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Posted Date: 21 November 2023

doi: 10.20944/preprints202311.1317.v1

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Review

# Persisting Shadows: Unraveling the Impact of Long COVID-19 on Cardiovascular, Nervous, and Respiratory Systems

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**Abstract:** The coronavirus disease 2019 (COVID-19), instigated by the zoonotic Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), rapidly transformed from an outbreak in Wuhan, China, into a widespread global pandemic. A significant post-infection condition, known as 'long- COVID', emerges in a substantial subset of patients, manifesting with a constellation of over 200 reported symptoms that span multiple organ systems. This condition, also known as 'post-acute sequelae of SARS-CoV-2 infection' (PASC), presents a perplexing clinical picture with far-reaching implications, often persisting long after the acute phase. While initial research focused on the immediate pulmonary impact of the virus, the recognition of COVID-19 as a multiorgan disruptor has unveiled a gamut of protracted and severe health issues. This review provides a summary of the primary effects of long COVID on the cardiovascular, nervous, and respiratory systems. It also delves into the mechanisms underlying these impacts and underscores the critical need for a comprehensive understanding of long COVID's pathogenesis.

**Keywords:** SARS-CoV-2; COVID-19; long-COVID; post-COVID; cytokine storm; ACE-2

## 1. Introduction

Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) leads to an acute multisystem illness known as coronavirus disease 2019 (COVID-19) [1]. This infection has resulted in a significant global pandemic with considerable mortality and morbidity[2]. While about 80% of affected individuals experience mild to moderate disease, 5% develop critical illness[3]. The common signs of COVID-19, including shortness of breath, high body temperature, coughing, and tiredness, can lead to serious health issues like lung infection, heart inflammation, and kidney damage[4].

SARS-CoV-2, an airborne zoonotic virus, primarily employs the angiotensin-converting enzyme 2 (ACE2) receptor for cell entry by binding its spike protein to the receptor; however, other receptors might also be involved[5]. ACE2, crucial in COVID-19 pathogenesis, is abundantly found in various tissues, including the lungs, heart, liver, kidneys, and gastrointestinal tract [6]. As a result, COVID-19 often manifests multi-organ damage, leading to conditions like acute myocardial injury, acute kidney injury, and acute respiratory distress syndrome (ARDS)[7,8].

The genome of SARS-CoV-2 is approximately 79% homologous to severe acute respiratory syndrome 1 (SARS-CoV-1) and 50% homologous to the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) genome [9]. As per the findings from the International Committee on Taxonomy of Viruses (ICTV) and the European Center for Disease Control (ECDC), SARS-CoV-2 is classified within the Coronaviridae family, the Orthocoronavirinae subfamily, and lineage B of the genus Coronaviruses[10]. The viral particles have a diameter ranging from 60 to 140 nm[11]. While the predominant shape of these particles is spherical or ellipsoidal, oval shapes have also been reported. The virus possesses an envelope and a helically symmetrical nucleocapsid [12].

The acute phase of COVID-19 generally lasts up to 4 weeks from the onset of the initial infection[13]. However, in a subset of patients, symptoms may continue beyond this period into a

post-acute phase known as 'long COVID'. Interestingly there are instances where patients experience prolonged symptoms for weeks or even months following the initial infection, regardless of its initial severity [14]. This has captured the attention of numerous organizations and research groups, including the World Health Organization (WHO), National Institute for Health and Care Excellence (NICE), National Health Service (NHS), and Centers for Disease Control and Prevention (CDC). This lingering condition has received various names, including 'post-acute sequelae of SARS-CoV-2 infection', 'post-acute COVID-19 syndrome', 'long-COVID-19', 'long-COVID,' 'long haulers COVID-19', 'long haulers,' and 'post-COVID syndrome.' Post SARS-CoV-2 implications pose a public health challenge with potentially severe repercussions[15]. However, definitions vary among authorities, particularly concerning the duration of symptoms that classify as "long-haul." According to CDC (<https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html>, accessed on 15 September 2023), long COVID is a "Wide range of new, returning, or ongoing health problems people can experience four or more weeks after first being infected with the virus that causes COVID-19" However, the WHO defined long COVID as an "Illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection, usually within three months from the onset of COVID-19, with symptoms and effects that last for at least two months, that cannot be explained by an alternative diagnosis" ([https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-\(covid-19\)-post-covid-19-condition](https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-post-covid-19-condition), accessed on 15 September 2023). According to the definition proposed by NHS long COVID is observed when "Symptoms lasting weeks or months after the infection has gone" (<https://www.nhs.uk/conditions/covid-19/long-term-effects-of-covid-19-long-covid/>, assessed on 15 September 2023). On the other hand, two different definitions for long COVID have been proposed by NICE Institute for Health and Care Excellence [16]: i) "On going symptomatic COVID-19 for people who still have symptoms between 4 and 12 weeks after the start of acute symptoms"; and ii) "post-COVID-19 syndrome for people who still have symptoms for more than 12 weeks after the start of acute symptoms".

The variability mentioned above in definitions for long COVID complicates the establishment of a unified criterion for research. To address this, WHO recently defined long COVID-19 (Post COVID-19) as a condition appearing in individuals with a history of suspected or confirmed SARS-CoV-2 infection, typically three months post-infection, with symptoms persisting for at least two months and not explained by an alternative diagnosis (reviewed in [17])

The scientific community has been actively conducting research since the first reported case of COVID-19, caused by the SARS-CoV-2, in early December 2019 in China[18]. With 771.820.937 cases and 6.978.175 deaths reported thus far, evidence suggests that symptoms can persist long after the acute phase of the infection (<https://covid19.who.int>, Accessed on 01 November 2023).

This review aims to summarize the symptoms encountered in the long COVID-19 period in the cardiovascular, nervous, and respiratory systems in particular, as well as to evaluate the possible mechanisms underlying these symptoms and explain them. We searched PubMed (Medline), ScienceDirect, WHO, and CDC websites using keywords related to long-term COVID-19 effects, SARS-CoV-2, and the pandemic. Keywords such as "long COVID-19", "Post COVID-19 syndrome", and "pandemic" were combined with Boolean operators for optimal retrieval. The search spanned 1 January 1, 2020, to 31 August, 2023. Eligible studies were original research articles in English on SARS-CoV-2 and its long-term effects. We included studies of all designs offering insights into the listed categories. We excluded studies on pediatric populations and those with follow-up periods shorter than 25 days post-acute phase.

## 2. Health Implications Related with Long COVID

Numerous biomedical discoveries have been made, with many patients reporting a variety of symptoms affecting multiple organs[19]. The term "long COVID" covers a range of complications, such as cardiovascular, thrombotic, and cerebrovascular diseases[20], type 2 diabetes[20], myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)[21], and dysautonomia, notably postural orthostatic tachycardia syndrome (POTS)[22]. These symptoms can persist for extended periods, and conditions like new-onset ME/CFS and dysautonomia are often considered permanent[23]. A

significant number of long COVID patients have found it challenging to rejoin the workforce[19], leading to a notable contribution to workforce deficits. As of the time of publication of this work, no treatments have been definitively confirmed as effective. Research into immune irregularities in long-term COVID patients, who initially experienced mild COVID-19 symptoms, reveals T cell anomalies such as T cell exhaustion, diminished CD4<sup>+</sup> and CD8<sup>+</sup> effector memory cells, and increased PD1 expression on central memory cells lasting at least 13 months [24]. A surge in cytotoxic T cells has been linked to the gastrointestinal symptoms of long COVID[25]. Further research indicates elevated cytokine levels, especially IL-1 $\beta$ , IL-6, TNF, and IP10[26]. A recent study also highlighted prolonged high levels of CCL11 linked with cognitive issues[27].

In the following paragraphs, we explore the impacts of long-term COVID on various bodily systems, specifically the cardiovascular (CV), nervous, and respiratory systems. Additionally, we strive to elucidate the potential mechanisms through which infection with SARS-CoV-2 can result in persistent symptoms and influence these particular systems.

2.1. Effect of Long COVID on the Cardiovascular System

SARS-CoV-2 infection impacts the CV system during the acute phase[28]; however cardiac complications can persist even after recovery from the acute phase of the infection[28,29]. Given the high prevalence of such complications during this stage, it is crucial to pay attention to the potential long-term cardiac implications of the disease. Emerging evidence, demonstrates a significant burden on the CV system during the long COVID period (reviewed in [30]). Symptoms specific to the CV system involvement of long COVID include palpitations, chest pain, breathlessness, and postural dizziness with or without syncope [31]. Palpitations and chest pain are the most common findings of the long COVID period [32] seemingly healthy individuals may experience dizziness and an increase in heart rate while resting [33].

Interestingly, in 2020, when long COVID was not yet widely recognized, Puntmann and coworkers [34] stressed the importance of ongoing monitoring for the long-term CV impacts of COVID-19. They found that among 100 individuals who had recovered from COVID-19, 78 showed abnormal results in cardiovascular magnetic resonance (CMR) imaging. These abnormalities included elevated myocardial native T1 (found in 73 participants), increased myocardial native T2 (in 60 participants), myocardial late gadolinium enhancement (in 32 participants), and pericardial enhancement (in 22 participants). Furthermore, ongoing myocardial inflammation was noted in 60% of the participants, irrespective of their preexisting health conditions, the severity and progress of the acute phase of their illness, or the time since their initial COVID-19 diagnosis. Subsequent studies, like the one carried out by Huang et al [35] with 26 recovered COVID-19 patients, also found significant cardiac involvement. In this cohort, 58% (15 patients) exhibited abnormal CMR results: 54% (14 patients) showed myocardial edema and 31% (8 patients) had late gadolinium enhancement (LGE). Patients with abnormal CMR had diminished right ventricular function, including lower ejection fraction, cardiac index, and stroke volume relative to body surface area. These findings suggest cardiac issues, including myocardial edema, fibrosis, and right ventricular dysfunction, are prevalent in some COVID-19 recoverees. Table 1 summarizes the main findings of studies focusing on the effects of long COVID on the CV system.

**Table 1.** Examples of studies examining the long-term cardiovascular system symptoms attributable to SARS-CoV-2 infection.

Follow up <sup>1</sup>		Main Findings/Symptoms	Ref
100	71 days	<ul style="list-style-type: none"><li>Cardiovascular issues were detected in 78% of participants</li><li>Ongoing Myocardial Inflammation was detected in 60% of participants</li></ul>	[34]
26	47 days	<ul style="list-style-type: none"><li>58% (15 patients) had abnormal findings on conventional CMR<sup>2</sup> imaging.</li><li>Myocardial edema was detected in 54% (14 patients).</li><li>LGE<sup>3</sup> was observed in 31% (8 patients).</li></ul>	[35]

		<ul style="list-style-type: none"><li>• Patients with positive CMR results had reduced right ventricle function, including lower ejection fraction, cardiac index, and stroke volume/body surface area.</li><li>• Quantitative mapping showed significant increases in global native T1, T2, and extracellular volume in patients with positive CMR results</li></ul>	
384	54 days	<div>In the study population:<ul style="list-style-type: none"><li>• 53% reported persistent breathlessness.</li><li>• 34% continued to experience cough.</li><li>• 69% suffered from ongoing fatigue.</li><li>• 38% of chest radiographs (X-rays) remained abnormal.</li><li>• 9% of the chest radiographs showed deterioration.</li></ul></div>	[36]
148	68 days	<ul style="list-style-type: none"><li>• 54% of the patients had late LGE and/or ischemia</li><li>• Myocarditis-like scar in 26% of patients</li><li>• Myocardial infarction was found in 19% of patients.</li><li>• 66% of patients with ischemic injury h no prior history of coronary disease.</li></ul>	[37]
346	109 days	<ul style="list-style-type: none"><li>•73% of participants reported cardiac symptoms at the time of measurement.</li><li>• Common cardiac symptoms included exertional dyspnea (62%), palpitations (28%), atypical chest pain (27%), and syncope (3%).</li><li>• Symptomatic individuals showed higher heart rates and increased imaging markers or contrast agent accumulation, suggesting cardiac inflammation</li><li>•329 days post-infection: 57% still experienced cardiac symptoms.</li></ul>	[38]
180	≥12 weeks	<div>In the study population:<ul style="list-style-type: none"><li>• 52% reported shortness of breath or fatigue.</li><li>• 34% experienced chest pain or discomfort.</li><li>• 37% had heart palpitations or arrhythmias.</li><li>• Acute pericarditis was diagnosed in 39 patients.</li><li>• Mild-to-moderate pericardial effusion was found in 12 patients.</li><li>• 27 patients had thickened and bright pericardial layers with small effusions (&lt; 5 mm) and possibly pericardial B-lines.</li><li>• Heart palpitations/arrhythmias and autoimmune/allergic disorders were significantly associated with acute pericarditis</li></ul></div>	[39]

<sup>1</sup> Median time between COVID-19 diagnosis and examination of participants post-diagnosis. <sup>2</sup> Cardiac Magnetic Resonance. <sup>2</sup> LGE: Late gadolinium enhancement.

In another study, Mandal et al. [36] analyzed 384 patients 54 days post-hospital discharge from COVID-19, finding significant ongoing symptoms and health issues. Persistent breathlessness was reported by 53%, cough by 34%, and fatigue by 69%. Additionally, 14.6% exhibited signs of depression. Among those discharged with high biomarkers, 30.1% still had elevated d-dimer levels, and 9.5% had high C-reactive protein levels. Chest X-rays remained abnormal in 38% of the patients, with 9% showing worsening conditions.

Kotecha et al. [37] studied 148 severe COVID-19 patients (32% with elevated troponin), undergoing convalescent CMR about 68 days post-hospitalization. Normal LV function was seen in



89%, but 54% had LGE and/or ischemia. Myocarditis-like scar was noted in 26%, infarction/ischemia in 22%, and both in 6%. The majority of myocarditis-like injuries were minor, affecting few myocardial segments without impacting LV function, and 30% showed active myocarditis. Myocardial infarction occurred in 19%, and inducible ischemia in 26% of those tested. Notably, 66% with ischemic injury lacked a prior coronary disease history. There was no widespread myocardial edema or fibrosis. The study highlights myocarditis-like injury and localized inflammation in many post-COVID-19 cases, with some showing ischemic heart disease, often without prior history.

In a subsequent study by Puntmann and coworkers [38], 346 COVID-19 patients without prior cardiac disease, 73% reported cardiac symptoms like dyspnea, palpitations, and chest pain, initially assessed at a median of 109 days after infection. Symptomatic patients exhibited higher heart rates and signs of cardiac inflammation, though severe heart disease or elevated cardiac biomarkers were rare. At a follow-up approximately 329 days post-infection, over half (57%) still experienced cardiac symptoms, with persistent symptoms more common in females and those with initial myocardial involvement. This suggests that ongoing cardiac inflammation may contribute to long-term cardiac issues in previously healthy individuals with mild COVID-19.

In a retrospective study by Dini et al. [39], 180 COVID-19 patients, exhibiting persistent or new symptoms  $\geq 12$  weeks post-negative SARS-CoV-2 test, were examined for potential heart involvement. Following a thorough physical examination, patients with suspected heart issues underwent comprehensive cardiovascular evaluations, including echocardiography as needed. Among them, 52% reported shortness of breath or fatigue, 34% had chest pain or discomfort, and 37% experienced heart palpitations or arrhythmias. Acute pericarditis was diagnosed in 22% (39 patients), with mild-to-moderate pericardial effusion in some and thickened pericardial layers with small effusions in others. The study found a significant association between heart palpitations/arrhythmias, autoimmune or allergic disorders, and acute pericarditis. It also noted a less likely hospitalization during the initial COVID-19 infection as a borderline contributing factor. The findings highlight a high prevalence of acute pericarditis in long COVID-19 patients, with specific symptoms and conditions linked to increased risk of pericardial disease.

Although the exact pathophysiological connection between long COVID-19 and CV system issues remains inconclusive, conditions like myocarditis and pericarditis may play a role. The aforementioned studies have uncovered a surprisingly high frequency of imaging abnormalities, suggesting widespread myocardial damage and inflammation in these patients. This finding is crucial for comprehending and managing the cardiac symptoms that persist in the extended recovery phase of COVID-19 [33].

The myocardium maintains a critical balance between the classical and non-classical pathways of the renin-angiotensin-aldosterone system (RAAS). An upsurge in the activity of the classical RAAS pathway, coupled with a suppression of the non-classical pathway, is correlated with adverse cardiovascular outcomes [40]. The enzyme ACE2 plays a crucial role in cardiac physiology and pathology. Specifically, the binding of SARS-CoV-2 to the ACE2 receptors on myocardial and endothelial cells results in diminished ACE2 activity, thereby impairing the conversion of angiotensin II (Ang II) to angiotensin-(1-7) [Ang 1-7] [40]. This reduction in ACE2-mediated conversion exacerbates the effects of the classical RAAS pathway, which are mediated by Ang II, leading to deleterious cardiovascular effects[41].

The heightened activity of Ang II characteristic of the classical RAAS pathway dominance is associated with a decrease in collagenase activity within the cardiac tissue. This enzyme reduction can contribute to pathological remodeling of both atrial and ventricular myocardium, potentially resulting in detrimental structural and functional changes to the heart [42].

Enhanced binding of angiotensin II (Ang II) to the Ang II Type 1 Receptor (AT1R) initiates a signaling cascade that leads to phosphorylation and increased catalytic activity of 'a Disintegrin and Metalloproteinase 17' (ADAM-17). Activation of ADAM-17 promotes the shedding of ACE2 from the cell surface, further decreasing Ang II clearance. The result is an amplification of Ang II-induced inflammatory responses, creating a self-perpetuating cycle of inflammation [42]. Moreover, the

reduction of ACE2 activity can contribute to myocardial fibrosis, potentially leading to symptoms such as fatigue and dyspnea, characteristic of post-acute sequelae of SARS-CoV-2 infection[19].

Myocardial injury in COVID-19 may result from indirect effects mediated by the systemic inflammatory response[43], primarily through the "cytokine storm" phenomenon [44]. In the context of a SARS-CoV-2 infection, cytokine storms can activate bone marrow-derived endothelial cells, resulting in pericardial inflammation[45]. The adverse inotropic effects of pro-inflammatory cytokines can impair cardiac contractility. Persistent activation of inflammatory signaling, mainly via tumor necrosis factor-alpha (TNFα) and interleukin-1 beta (IL-1β), can lead to widespread cardiomyocyte apoptosis and subsequent abnormal left ventricular remodeling, predisposing to acute heart failure. Furthermore, cytokine storms stimulate monocytes/macrophages to release matrix metalloproteinases, accelerating the growth and rupture of atherosclerotic plaques, promoting the release of procoagulant factors, and causing hemodynamic changes, thus elevating the risk of Acute Myocardial Infarction (AMI) [46].

Cytokine storms are also linked with lymphopenia, characterized by reduced lymphocyte counts[47]—the inflammatory response results in lymphocyte depletion, impairing the body's ability to fight the SARS-CoV-2 infection. Consequently, cytokine production is deregulated, leading to damage to healthy cells, initially in the lungs and potentially extending to other organs, including the heart[48].

2.2. Effect of Long COVID on the Nervous System

Individuals with long COVID can exhibit a broad spectrum of symptoms, including persistent neuropsychiatric issues that may arise or persist for months following the initial infection [19,49,50]. Recognized as a condition affecting multiple organs, long-term COVID-19 definitively involves both the Central Nervous System (CNS) and Peripheral Nervous System (PNS), contributing to the enduring nature of the disease[51,52].Approximately one-third of individuals who test positive for SARS-CoV-2 experience neurological and neuropsychiatric symptoms early in the course of the disease, and these symptoms can persist long after the acute infection has resolved. Commonly reported symptoms include anosmia (loss of smell), ageusia or dysgeusia (altered taste), headache, fatigue, cognitive impairment ('mental fog'), and memory loss, enduring for weeks or even months[53,54]. Other observed issues include impaired concentration, sensory disturbances, and depression[55]. Numerous studies conducted globally have consistently reported fatigue as the most frequent and debilitating symptom of long COVID-19, independent of the disease's initial severity or the occurrence of respiratory distress[56,57]. Moreover, SARS-CoV-2 infection can precipitate inflammatory neurological syndromes, such as encephalitis and acute disseminated encephalomyelitis, along with ischemic and hemorrhagic strokes [58]. Table 2 summarizes the main findings of studies focusing on the effects of long COVID on the central nervous system.

**Table 2.** Examples of studies examining the long-term symptoms of SARS-CoV-2 infection in the nervous system.

n	Follow up <sup>1</sup>	Main Findings/Symptoms	Ref
1276	6months-1 Year	<ul style="list-style-type: none"><li>• Overall sequelae symptoms decreased from 68% at 6 months to 49% at 12 months.</li><li>• Incidence of dyspnoea increased slightly from 26% to 30% between the 6-month and 12-month visits.</li><li>• Anxiety or depression increased from 23% at 6 months to 26% at 12 months. [52]</li><li>• No significant change was observed in the 6-minute walk distance between the two visits.</li><li>• 88% of previously employed patients returned to their original work by 12 months.</li></ul>	

		<ul style="list-style-type: none"> <li>• Women had higher odds than men for experiencing fatigue or muscle weakness, anxiety or depression, and diffusion impairment (related to lung function).</li> <li>• At 12 months, participants had more mobility issues, pain, discomfort, and anxiety or depression compared to controls, and exhibited more prevalent symptoms.</li> </ul>	
2433	1 year	<ul style="list-style-type: none"> <li>• Common symptoms included fatigue, sweating, chest tightness, anxiety, and myalgia.</li> <li>• Higher risk of fatigue was associated with older age, female sex, and severe disease during hospital stay.</li> <li>• Older age and severe disease increased the likelihood of having at least three symptoms.</li> <li>• Median CAT (COPD Assessment Test) score was 2, with 6.6% (161 patients) having a score of at least 10.</li> <li>• Severe disease and coexisting cerebrovascular diseases were independent risk factors for a CAT score of at least 10.</li> </ul>	[59]
165	6 months	<ul style="list-style-type: none"> <li>• Patients experienced a range of symptoms: <ul style="list-style-type: none"> <li>• Fatigue was reported by 34%.</li> <li>• Memory or attention issues by 31%.</li> <li>• Sleep disorders by 30%.</li> </ul> </li> <li>• 40% of patients showed neurological abnormalities, including: <ul style="list-style-type: none"> <li>• Hyposmia (loss of smell) in 18.0%.</li> <li>• Cognitive deficits in 17.5%.</li> <li>• Postural tremor in 13.8%.</li> <li>• Subtle motor or sensory deficits in 7.6%.</li> </ul> </li> <li>• Factors such as older age, pre-existing comorbidities, and the severity of COVID-19 were independent predictors of neurological issues.</li> <li>• Pre-existing vulnerabilities and the severity of SARS-CoV-2 infection influence the prevalence and severity of long-term neurological manifestations</li> </ul>	[60]
120	110 Days	<ul style="list-style-type: none"> <li>• Persistent symptoms among the participants included: <ul style="list-style-type: none"> <li>• Fatigue in 55%.</li> <li>• Dyspnea in 42%.</li> <li>• Memory loss in 34%.</li> </ul> </li> <li>• Concentration and sleep disorders in 28% and 30.8%, respectively.</li> <li>• No significant differences in symptoms were found between patients treated in general wards and those in ICU<sup>2</sup>.</li> <li>• Health-related quality of life aspects like mobility, self-care, pain, anxiety or depression, and usual activities were affected in both groups, with a slight difference in pain in the ICU group.</li> </ul>	[54]
100 (32 in ICU,	48 Days	<ul style="list-style-type: none"> <li>• New, illness-related fatigue was reported by 72% of participants in the ICU group and 60.3% in the ward group.</li> </ul>	[61]



62 in hospita l ward)	<ul style="list-style-type: none"><li>Breathlessness was the second most common symptom, vis., 65.6% in the ICU group and 42.6% in the ward group.</li><li>Psychological distress: 46.9% in the ICU group and 23.5% in the ward group.</li><li>A clinically significant drop in EQ5D (a measure of health-related quality of life) was observed in 68.8% of the ICU group and 45.6% of the ward group.</li></ul>
236.379 6 Months	<ul style="list-style-type: none"><li>Within 6 months post-diagnosis, 33.62% had a neurological or psychiatric diagnosis while 12.84% received their first such diagnosis.</li><li>For patients admitted to Intensive Therapy Units (ITUs): 46.42% received a neurological or psychiatric diagnosis and 25.79% had their first such diagnosis.</li><li>Specific incidence rates in the whole COVID-19 cohort included: Intracranial hemorrhage: 0.56%; Ischemic stroke: 2.10%; Parkinsonism: 0.11%; Dementia: 0.67%; anxiety disorder: 17.39%; Psychotic disorder: [62] 1.40%.</li><li>In the ITU group, the above incidences were higher: Intracranial hemorrhage: 2.66%; Ischemic stroke: 6.92%; Parkinsonism: 0.26%; Dementia: 1.74%; Anxiety disorder: 19.15%; Psychotic disorder: 2.77%.</li><li>Neurological and psychiatric diagnoses were more common in COVID-19 patients than those with influenza or other respiratory tract infections.</li></ul>

<sup>1</sup> Median time between COVID-19 diagnosis and examination of participants post-diagnosis. <sup>2</sup> ICU: Intensive care Unit.

SARS-CoV-2 has brain tropism and the neurological dysfunctions that have been reported may be due to the Renin – Angiotensin System (RAS) damage of the nervous system. The imbalance of the two aspects of RAS: (1) ACE/Ang II/AT1R, and (2) ACE2/Ang-(1-7)/Angiotensin II Type 2 Receptor (AT2R) in the brain leads to neuroinflammation, neurotoxicity, and Blood-Brain Barrier (BBB) disruption among other things. AT1R, among others, causes inflammation as well as oxidative stress[63]. AT2R has an essential role in the neuraxon regeneration, i.e. it protects the brain by conducting to neuronal survival and in the case of SARS-CoV2 infection it protects one against the deleterious effects of AT1R along with MasR[64].

Various post COVID-19 effects, such as hyposmia/anosmia and memory/cognitive impairment, have been attributed to hypometabolism in different areas of the brain. For example, hypometabolism of the brainstem is associated with hyposmia/anosmia, while hypometabolism of the cerebellum or frontal cortex is linked to memory/cognitive impairment. The Positron Emission Tomography (PET) scans of long COVID patients who express persistent complaints at least three weeks after the onset of their acute infection symptoms showed hypometabolism in their bilateral rectal/orbital helix (containing the olfactory helix), in the right temporal lobe (amygdala and hippocampus extending into the right thalamus), in the bilateral brainstem bridge/myelin and in the bilateral cerebellum. These findings could be indicating the involvement of the ACE2 receptor in the neurotropism of SARS-CoV-2, particularly in the olfactory bulb. This is likely due to the route of dissemination from the nose to the olfactory bulb, where the ACE2 receptor has a strong presence, it has been hypothesized that the ACE2 receptor is the cause of several coronaviruses[65].

As aforementioned cytokine storm, which is a systemic hyperinflammatory state characteristic of the acute phase of COVID-19, not only activates neuroglial cells but also increases the risk of neurological complications post-infection[66]. Various viruses, including SARS-CoV-2, can infiltrate

the CNS through hematogenous routes, triggering immune-induced neurological disorders [67]. SARS-CoV-2 has neurotropic properties; during severe infections, it can infect brain-resident cells such as macrophages, microglia, and astrocytes. These cells, when infected, contribute to a proinflammatory state within the CNS[68].

The cytokine storm can also induce cerebral perfusion anomalies, compromise the integrity of the blood-brain barrier (BBB), disrupt astrocytic functions essential for synaptogenesis, and cause neurotransmitter imbalances [69]. This cascade of events can dysregulate neurogenesis and disrupt the normal functioning of neurons, oligodendrocytes, and neuroglial cells[70]. Consequently, disturbances in neuronal plasticity, synaptic function, myelination, and BBB maintenance may lead to cognitive deficits and an array of long-term neuropsychiatric symptoms associated with COVID-19 [71]. Elevated pro-inflammatory cytokine levels have been implicated in causing confusion and altered consciousness [72], and the excessive release of cytokines and chemokines can also result in brain damage through microglial activation[73]. Additionally, an imbalance between TH17 cells and regulatory T cells (Tregs) has been linked to learning and sleep disturbances[74].

2.3. *Effect of Long COVID on the Respiratory system*

The respiratory system is notably the most commonly affected by SARS-CoV-2. However, respiratory symptoms may persist beyond the acute phase of infection into what is known as the 'long COVID-19' phase, even after patients have ostensibly recovered. Various studies have documented abnormalities in pulmonary function tests (PFTs) and chest CT images persisting for months following hospital discharge. Dyspnea and cough have been the most frequently reported persistent respiratory symptoms [75-77]. Table 3 summarizes the main findings of studies focusing on the effects of long COVID on the respiratory system.

**Table 3.** Examples of studies examining the long-term respiratory system symptoms attributable to SARS-CoV-2 infection.

n	Follow up <sup>1</sup>	Main Findings/Symptoms	Ref
478	4 months	<ul style="list-style-type: none"><li>• 16.3% (78 patients) reported new-onset dyspnea</li><li>• 4.8% (23 patients) experienced new-onset cough.</li><li>• Patients with new-onset dyspnea:<ul style="list-style-type: none"><li>• Were younger on average (56.1 years) compared to those without dyspnea (61.9 years).</li><li>• Had more severe COVID-19, with 56.4% requiring ICU<sup>2</sup> admission compared to 24.5% in the non-dyspnea group.</li><li>• Had a higher incidence of pulmonary embolism (18.0% vs 6.8%).</li></ul></li><li>• Among patients reassessed at ambulatory care 19.3% had fibrotic lung lesions, with 97% showing lesions covering less than 25% of the lung.</li><li>• Patients with fibrotic lesions:<ul style="list-style-type: none"><li>• Were older on average (61 years) compared to those without lesions (56 years).</li><li>• More frequently required ICU management (87.9% vs 47.4%).</li><li>• Had lower total lung capacity and diffusing capacity of the lung for carbon monoxide (D LCO).</li></ul></li><li>• A combination of new-onset dyspnea, fibrotic lesions, and D LCO below 70% predicted was observed in 8 out of 478 patients.</li></ul>	[75]
76	3 months	<ul style="list-style-type: none"><li>• Common included fever, sputum production, fatigue, diarrhea, dyspnea, cough, chest tightness on exertion, and palpitations.</li></ul>	[78]

		<ul style="list-style-type: none"> <li>• Serum troponin-I levels during acute illness were highly correlated with post-discharge fatigue.</li> <li>• Lymphopenia was correlated with post-discharge symptoms of chest tightness and palpitations on exertion.</li> <li>• Lung function tests like FEV1, FVC, FEV1/FVC, total lung capacity, and diffusion capacity were mostly normal (&gt;80% predicted).</li> <li>• Lung HRCT scans returned to normal in 82% of patients. However, 42% of participants exhibited mild pulmonary function abnormalities 3 months post-discharge.</li> </ul>	
200	42 days	<ul style="list-style-type: none"> <li>• The most frequent initial symptom was dyspnea (59.5%), followed by weakness (55.5%), myalgia (53.5%), and shivering (51.5%).</li> <li>• Six weeks post-discharge: <ul style="list-style-type: none"> <li>• None of the patients were readmitted.</li> <li>• 42% (94 patients) were symptom-free.</li> <li>• The most common lingering symptom was fatigue (19.5%), followed by dyspnea (18.5%), weakness (18%), and activity intolerance (14.5%).</li> </ul> </li> </ul>	[77]
119	61 days	<ul style="list-style-type: none"> <li>• 87% of patients showed radiographic resolution of pulmonary infiltrates.</li> <li>• 44% had modified Medical Research Council Dyspnea scale grades above their pre-COVID-19 baseline.</li> <li>• Persistent symptoms included: <ul style="list-style-type: none"> <li>• Fatigue in 68%.</li> <li>• Sleep disturbances in 57%.</li> <li>• Breathlessness in 32%.</li> </ul> </li> <li>• 38% had a slow 4-Meter Gait Speed (4MGS) of less than 0.8 meters per second.</li> <li>• 35% showed a desaturation of &gt; 4% during the Sit-to-Stand test.</li> <li>• Out of 56 thoracic computed tomography scans, 75% revealed COVID-19-related interstitial and/or airways disease.</li> </ul>	[79]
41	7 months	<ul style="list-style-type: none"> <li>• Common CT patterns of abnormalities included: <ul style="list-style-type: none"> <li>• Parenchymal band in 41%.</li> <li>• Interlobular septal thickening in 32%.</li> <li>• Traction bronchiectasis in 29%.</li> </ul> </li> <li>• 61% of patients showed complete radiological resolution.</li> <li>• 29% of patients developed pulmonary fibrosis.</li> <li>• Oxygen consumption and metabolic equations were decreased, and ventilatory equivalent for CO<sub>2</sub> was increased in the fibrosis group.</li> <li>• Older patients with severe conditions are more prone to fibrosis, potentially leading to cardiopulmonary insufficiency.</li> </ul>	[80]
59	30 days	<ul style="list-style-type: none"> <li>• 89.8% (53/59) showed a typical transition from early to advanced and then to dissipating phases of the disease.</li> <li>• 39% (23/59) developed fibrosis (group A), while 61% (36/59) did not show definite fibrosis (group B).</li> </ul>	[81]

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- Comparisons between the two groups showed:
    - Group A patients were older (mean age 45.4 vs. 33.8 years).
    - They had longer Length of Stay in the hospital (19.1 vs. 15.0 days).
    - Higher rate of ICU admission (21.7% vs. 5.6%).
  - Pulmonary fibrosis can develop early post-hospital discharge in COVID-19 patients.
  - Older patients with severe illness are more prone to developing fibrosis, as indicated by thin-section CT results.
- 

<sup>1</sup> Median time between COVID-19 diagnosis and examination of participants post-diagnosis. <sup>2</sup> ICU: Intensive Care Unit.

Schwensen et al.[82] suggested that pulmonary fibrosis (PF) may be a long-term complication in patients who have experienced severe COVID-19. They reported a case involving an 80-year-old patient with no prior history of lung disease whose lung CT scan was normal two months prior to SARS-CoV-2 infection. However, a high-resolution CT scan on day 39 post-infection revealed bilateral consolidations, septal thickening, traction bronchiectasis, and infiltrative and parenchymal changes indicative of extensive pulmonary fibrosis. The comparative analysis of CT scans demonstrated the development of significant fibrosis in lungs that were previously healthy. Consequently, the study highlights that acute respiratory distress syndrome (ARDS), which was reported in up to 42% of hospitalized COVID-19 patients, could be a contributing factor to the development of pulmonary fibrosis.

It has been previously demonstrated that ACE2 is linked to acute lung injury, and one proposed mechanism as far as fibrosis development resulting from the previous SARS pandemic is the direct stimulation of the Transforming Growth Factor- $\beta$  (TGF- $\beta$ ) by the nucleocapsid protein of SARS-CoV-1 and since the nucleocapsid core of SARS-CoV-2 is almost 90% similar to that of SARS-CoV-1 it may be valid[83]. The downregulation of ACE which further regulates Angiotensin II may lead to the stimulation of TGF- $\beta$ . In addition to TGF- $\beta$ , the production of advantageous factors such as Platelet Derived Growth Factor (PDGF) and Vascular Endothelial Growth Factor (VEGF) is also found, resulting in the activation of fibroblasts which are the activated macrophages and neutrophils that release pro-fibrotic mediators that promote the accumulation of myofibroblasts by stimulating collagen production[84].

Pulmonary myofibroblasts can arise from various progenitors, and they typically undergo apoptosis, concluding the healing process[85]. Following their differentiation from fibroblasts, myofibroblasts stimulate collagen synthesis. However, during fibrosis, the normal cessation of extracellular matrix (ECM) production is disrupted, and increased tissue stiffness exacerbates cell injury, leading to further myofibroblast activation[86]. This creates a self-sustaining loop of activation, resulting in irreversible fibrotic changes. These cells organize into fibrotic foci within the lung tissue[87]. Growth factors, particularly those targeting tyrosine kinase pathways, persistently stimulate the formation and development of these fibrotic areas, which may regress naturally or progress to chronic pulmonary fibrosis due to excessive collagen buildup[39].

During a SARS-CoV-2 infection, the virus targets respiratory epithelial cells, triggering local innate immune responses that include the release of inflammatory cytokines and chemokines. These inflammatory mediators recruit additional immune cells such as monocytes, macrophages, neutrophils, dendritic cells (DCs), and natural killer (NK) cells, and activate adaptive immune responses involving CD4+ and CD8+ T cells. The continued presence of inflammatory cytokines like IL-2, IFN- $\gamma$ , and TNF- $\alpha$  promotes myelination and urgent granulation tissue formation, aggravating lung injury and epithelial damage [88]. These cytokines increase lung capillary permeability, leading to the development of diffuse bilateral ground-glass opacities, hypoxemia, and ultimately, long-term fibrotic alterations [89]. The cytokine storm induced by SARS-CoV-2 infection can result in severe respiratory complications such as ARDS. Lung autopsies from COVID-19 fatalities have shown

significant macrophage infiltration in the bronchial mucosa, confirming the extent of the inflammatory response [90].

### 3. Potential Mechanisms Resulting in Long COVID-19

The long-term COVID-19 syndrome is still poorly understood by the scientific community, although it affects a relatively large proportion of acute COVID-19 survivors. This work highlights the impact of long-term COVID-19 on the cardiac, nervous, and respiratory systems. Consequently, the pathophysiological mechanisms proposed for persistent symptoms involve:

- i) **Direct Damage of the organs/system via the ACE2 receptor:** ACE2 has a pivotal role in developing cardiac, brain and pulmonary complications as already mentioned[63,84,91]. The Renin - Angiotensin - Aldosterone System (RAAS) is a signaling pathway that acts as a homeostatic regulator of the vascular function. The Ang II depending on the receptor type can have different effects, the classic effects (increased oxidative stress, inflammation, fibrosis and vasoconstriction, occur) and the opposite effects[92]. The ACE2 is a homologue of the ACE[93] and has an important role in the RAAS. ACE2 regulates the action of ACE by decreasing the amount of Ang II and increasing the amount of Ang (1-7). Furthermore, the ACE2 beyond participating in the RASS system, is the gateway for the entry of SARS-CoV-2 [47]. The virus competes with Ang II, and its binding blocks the ACE2 activity. This results in a decrease of the enzyme activity at the membrane, resulting in an imbalance of ACE/ACE2 and, consequently of the RASS. This imbalance will lead to an increase in the abnormal activation of the ACE/Ang II/AT1 receptor axis and thus an increase in the Ang II vasoconstriction and a decrease in the Ang vasodilation (1-7) [94].
- ii) **Indirect damage through the immune system:** Myocardial injury in COVID-19 can occur indirectly through an overactive inflammatory response, often referred to as a 'cytokine storm' [43,44]. This hyperinflammatory state poses a significant risk not only to the cardiovascular system but also to the brain and respiratory tissues [88]. Typically, COVID-19 patients exhibit an imbalanced immune profile: an overzealous innate immune response coupled with a diminished adaptive immune response. This manifests as a reduction in various immune cells—lymphocytes, cytotoxic and helper T cells, B cells, and Natural Killer (NK) cells—particularly in severe cases [95]. The cytokine storm triggered by SARS-CoV-2 infection results in the rampant release of proinflammatory cytokines, creating a disequilibrium between proinflammatory and anti-inflammatory processes [89,96,97]. Elevated levels of interleukin-6 (IL-6) during the acute phase have prompted investigations into its role in long-term COVID-19 sequelae[98-100], suggesting that persistent inflammation could underlie the pathophysiology of Long COVID. Further research is essential to elucidate these mechanisms and identify effective treatments to improve the long-term outlook for patients.
- iii) **Therapeutic implications:** Antiretroviral therapies, including azithromycin, and tocilizumab have been associated with electrophysiological alterations and potential interactions with cardiovascular drugs, warranting cautious use and monitoring[44] . Concurrently, the role of RAAS inhibitors in modifying ACE2 levels is under scrutiny, given their potential dual impact on the disease process[101]. Moreover, severe COVID-19 cases requiring prolonged mechanical ventilation can suffer from heightened intrapulmonary pressure, leading to or exacerbating pulmonary fibrosis[102]. Additionally, the high concentrations of oxygen used to treat critically ill patients can generate free radicals, damaging pulmonary epithelium and contributing to oxidative stress. This stress not only perpetuates the inflammatory state but also may activate fibrogenic pathways, further complicating recovery[103].
- iv) **Sociopsychological factors:** The pervasive impact of COVID-19 extends beyond the physical to the psychological, with social isolation, the stress of a novel and potentially fatal virus, and the anxiety surrounding transmission and stigma all contributing to long-term psychiatric conditions. Post-acute sequelae may include PTSD, depression, anxiety, and obsessive-compulsive symptoms[52,104]. The enforced solitude, disruption of normal work routines, and financial strains—compounded by the overarching threat of a global health emergency—can



engender loneliness, anxiety, and significant behavioral shifts [105,106]. Consequently, the occurrence of anxiety disorders, depressive states, and cognitive deficits is thought to be multifaceted in origin, encompassing a spectrum of physical, functional, and sociopsychological contributors [62].

### 3.1. Risk factors Contributing in the Development of Long COVID

Risk factors for severe COVID-19, leading to hospital admission and increased mortality, include advanced age, male sex, non-white ethnicity, disability, and existing comorbidities like obesity, cardiovascular disease, respiratory conditions, and hypertension [107,108]. Conversely, determinants for long COVID-19 are not as well established.

Emerging studies indicate that a severe initial phase of COVID-19 may predispose individuals to long-term sequelae [109]. This correlation is supported by the study of Sudre et al. [110], who observed that experiencing over five symptoms in the first week of illness was associated with prolonged COVID-19. They reported a tripling in the incidence of long COVID-19 among those with a severe initial infection. This association is corroborated by findings from Plywaczewska-Jakubowska and coworkers [111], who noted that long COVID-19 was significantly more prevalent in patients who experienced severe acute symptoms.

However, certain risk factors for acute COVID-19 do not necessarily predispose individuals to long COVID-19. Pazukhina et al. [112] conducted a prospective cohort study and noted a distinction between sexes: while men were more prone to acute COVID-19, women were more likely to suffer from long-term symptoms, contradicting earlier acute phase observations. They found a doubled risk of prolonged symptoms in women at both 6 and 12 months post-infection, aligning with previous research[52]. The sustained elevation of the inflammatory marker IL-6 in women and the heightened activity of T cells—attributable to the double presence of the X chromosome, which contains numerous immune-related genes—may contribute to this disparity[113,114]. Additional factors, such as stress, poor sleep quality, and depression, may exacerbate long COVID-19 in women[115].

Age is another key risk factor. Certain age demographics, notably individuals aged 35-49 years (26.8%), 50-69 years (26.1%), and 70 years or older (18%), are more susceptible to enduring symptoms of SARS-CoV-2 infection[116].

Chronic health conditions also influence long COVID-19 susceptibility. Pre-existing asthma, for instance, has been strongly associated with persistent COVID-19 symptoms[61,110]. Additionally, chronic inflammation and obesity-related immunometabolic disturbances may not only exacerbate the acute phase but also contribute to long COVID-19 syndrome[117]. Debski et al.[118] reported a higher BMI as a risk factor for post-COVID-19 syndrome. Interestingly, ethnicity seems to differ in its impact on long COVID-19, with non-white ethnic minority groups showing a lower risk of developing prolonged symptoms[119,120].

## 4. Potential Therapies for long COVID-19 Syndrome

Several guidelines have been developed that focus on the treatment and management of long COVID-19. For example, NICE, has proposed comprehensive assessment, investigation, and management approaches (<https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-51035515742>; accessed on 15 October 2023). Similarly, the NIH has released treatment guidelines for COVID-19, but these offer limited guidance for managing long-term COVID-19 effects (<https://www.covid19treatmentguidelines.nih.gov/>, accessed on 15 October 2023).

While a significant portion of research has appropriately focused on the acute phase of COVID-19, there is a growing recognition of the need to address long-term effects of the disease. In this context, drug repurposing is emerging as a critical area of investigation. Antihistamines are under consideration following cellular studies indicating that histamine-1 receptor antagonists might inhibit SARS-CoV-2 entry into cells expressing the ACE2 receptor, but their efficacy for treating long COVID-19 remains to be established[24,121].

Monoclonal antibodies like Leronlimab, which is used for HIV and has shown to reduce viral plasma levels in acute COVID-19 patients, are being investigated for their potential in mitigating long-lasting COVID-19 symptoms[122]. Tocilizumab, which blocks interleukin-6 receptors, was tested in a small clinical trial for acute COVID-19, and research into its long-term effects is ongoing. Melatonin, noted for its antioxidant properties, is also being considered for the treatment of long-term COVID-19 effects (reviewed in [123]).

For the cardiovascular manifestations of long COVID-19, NICE guidelines suggest beta-blockers as treatment options for conditions such as angina, cardiac arrhythmias, and acute coronary syndromes[124]. Sulodexide has been found to reduce symptom severity in patients with endothelial dysfunction[125]. The effectiveness of Cognitive Behavioral Therapy (CBT) has been brought into question due to reported adverse effects[126]. The use of intravenous vitamin C to alleviate fatigue in long COVID-19 patients has been recently reviewed[127].

The persistent neurological complications post-COVID-19 have made Biofeedback (BFB) therapy an area of interest, with potential benefits for headaches, seizures, and insomnia and Neurofeedback (NFB) has been documented for its long-term effectiveness [128]. For long-term neurological symptoms, glucocorticoids may be beneficial [129], and medications like tryptans and indomethacin could address prolonged symptoms such as headaches [130,131].

Pulmonary symptoms often persist post-acute COVID-19. Critical Care guidelines recommend chest imaging for early detection of pulmonary impairment and the use of corticosteroids to improve function[132]. Hyperpolarized MRI has been cited for its ability to detect gas exchange abnormalities[133]. According to Mayo Clinic recommendations, managing factors that worsen dyspnea, such as smoking cessation and avoiding pollutants, is crucial[134]. Treatment for pulmonary fibrosis should follow idiopathic pulmonary fibrosis guidelines and anti-fibrotic therapies are being considered as promising options [135]. Clinical trials are also evaluating the efficacy of hyperbaric oxygen therapy, montelukast, and pirfenidone for respiratory conditions associated with long COVID.

## 5. Conclusions

To conclude, this work has reviewed the association between long COVID and its implications for the cardiovascular, nervous, and respiratory systems. Numerous individuals have been, and continue to be, affected by the SARS-CoV-2 pathogen, leading to global concerns about the long-term effects of the virus. These post-acute manifestations of infection are emerging as a complex and diverse syndrome, impacting various bodily systems—including the cardiac, nervous, and respiratory systems, which this research investigates. These effects contribute to a range of symptoms that diminish quality of life, functional capacity, and workability. Currently, the nature of long COVID-19 is elusive, with many unanswered questions. A deeper comprehension of its pathogenesis, risk factors, symptoms, and treatment are imperative. The definition of 'long symptoms' remains uncertain due to variations in the duration described across studies, presenting a wide array of individuals experiencing persistent symptoms for weeks or more post-infection. While data on the effects of vaccination are limited, the findings are promising, underscoring the critical need for investment in research and healthcare resources to alleviate the enduring health, social, and economic repercussions of the post-COVID-19 condition.

**Supplementary Materials:** Not Applicable.

**Author Contributions:** Conceptualization, C.-M. S. and C.P.; methodology, C.-M. S.; software, C.P.; validation, C.-M. S. and C.P.; formal analysis, C.M.S.; investigation, C.-M. S. and C.P.; resources, C.-M. S. and C.P.; data curation, C.-M. S. and C.P.; writing—original draft preparation, C.-M. S. and C.P.; writing—review and editing, C.-M. S. and C.P.; visualization, C.-M. S. and C.P.; supervision, C.P.; project administration, C.P.; funding acquisition, C.P. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** No new data were created in this study.

**Conflicts of Interest:** The authors declare no conflict of interest.

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