose individuals have manifested worsening diabetes mellitus, subacute thyroiditis, and bone demineralization. It is also important to highlight the role of SARS-CoV-2 in exocrine pancreatic injury by increasing amylase and serum lipase in up to 17% of patients affected by the disease [121] [127]. In addition, scientific findings demonstrate that patients with SARS-CoV-2 and other coronaviruses had higher plasma glucose levels than patients affected by other pathologies associated with hyperglycemia [127] [128].

The relationship of high levels of biomarkers associated with inflammation such as IL-6, serum ferritin and C-reactive protein, in addition to the parameters of clotting factors such as D-dimer, and the increased levels of mortality in COVID-19 patients with diabetes mellitus, are explained by the more severe pancreatic damage due to the presence of ACE-2 in these cells [129]. COVID-19 may also promote insulin resistance in patients with type II diabetes and obesity, since it induces a serum increase in fetuin A glycoprotein, which induces insulin resistance through the Ras-MEK-ERK, preventing the action of the hormone on the control of hyperglycemia in these individuals [127].

Thromboembolic events are present in the post-COVID-19 sequelae due to the persistent hyperinflammation state [12]. This acute systemic inflammation begins in the infection phase, follows through disease, and can cause disruptions in the coagulation and fibrinolysis cascade, including increased levels of plasminogen activator inhibitor-1 (responsible for the activation of the coagulation cascade and the fibrinolytic reaction). The result of this is low tissue healing and thrombosis since the clots are not properly degraded [130].

The treatment must be chosen from the acute phase of the disease to hospital discharge decreasing possible sequelae and avoiding future admissions. According to Myall *et al.* (2021), early treatment with corticosteroids demonstrated rapid and significant improvement in patients with persistent inflammation after infection by SARS-CoV-2 [41]. Studies also have been showing the importance of physical rehabilitation in fatigue reducing and in shortness of breath and improving conditioning in post-COVID-19 patients. For myalgia control, some experts suggest analgesics and adjuvant physiotherapy [117]. In addition, participation in rehabilitation can improve patients' mental health, reduce depression, and provide a sense of normalcy and control over their recovery [110].

According to Rahmati *et al.* (2023) the main types of activities that are carried out for the clinical rehabilitation of patients with long-term COVID are mainly physical walking training with and without light weights; manual exercises to strengthen palmar strength; respiratory training at rest and in action; vocal and auditory stimulation; psychotherapy and psychiatric follow-up [131].

These data must be analyzed and collected through tests such as: the 6-minute walk test (6MWT), the Barthel index to assess the individual's general activities, the sit-to-stand test (STST), the independent functional measurement (FIM) and handgrip strength to assess the functional capacity of COVID-19 survivors before and after interventions [131] [132].

For the evaluation of lung function, quantification reports should be made, such as: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), lung carbon monoxide diffusion capacity (DLCO) and severity of dyspnea. In addition, parameters are also used to assess the mental health of individuals, through the Anxiety and Depression Scale, Generalized Anxiety Disorder-7, Patient Health Questionnaire, Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale [133].

There is a need for public health surveillance for cases of Long COVID. Ayoubkhani *et al.* (2021) investigating 47,780 individuals who survived the disease showed that about 1/3 of these individuals were readmitted to the hospital sector for various problems and 5875 patients in the group died after hospital discharge. The main complaints related were multiple organ dysfunction, respiratory difficulty, diabetes, and cardiovascular disease, not limited to elderly individuals. In this sense, treatments and clinical protocols chosen for these individuals must be studied with the entire multidisciplinary team, due to the complications are systemic and must be adopted in terms of public health [11] [134].

Thus, a series of actions can direct assistance to the individual affected with Long COVID, such as 1) clinical mapping exams of the current symptomatic status; 2) tracking and referring the individual to the respective specialties within the multi-professional team, according to the symptoms and sequelae presented; 3) clarification of the patient regarding the basic treatment procedures that will be administered in the hospital environment or at his home; and 4) the long-term follow-up of the individual, until his clinical condition evolves posi-

tively or is completely restored [11] [135].

5. Conclusion

Major complaints after SARS-CoV-2 infection with increased rates of multiorgan dysfunction include multiple dysfunctions. Early corticosteroid treatment is effective in patients with persistent inflammation after SARS-CoV-2 infection, and physical rehabilitation is highly recommended to reduce fatigue, shortness of breath and improve fitness in post-COVID-19 patients. In addition to the critical factors related to the sequelae reported so far, there is a need for public health surveillance for these cases, including a more comprehensive analysis of molecular biology tools that can clarify and assist in the prognosis, treatment, and preventive methods for potentially more serious disorders in post-COVID-19 patients.

Acknowledgements

We thank the Fundação de Amparo a Ciência e Tecnologia de Pernambuco (FACEPE) for the financial support through the FACEPE/PPSUS-2020 APQ-0260-2.02/20 research notice; Coordination for the Improvement of Higher Education Personnel (CAPES) under Grant 11/2020 No. 88887.507421/2020-00; CNPq/Productivity 2020 (process n. 308489/2019-5); CNPq/Productivity (process n. 313238/2021-9).

Authors' Contribuitions

Study conception and design (CMM), data acquisition and analysis and interpretation (BRSB, LCOC, GFS, GASS, MRCFL, EGO, ANDS, LSM, LRSL, BFSM, and CMM), manuscript writing (BRSB, LCOC, GFS, GASS, MRCFL, EGO, ANDS, LSM, LRSL, BFSM and CMM). Manuscript Formatting (MCVI), Critical Manuscript Review for Important Intellectual Content (CMM). Administrative, technical or material support (CMM, ACF) and supervision of studies (CMM, ACF). All authors made a significant contribution to this study and approved the final manuscript.

Conflicts of Interest

All authors declare that there is no conflict of interest.

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