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*Review*

# Overview and Pathophysiology of Long COVID

**Elisa Perego**

Institute of Archaeology, University College London, 31-34 Gordon Sq., London WC1H 0PY, UK; e.perego@ucl.ac.uk or elisaperego78@yahoo.it

**Abstract**

Long COVID is the disease entity triggered and potentially driven by SARS-CoV-2 infection. It is an heterogeneous condition characterized by dozens of different symptoms, signs and sequelae, which can affect all organs and body systems and evolve over the disease course. Clinical manifestations of Long COVID can vary from individual to individual and across the broader patient population. Pathology can range from asymptomatic and subclinical manifestations to fatal outcomes. Over 400 million people worldwide are estimated to suffer, or have suffered, from Long COVID, making the sequelae of SARS-CoV-2 infection one of the greatest public health challenges of the 21st century. This article provides an updated overview of epidemiology, definitions, main concepts and terminology for Long COVID. It also summarizes key evidence of pathology and disease mechanisms in major organs and body systems, such as the immune system, cardiovascular system, endothelium, heart, lungs, central nervous system, peripheral nervous system, gastrointestinal system, hapatobiliary system, pancreas and kidney. Heterogeneity in manifestations, potential risk of death and the degree of disability in several disease subsets call for timely diagnosis of each Long COVID types and a fuller understanding of their pathophysiological underpinnings. Further research is recommended to better understand pathobiology, develop effective clinical trials, and identify treatments and scalable biomarkers.

**Keywords:** Long COVID; COVID-19; Post-COVID-19 condition; SARS-CoV-2; Post-acute sequelae of SARS-CoV-2 (PASC); Post-COVID-19 conditions; case definition; pathophysiology

## 1. Introduction

Long COVID is the disease entity triggered and potentially driven by SARS-CoV-2 infection. The virus "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) is the causative agent of Coronavirus disease 2019 (COVID-19) and the driver of the COVID-19 pandemic. After the first case was officially reported in Wuhan, China, in late 2019 [1], the World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020 [2]. Initially, research and clinical guidance focused on the acute manifestations of the disease and the clinical entity known as COVID-19 pneumonia [3–6]. Recovery for survivors was expected by two weeks for mild COVID-19 cases and three–six weeks for severe ones [7]. However, it soon became clear SARS-CoV-2 infection was followed by prolonged symptoms, signs and sequelae, which lasted more than two–six weeks and affected the whole body [8–15]. The WHO openly recognized the long-term health effects of SARS-CoV-2 infection on 21 August 2020, after intense advocacy from COVID-19 survivors [16,17]. Advocacy coalesced around the patient-coined term Long COVID, which moved from the patient community to the media and the scientific literature by (northern

Check for updates

Academic Editors: Lawrence D. Hayes and Nilihan Sanal-Hayes

Received: 1 February 2026
Revised: 3 March 2026
Accepted: 11 March 2026
Published: 18 March 2026

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hemisphere) late spring to summer–autumn 2020 [10]. The term has remained prominent since then in advocacy [18], biomedical literature [19,20] and clinical guidelines [21,22].

Long COVID is characterized by multi-system pathology [20,23], with heterogeneous presentations across the patient population, ranging from subclinical to fatal [22]. It is estimated to affect, or have affected, hundreds of millions of people worldwide [24–26]. Together with an estimated death toll from COVID-19 of at least 20–28 million by 2022–2023 [27,28], morbidity makes SARS-CoV-2 infection one of the greatest public health emergencies of our times [8]. The costs for Long COVID are estimated at an average annual burden of 1 trillion dollars globally as of 2025 [29]. In addition, SARS-CoV-2 re-infections are well-documented, especially after the emergence of the variant of concern (VOC) Omicron in late 2021 [30], and are contributing to the significant disease burden of Long COVID [31]. Mortality from COVID-19 remains significant, with around 200,000 deaths and two million hospitalizations estimated in 2022–2024 for the US alone [32]. However, reduced surveillance prevents a full appraisal of the pandemic's magnitude.

Multiple not mutually exclusive mechanisms have been proposed to cause pathology in Long COVID; these include but are not limited to viral persistence [33,34], immune dysfunction [35–37], autoimmunity [38], damage to organs and tissues down to the cellular and subcellular level [39–42], microbiome dysbiosis [43], DNA modifications [44,45], reactivation of latent pathogens [46,47] and chronic inflammation [48]. All organs and body systems can be affected [19,20,22].

COVID-19 and Long COVID are among the most studied disease entities in medical history, with over 400,000 publications listed in repositories such as LitCovid [22]. However, further research is needed to better understand pathobiology, develop effective clinical trials, and identify treatments and scalable biomarkers. There is also a need for updated syntheses and additional clarity on definitions, terminology, key concepts and pathophysiology. These are gaps in knowledge this review will contribute to remedy (Addendum 1), including by providing in-depth, up-to-date evaluation of multi-organ involvement in Long COVID.

## 2. Nomenclature and Classification

Long COVID is the patient-coined term for the disease entity triggered and potentially driven by SARS-CoV-2 infection [9,10,22]. The term Long COVID covers the long-term symptoms, signs and sequelae from SARS-CoV-2 infection, as well as the disease processes triggered by such infection [9,22]. It can also be used as an umbrella term for the plethora of conditions precipitated by COVID-19 [21], including those meeting the case definition for conditions which already existed before the pandemic (e.g., diabetes) [49] but can manifest with novel, COVID-19-specific features [22] (below). Additional terms to address SARS-CoV-2 sequelae have been coined and/or adopted by entities such as health bodies (e.g., the WHO). These terms are often used as synonyms for Long COVID, although some differences in usage and meaning remain. They include but are not limited to: post-COVID-19 condition, or PCC [50]; post-acute sequelae of COVID-19, or PASC [51,52]; post-COVID-19 conditions, or PCC [52]; and post-COVID-19 syndrome, or PCS [53] (Addendum 2, below). Other terms coined or used within the patient community of COVID-19 survivors, such as Long-Haul COVID, have achieved national and international recognition [9,15] and are attested in the biomedical literature [54].

Numerous case definitions for Long COVID have been proposed [23,55]. These include but are not limited to: the case definition for post-COVID-19 condition (Long COVID) by the WHO [50,56]; post-COVID-19 syndrome (also known as Long COVID) by the National Institute for Health and Care Excellence (NICE) in the UK [57,58]; the US Government working definition for Long COVID, or USG [22]; and the 2024 NASEM Long COVID definition, put forward by the US National Academies of Sciences, Engineering,

and Medicine (NASEM) [21,22]. These classifications of Long COVID remain arbitrary to an extent, but case definitions are important for recognition and clinical diagnosis (Addendum 2, below). In acknowledging complexity and variability in Long COVID definitions, this review:

(1) Focuses on Long COVID as non-recovery from SARS-CoV-2 infection; it therefore recognizes there are prolonged disease courses the outcomes and duration of which cannot be established a priori in single individuals and patient cohorts [9,22,59]. Death and severe disability are possible outcomes. Subclinical and pauci-symptomatic manifestations are also possible;
(2) Acknowledges the continuum of disease between COVID-19 and Long COVID [9,12,22];
(3) Recognizes the broad, heterogeneous sequelae of SARS-CoV-2 infection, beyond any narrow definitions of Long COVID based on a few symptoms only [22];
(4) Acknowledges the complex and varied disease pathways following SARS-CoV-2 infection, which can vary from patient to patient [9];
(5) Avoids any strict, arbitrary threshold between "acute" disease and later pathology (e.g., four weeks, three months). While such thresholds can be important for epidemiological surveillance, data collection and the development of case definitions [9,21,22,50], pathophysiology is better understood by addressing the natural history of COVID-19 from infection to later sequelae. The term "acute COVID-19" is therefore used in this review for simplicity, as to indicate the first weeks of disease from infection. It is however acknowledged that the terms "acute and "post-acute" may carry unresolved issues in medical usage [12,59]; in addition, the point at which COVID-19 moves out from its "acute" phase remains to be better elucidated and can vary from patient to patient [9,22].

## 3. Overview

Dozens of symptoms have been associated with COVID-19 and Long COVID [60,61], which reflects the multi-system, heterogeneous nature of these disease entities. Studies have attempted to identify Long COVID subtypes and clusters of symptoms, but this research may still lack precision and granularity [62]. Already in 2020, COVID-19 was described as a "rampage through the body" [63], with "protean manifestations ranging from head to toe, wreaking seemingly indiscriminate havoc on multiple organ systems" [64]. Similarly, vast biological abnormalities and sequelae have been identified across multiple organs and body systems in Long COVID, including but not limited to: lung [65,66], heart [67], brain mboxciteB68-covid-4158065,B69-covid-4158065,B70-covid-4158065, kidney [71], liver [72], thyroid [73,74], pancreas [75], esophagus [76], intestine [77], spleen [40], skin [78] and eye [79]. The vasculature, coagulation cascade and endothelium can be severely affected [80,81]. The musculoskeletal, endocrine and reproductive systems can also be affected [19,82–84].

Long COVID can manifest with a relapsing–remitting pattern and progression or worsening over time [55,61]. Symptoms and signs can flare or abate and change over the disease course [60]. Some symptoms and signs, such as post-exertional malaise (PEM), tachycardia on standing, and dizziness, can overlap with other conditions associated with infections, such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and postural orthostatic tachycardia syndrome (POTS) [19,60]. Pathology in Long COVID can be subclinical, pauci-symptomatic [22] and/or be present in people who are not classified as having symptomatic disease in studies [66,70]. Severe, sometimes life-threatening conditions and events, such as cardiovascular events [85], have been reported with a delayed onset from infection, including with fatal outcomes [86]. Heightened risk for adverse outcomes, such as death, amputations and incident diagnoses of new-onset health

conditions, has been documented in large cohorts months to years after the initial infection as compared to uninfected controls [51,87–89]. Other patients might experience a resolution of symptoms and improvement of function with time [90]. However, it remains unclear to what extent subclinical damage might remain undiagnosed after apparent recovery. The longest-term health effects of SARS-CoV-2 infection remain to be elucidated, although there are growing concerns about neurodegenerative sequelae and oncogenesis [91–94]. Sequelae have been reported in SARS survivors almost 20 years after infection with SARS-CoV-1 [95]. This suggests COVID-19 survivors may face decades-long disease, especially if no treatment is provided.

Objective biomarkers of pathology in Long COVID are abundant and documented by tests such as (ventilation perfusion or VQ) single-photon emission computed tomography combined with computed tomography (SPECT-CT), cardiac magnetic resonance (CMR) and positron emission tomography (PET) scans [65,67,69]. Many people living with Long COVID, however, do not necessarily have access to this kind of testing, which might remain confined to research settings, or concierge and private services. Moreover, some tissue damage appears to be better (or only) identifiable through biopsies and autopsies [22], while current imaging techniques can have limitations [96–101] (Addendum 3, below). These factors may create significant gaps between people's extent of suffering and access to diagnosis and care [102]. Disability from Long COVID can be profound, with unmet needs that require urgent action from policymakers [102–104].

## 4. Epidemiology

Prevalence and incidence of Long COVID remain subject to uncertainty in view of heterogeneity in study design, use of different case definitions, unequal access to testing to identify subclinical pathology, and reduced surveillance in 2022–2025 as compared to the early pandemic. On average, risk of Long COVID is amplified by severe infection and attenuated by vaccination. However, persistent symptoms and sequelae are also documented following mild, pauci-symptomatic and apparently asymptomatic infection as well as in vaccinated cohorts [19,51,88]. Individuals of all ages, genders and prior health statuses have been found to develop Long COVID [19–21]. Risk factors reported in the literature include having one or more pre-existing conditions at the time of infection and being a female, although variability exists across studies [19,22,23,60,105].

A number of studies as well as estimates by the WHO have suggested around 200–409 million people might have suffered from Long COVID as of 2022–2023 [24–26], including 36 million in the European region alone [106]. A systematic review and meta-analysis based on 429 studies dating up to 2024 showed a global pooled Long COVID prevalence of 36% [107]. The Household Pulse Survey estimated 6–10% adults experienced Long COVID in the US in 2022–2023 [108]. The Office for National Statistics (ONS) Survey estimated that 1.9 million people in private households in the UK were experiencing self-reported Long COVID as of 5 March 2023 (2.9% of the country's population) [109]. Studies on smaller patient cohorts have suggested around 50–87% hospitalized COVID-19 survivors from 2020 could suffer from persistent symptoms and sequelae for months to years following SARS-CoV-2 infection [13,90,110,111]. Moreover, symptoms and sequelae could be worsened by a subsequent Omicron infection in these individuals [111]. Research on non-hospitalized patients, vaccinated cohorts, and individuals first infected after the emergence of Omicron has generally reported lower estimates, for example of 5–10% in some works [19,20,23,112,113]. However, variability exists across studies. For example, Fang and colleagues reported that up to 36% hospitalized Omicron survivors in a sample from China presented with a range of pulmonary sequelae around six months post infection [114]. Liu and co-authors reported that almost half of over 300 mild and asymp-

tomatic 2022 Omicron patients from Shanghai showed pulmonary involvement on CT scan; while radiological patterns in the study pointed to less severe lung pathology on average compared to pre-Omicron variants, these data highlight the significant disease burden of Omicron, including in apparently asymptomatic and pauci-symptomatic individuals [115]. In addition, several studies have identified high frequency of abnormal imaging findings in COVID-19 survivors on tests such as CMR, low-field-strength MRI, V/Q SPECT-CT and CT lung scan, including in non-hospitalized, pauci-symptomatic and some Omicron cohorts [65–67,114]. While based on small, or relatively small, patient cohorts, this evidence suggests pathology, including following Omicron infection, could be more widespread than revealed by some large-scale surveys focusing on symptomatic individuals identifying as having Long COVID. Further research is recommended to better pinpoint incidence and prevalence, while acknowledging that even lower estimates of 2–10% would indicate that Long COVID is already one of the commonest medical conditions worldwide.

## 5. Pathophysiology

SARS-CoV-2 is an airborne pathogen that mainly transmits through aerosols emitted by the infected individual and inhaled by the recipients [116]. Transmission by droplets and fomites has also been discussed [117]. There is concern about other modes of transmission, such as vertical transmission from mother to fetus [118], which deserve further research. SARS-CoV-2 exploits the angiotensin-converting enzyme 2 (ACE2) receptor for cell entry, which is expressed in multiple organs and body tissues [119]. This can contribute to an explanation of the extent of multi-system pathology and the broad range of symptoms, signs and sequelae following SARS-CoV-2 infection.

SARS-CoV-2 is composed of four structural proteins: spike (S), composed of the two subunits S1 and S2, nucleocapside (N), envelope (E) and membrane (M); 16 nonstructural proteins (NSPs); and 9 accessory proteins (ORFs) [120,121]. All four structural proteins are involved in the virus life cycle and contribute to pathology, namely S [122,123], E [124,125], M [126] and N [127]. Nonstructural and accessory proteins have also been reported to contribute to pathology [121], such as ORF8 [128]. Nonetheless, further research is recommended to uncover each protein's contribution to disease insurgence and progression in Long COVID.

SARS-CoV-2 was suggested to be able to persist in the body beyond a few days or weeks from infection already in 2020 [9,59], with evidence becoming increasingly significant over time [33]. Viral reservoirs and the presence of viral proteins have been reported in multiple body tissues months to years from the initial infection [34,129]. The contribution of viral persistence—broadly defined—to pathology and symptomatic disease is the object of extensive research and scholarly discussion. Potential therapeutics targeting viral reservoirs are also being addressed in the literature [130].

Infection with SARS-CoV-2 leads to multifaceted ramifications across body systems, with temporal evolution of injury documented across multiple organs [72,131–133]. Pathology in Long COVID is likely multifactorial, with intertwined mechanisms of direct viral effects and exuberant, dysregulated immune and inflammatory responses, which can persist in time [33,34,134,135]. The host–virus interaction triggers prolonged biological processes which can develop longitudinally and spatially across the body from infection to later sequelae [9,132]. Studies on the early phases of SARS-CoV-2 infection, including imaging and autopsies, foreground pathological mechanisms which can persist and evolve in the late and chronic phases of the disease entity, such as but not limited to endotheliitis, thrombus formation and angiogenesis [6,136]. Damage across all body systems is documented, including fatal injuries, injuries leading to transplantation, obliteration of the vascular bed of organs, disruption to organ architectures, parenchymal damage and

more subtle, subclinical damage to cells and tissues, which might remain asymptomatic or pauci-symptomatic and underdiagnosed if no specialized testing is provided [6,66,70,133]. Some key mechanisms and manifestations of pathology in major organs and body systems are detailed below.

### 5.1. Immune System

SARS-CoV-2 infection has been increasingly recognized to impact the immune system, with long-term immune perturbations, including reported forms of hypoimmunity, immunodeficiency and autoimmunity [36–38]. The clinical impact, prevalence and post-infection duration of these sequelae, which can affect both the innate and adaptive immune system [137], deserve further attention. Immune dysfunction can contribute to the reactivation of latent pathogens and increased susceptibility to other infections, which have been reported following SARS-CoV-2 infection [47,138,139]. Lymphopenia was already flagged as a marker of COVID-19 severity in early 2020 and a predictor of prognosis and adverse outcomes [140]. Lymphopenia was then reported to persist beyond acute COVID-19 in at least a subset of survivors, including in association with persistent symptoms [141]. Research has increasingly focused on the presence of prolonged abnormalities in lymphocyte subsets, such as B cells, CD4+ T cells, CD8+T cells, Natural Killer (NK) cells and Regulatory T cells (Tregs) [142,143], which have been reported even when total T-cell counts had normalized [144]. When compared to clinical data, immune dysfunction in these cohorts can correlate with broader evidence of prolonged disease such as radiological abnormalities [142]. Evidence of activated T lymphocytes across multiple body regions in 24 COVID-19 survivors as compared to prepandemic controls has been reported by Peluso and colleagues on whole-body PET imaging, together with evidence of viral persistence in the gut in a subset of their Long COVID cohort [145]. T cells exhaustion pathways have also been noted, together with persistent immune activation, proinflammatory responses, and the presence of autoantibodies in some cohorts [146,147]. Kwissa and colleagues reported ongoing elevation of IgG titers for SARS-CoV-2 E and N proteins in their Long COVID cohort as compared to convalescents. Elevation persisted for the six-month study duration, together with elevated serum cytokine profiles and higher rates of autoantibodies, pointing to prolonged immune dysregulation [148]. Deficiencies in dendritic cells (DCs) have been documented for at least seven months following SARS-CoV-2 infection [35]. Neutrophil dysfunction has also been reported [149]. Prolonged dysregulation of the complement system, a key part of the innate immune system, has been noted, with evidence of thromboinflammation and tissue damage [150]. Mast cells (MC) activation and degranulation have been proposed to contribute to pathology in acute and Long COVID, with manifestations in organs such as the lungs and brain [151–153], and more general symptoms and signs, such as urticaria, skin irritation, rhinitis, wheezing, congestion, fatigue and gastrointestinal issues [154]. As many studies have been primarily carried out in research settings, evaluation of immune dysfunction in clinical facilities and larger cohorts is recommended following SARS-CoV-2 infection.

Autoimmunity, a condition of abnormal immune responses where the body attacks its own healthy cells, tissues and components [155], has been proposed to contribute to Long COVID, with heightened risk of developing autoimmune diseases after SARS-CoV-2 infection [156]. A 2025 meta-analysis and systemic review, comprising 97 million individuals, found that SARS-CoV-2 infection increases the risk of autoimmune diseases, particularly those affecting vascular and connective tissues [157]. Autoantibodies have been found in multiple, but not all, Long COVID cohorts and individuals [38], including but not limited to antinuclear antibodies (ANA), ACE and antiphospholipid (aPL) antibodies, anti–IFN-α-2 antibodies, autoantibodies against components of the cardiovascular sys-

tem such as anti-cardiolipin and anti-apolipoprotein A-1 antibodies, and autoantibodies against G-protein coupled receptors (GPCRs) and chemokine receptors [147,158,159]. Further research is needed to assess prognostic value, outcomes, association with different Long COVID phenotypes and recognition of de novo autoantibody production following SARS-CoV-2 infection.

### 5.2. Cardiovascular System and Endothelium

Evidence from, but not limited to, imaging, autopsy and biopsy, has showed the endothelium and cardiovascular system to be major targets of pathology in acute and Long COVID [158,160–162]. SARS-CoV-2 infection has been linked to severe vascular compromise through multiple mechanisms, with the development of macro- and microvascular complications, damage to the vascular bed of organs, and heightened risk for cardiovascular, cerebrovascular and thrombotic sequelae [162–166]. Symptoms and signs are numerous, including chest pain, chest pressure, pain in other body areas, palpitations, numbness, dizziness, shortness of breath, fatigue, visible alterations to blood vessels, skin lesions, swelling, hypoxia, hypertension, exercise intolerance, and abnormal heart rates [158,167]. Some manifestations can be more subtle, with pathology being asymptomatic or paucisymptomatic, or not classified as symptomatic Long COVID in studies [66]. Bruno and colleagues, for example, reported that SARS-CoV-2 infection was associated with accelerated, long-term vascular aging, especially in women, in a sample of 2390 COVID-19 survivors and controls [168]. Dai and co-authors used coronary CT angiography (CCTA) to show that coronary atherosclerotic plaques post COVID-19 were more prone to becoming high-risk plaques and showing elevated risk of target lesion failure. In addition, COVID-19 survivors in their study reported worse cardiovascular outcomes compared to controls [169].

The vascular endothelium is at the interface between blood compartment and tissue, playing a key role in vessel functioning and homeostasis [170]. It can be affected by direct viral action and indirect factors such as host immunoinflammatory responses [167,171], with disrupted endothelial function persisting beyond acute SARS-CoV-2 infection [170]. Endothelial injury, structural damage to the endothelium, and endothelial dysfunction have been recognized, with manifestations of endotheliopathy and endotheliitis [6,171,172]. Markers of endothelial cell damage and activation have been identified across body systems; endothelium-associated complications are attested in multiple organs with clotting abnormalities [153,161,171,173–175]. Ciceri and colleagues posited in early 2020 that endothelial damage and microvascular thrombosis could spread spatially and temporally in the lung and to the microvascular bed of other organs such as the kidney and brain [132]. It can be suggested that progression of these biological processes beyond a few weeks from infection would contribute to an explanation of the vascular and thrombotic manifestations in Long COVID.

Additional vascular pathology in the form of vasculopathies and vasculitic manifestations has been recognized in multiple body systems, including far from infection [176–179]. Vascular pathology can present with COVID-19-specific manifestations despite apparent similarities with non-COVID-19 phenotypes; for example, Gawaz and colleagues found that COVID-19-related vasculitic skin lesions differed from classic leukocytoclastic vasculitis on electron microscopy and immunohistochemistry despite apparent similarities by eye [180]. Kawasaki-like disease manifestations have been attested following SARS-CoV-2 infection since early 2020 [181]. Kawasaki disease (KD) is a vasculitis already known pre-pandemic, which shares similarities with COVID-19-specific phenotypes such as the multi-system inflammatory syndrome seen in children weeks after infection (MIS-C) [182,183]. Further

research is needed to elucidate similarities and differences in pathobiology between Long COVID phenotypes, KD and MIS-C.

Altered vascular transformation and angiogenesis have been implicated in the development of Long COVID, with evidence of abnormal vessel growth and repair [41,184]. For example, angiogenesis-related biomarkers such as vascular endothelial growth factor A (VEGF-A) were increased in plasma in a Long COVID cohort studied by Phillippe and colleagues, as compared to controls; they correlated with persistent lung impairment, persistent lung abnormalities on CT scan and raised levels of von Willebrand factor (VWF), a marker of endothelial dysfunction [185]. Pathological angiogenesis has also been linked to acute COVID-19 [186–189]. COVID-19 lungs, for example, were found to display distinctive angiocentric features on autopsy compared to uninfected and influenza A (H1N1) controls in a small sample analyzed by Ackermann and colleagues [6,188,189].

Microvascular changes have been reported in Long COVID cohorts, such as in the microvasculature of the eye via techniques like optical coherence tomography angiography (OCT-A) [190]. Nailfold videocapillaroscopy (NVC) has showed extensive microvascular damage in a sample of patients diagnosed with Long COVID, compared to matched healthy controls, including dilated capillaries, microhaemorrhages, abnormal shapes and reduced capillary density, which persisted for at least one year following SARS-CoV-2 infection [191]. Microvascular damage in acute COVID-19 has been identified with the same technique [192]. Hypercoagulability at different time points from infection, prolonged pro-thrombotic states, and coagulopathies, where the blood's ability to clot is altered, have been widely reported [193–195], with the presence of thrombi, micro-thrombi, impaired fibrinolysis, platelet hyperactivation [196], and overt clinical manifestations such as pulmonary embolism (PE), deep vein thrombosis (DPV), ischaemia, reduced exercise capacity and desaturation beyond acute SARS-CoV-2 infection [197–199]. Pretorious and colleagues have reported the presence of fibrin(ogen) amyloidogenic particles deposits (microclots) resistant to fibrinolysis in plasma samples of people with acute and Long COVID [200,201]. Additional research is recommended to shed further light on coagulopathy, vasculopathy, angiogenesis and endothelial dysfunction in Long COVID while deploying scalable biomarkers.

### 5.3. Heart

In the cardiovascular system, the heart is a major locus of pathology in acute and Long COVID. Multiple mechanisms have been highlighted in the literature, including direct viral cardiotoxicity, immune-thrombotic changes, endothelial dysfunction, thrombus formation, ischemia, and dysregulated immune responses, with distinct phases and phenotypes of injury [202,203]. Sequelae of infection include but are not limited to arrhythmias, dysrhythmias, impaired left ventricular ejection fraction, heart failure, acute myocardial infarction (AMI), cardiomyopathy, pericarditis, and myocarditis-like changes with inflammation of the heart muscle, cardiac remodeling and risk of deterioration of cardiac function [158,162,204–207]. Symptoms and signs include chest pain, dyspnea, palpitations, prolonged QT interval, exercise intolerance and heart rate abnormalities such as tachycardia [158,204]. They can be associated in some cohorts with positive laboratory measurements, such as troponin and high-sensitivity troponin T ((hs-cTnT), and/or evidence of cardiac injury on imaging and biopsy, especially in the first weeks to months post infection [208].

Cardiac damage can be catastrophic, leading or contributing to death, or more subtle, with residual injury and pauci-symptomatic or asymptomatic sequelae. For example, Karaviti and colleagues reported persistent reduction in left ventricular global longitudinal strain (GLS), indicating subclinical myocardial dysfunction, in a sample of children with

a history of SARS-CoV-2 infection, who could also experience persistent symptoms such as fatigue and palpitations; in addition, children with more severe symptoms in their sample tended to show elevated serum intracellular adhesion molecule-1 (sICAM-1) levels, suggesting endothelial activation [209]. Di Chiara and co-authors reported that subclinical cardiac contractility alterations on echocardiography were associated with reduced Tregs, shorter telomeres and elevated inflammatory markers three months post-infection in a subset of 16 children from a sample of 67 who had COVID-19 [210]. Hanson and colleagues, on the other end, analyzed the cardiac tissue of 21 deceased COVID-19 patients on autopsy and found significant evidence of multifaceted and multifactorial pathology, including the presence of the SARS-CoV-2 virus, thrombi, masses of inflammatory cells, and neutrophil extracellular traps (NETs) in cardiac tissues, together with vasculitis-like manifestations, angiogenesis and borderline myocarditis; COVID-19-associated cardiac injury in the study presented distinctive features compared to non-COVID-19 controls [203]. Pellegrini and colleagues showed evidence of myocyte necrosis in 14 out of 40 hearts from patients who died from COVID-19. Necrosis was associated in most cases with thrombi, and/or micro-thrombi in myocardial capillaries, arterioles and small muscular arteries; moreover, COVID-19-related micro-thrombi could display distinctive features compared to controls [211]. Tangos and co-authors reported SARS-CoV-2 to infect cardiac cells such as cardiomyocytes, leading to cell damage and apoptosis and impaired cardiomyocyte function [212]. Che and colleagues showed that histopathological and electron microscopic analyses on biopsy in a small sample of Long COVID patients with severe cardiac manifestations, including sudden death during exercise, together with proteomics and a mouse model, pointed to mitochondrial damage in the cardiomyocytes and additional sequelae of infection such as myocarditis [213]. Cao and co-authors used an overweight mouse model to suggest that SARS-CoV-2 S protein can cause long-term transcriptional perturbations of mitochondrial metabolic genes, cardiac fibrosis and myocardial contractile impairment [123].

In the context of imaging [214], CMR has helped elucidate the cardiovascular sequelae of SARS-CoV-2 infection, including in MIS-C [215]. Puntmann and colleagues, for example, reported high percentages (up to 78%) of cardiac involvement on CMR weeks to months after mild COVID-19, which they attributed to subclinical inflammatory cardiac sequelae, and could be associated with cardiac symptoms in their early pandemic sample [67,216]. A 2022 systematic review of CMR in post COVID-19 cohorts showed that myocardial and pericardial involvements were widely reported across the sample of 2954 COVID-19 adult survivors from 16 studies (although with variable prevalence across different studies) [217]. Vallejo Camazón and colleagues, on the other hand, used adenosine stress perfusion CMR to show coronary microvascular ischemia in a cohort of Long COVID patients with persistent angina-like chest pain [218]. Impaired coronary microvascular blood flow has been described via PET imaging months from infection in individuals with ongoing chest pain or dyspnea, as compared to uninfected controls [219]. SPECT myocardial perfusion imaging (MPI) has suggested that patients who had COVID-19 and developed Long COVID are more likely to have myocardial ischaemia than controls [220,221]; ischaemia on SPECT-MPI might be especially significant in survivors of COVID-19 pneumonia and those with persistent dyspnea and chest pain [222]. Further research is highly recommended to identify cardiac complications following SARS-CoV-2 infection, including by deploying adequate testing, such as high-quality imaging, to patients who remain symptomatic but face accessibility challenges.

### 5.4. Lungs

Radiological and histological research, including on autopsy, has revealed multifaceted damage to the lung [6], which can be identified months or years after the initial infection [42]. Studies have reported evidence of, but not limited to, chronic lung injury, damage to the pulmonary vascular integrity, microvascular lung thrombosis, endotheliitis, residual clot burden, abnormalities in microcirculation associated with a higher risk of hypercoagulation, and presence of ongoing disease in the microvasculature and walls of the alveolar sac [6,42,65,136,223,224]. Symptoms and signs include persistent cough, dyspnea, heart rate abnormalities, chest pain, exercise intolerance, fatigue, desaturation and impaired diffusing capacity of the lung for carbon monoxide (DLCO) [225]. In extreme cases, lung pathology can result in lung transplant or death far from infection [133,223,224,226–228].

Imaging such as but not limited to (VQ) SPECT-CT has revealed evidence of perfusion and diffusion defects, mismatched perfusion defects consistent with PE, post-embolic sequelae, matched ventilation–perfusion defects potentially indicative of parenchymal lung disease, and reverse mismatched defects, more likely indicating parenchymal or airway diseases; these different radiological patterns point to multifaceted pulmonary sequelae [65,229–231]. Persistent perfusion defects have been flagged as a risk for later complications such as pulmonary hypertension and right heart failure [65]. Lung perfusion abnormalities had already been identified in acute COVID-19 in 2020 with the same technique and associated with embolic manifestations, perfusion shunting, lung parenchymal infiltrates and other complications of COVID-19 pneumonia [232,233]. The presence of different phenotypes and imaging patterns in acute disease [232] might contribute to an explanation of the multiplicity and variability of symptoms, signs and sequelae in pulmonary Long COVID. Additional imaging techniques such as dual energy computed tomography (DECT) have further revealed evidence of perfusion defects and ground-glass parenchymal lesions months post infection, which could correlate with persistent symptoms and laboratory test abnormalities such as raised ddmer [234]. A study which used cardiopulmonary 18F-FDG PET/MRI, pulmonary DECT and plasma protein analysis revealed a high prevalence of pulmonary and cardiac abnormalities in a Long COVID cohort for at least nine to twelve months post infection [235]. Phase-resolved functional lung (PREFUL) MRI has been used to identify distinct phenotypes of lung perfusion in pediatric patients, which correlated with heart rate and fatigue severity in the study [236]. Grist and colleagues used hyperpolarized Xenon-129 Magnetic Resonance Imaging (Hp-XeMRI) to reveal pulmonary abnormalities and impaired gas transfer in the lung at least six months post infection, which could correlate with breathlessness and indicate COVID-19-induced microstructural abnormalities as well as the presence of micro-thrombi in their sample [42]. Similar imaging approaches have been further employed to elucidate SARS-CoV-2 sequelae, for example by identifying different phenotypes of pulmonary Long COVID in a sample of 135 individuals who had COVID-19 and controls [237]. Tests such as V/Q SPECT-CT and Hp-XeMRI can be used to identify lung abnormalities not apparent on more standard tests such as CT lung scan and spirometry [42,231], although tests such as CT lung scans can still reveal long-term residual abnormalities following SARS-CoV-2 infection, such as ground-glass opacities, air trapping, reticular opacity and bronchial dilatation [238]. In addition, imaging such as V/Q SPECT-CT can reveal unusual distal small vessel-related deficits, which can be underestimated on tests such as conventional CT pulmonary angiogram (CTPA): involvement of sub-subsegmental vessels in the lung is an important feature of SARS-CoV-2 infection [6], with formation of thrombi in situ [136].

In addition to imaging, histological analysis after acute COVID-19 pneumonia has revealed pulmonary damage including but not limited to organizing pneumonia, fibrosis, vascular abnormalities [224,238], capillary thrombi, inflammatory patterns, and diffuse

alveolar damage (DAD); manifestations can evolve with time and differ from patient to patient [239]. Other studies, including but not limited to animal models, have shown prolonged inflammation, impaired lung repair and chronic fibrosis [240], migration of pro-inflammatory and pro-fibrotic immune cells from blood into lung one year after SARS-CoV-2 infection [223], persistent alveolar damage and fibrotic pathways [241] and viral persistence for months post infection [242]. Long-term evaluation of pulmonary sequelae is therefore highly recommended, especially in patients who remain symptomatic but face challenges in accessing appropriate care, evaluation and imaging.

### 5.5. Central Nervous System

Long-term pathology following SARS-CoV-2 infection is well-documented in the central nervous system (CNS), consisting of the brain and spinal cord [243,244]. Dysfunction and damage are likely multifactorial, with several putative mechanisms addressed in the literature. The neuroinvasion potential of SARS-CoV-2 has been widely discussed [245]. SARS-CoV-2 was found to persist for several weeks in the brainstem in an animal model while contributing to disrupted neuronal activity and neurological manifestations in the sampled hamsters [94]. Accumulation of SARS-CoV-2 S protein in the skull–meninges–brain axis of human COVID-19 patients has been observed by Rong and colleagues on optical clearing and imaging, replicated in mice, and prospectively linked to neurological sequelae in Long COVID [246].

Symptoms and signs of brain pathology in Long COVID include but are not limited to memory loss, difficult concentrating, deficits in executive function, headache and "brain fog" [247]. Long-term sequelae have also been identified in people who appeared or reported to be asymptomatic or minimally symptomatic [70]. Imaging studies, including when carried out in association with additional analysis such as transcriptomic analysis, have revealed altered tissue microstructure and neurochemical profiles [248], structural changes such as reduced gray matter concentrations (GMC) and altered connectivity patterns [249], neuroinflammation [250,251], disruption to blood–brain barrier (BBB) function [252], and impaired brain energy metabolism with anterior cingulate dysfunction associated with cognitive impairment [253]. Seo and colleagues reported elevated astroglial damage-associated proteins with structural and microstructural alterations across multiple cortical and subcortical regions, including cortical thinning in the insular and cingulate cortices, increased paramagnetic susceptibility in the hippocampus, and enlarged choroid plexus volume; the study analyzed blood proteins and brain MRI in a Long COVID cohort denominated Cog-PASC (with cognitive impairment) one year after infection [254].

Vascular and microvascular damage in the brain has been connected to acute and Long COVID, including in patients with long-term cognitive impairment [255,256]. Strokes, brain hemorrhages and related sequelae have also been described post COVID-19 in young patients with no pre-existing cerebrovascular risk [257]. Microglial reactivity and consequent neural dysregulation has been shown in animal models and humans with persistent cognitive deficit [258]. Cerebral hypometabolism across different brain regions has been reported in multiple studies carried out at different time points post infection in both adults and children; imaging abnormalities tend to correlate with evidence of cognitive decline and neurological symptoms [68,69,259,260]. Brain SPECT-CT has been used to identify persistent cerebral vascular flow pathology in Long COVID cohorts [261]. Given the extent of cognitive sequelae following SARS-CoV-2 infection, additional research is strongly recommended to validate in larger human cohort findings that derive from exploratory studies and animal models while facilitating access to existing testing for patients.

Spinal cord involvement following SARS-CoV-2 infection has also been reported, with manifestations including but not limited to spinal cord ischaemia, spinal cord infarction,

myelitis, and evidence of inflammatory changes in the cerebrospinal fluid. Long-term impairment, such as inability to walk, and neurological sequelae have been noted in these cohorts [262–265]. Peluso and colleagues reported evidence of T cell activation in the spinal cord and gut wall, identified via whole-body PET, which was linked to symptomatic Long COVID in their sample [145]. In a study by Apple and colleagues, abnormalities in cerebrospinal fluid were usually associated with cognitive symptoms in a cohort of mild COVID-19 survivors [266]. Further research is recommended to identify spinal cord pathology in patients with Long COVID, including in those with less severe manifestations than, for example, spinal cord infarction and otherwise presenting unexplained neurological symptoms.

### 5.6. Peripheral Nervous System

Pathology in the peripheral nervous system (PNS) has been documented following SARS-CoV-2 infection and described in Long COVID, with evidence of neuropathy, polineuropathy, and peripheral neuropathy with heterogeneous patterns of fiber damage [267–269]. Small-fiber neuropathy (SFN) has been associated with Long COVID including via skin biopsy and/or quantitative sensory testing abnormalities [270,271]. Putative mechanisms of PNS involvement in Long COVID include direct nerve damage from the virus, autoimmunity and indirect damage from factors mediating inflammatory responses and immune dysregulation. Clinical manifestations comprise symptoms and signs of pain, numbness, weakness, tingling, hyperalgesia and allodynia. Among the components of the PNS, dysfunction in the autonomic nervous system (ANS) has been widely discussed, with various clinical manifestations of dysautonomia, such as but not limited to tachycardia on standing, anomalous fluctuations in blood pressure and heart rates, orthostatic intolerance, fatigue and cognitive impairment [272]. Further research is recommended to better elucidate PNS sequelae in Long COVID while supporting patients in accessing testing and treatments already available.

### 5.7. Gastrointestinal System

Gastrointestinal (GI) clinical manifestations are commonly reported following SARS-CoV-2 infection [60,273–275]. Numerous sequelae have been attested in Long COVID, including symptoms and signs of nausea, vomiting, gastroesophageal reflux disease (GERD), diarrhea, constipation and manifestations linked to dysautonomia [272]. GI sequelae can correlate with other persistent symptoms as well as markers of inflammation and immune perturbations [275]. Severe GI complications, generally but not always reported in the first days or weeks post infection, include perforations, necrosis, ischemia, ulcers, thrombosis, bleeding, amputation of portions of the intestine, and death [43,77,276–278]. Endotheliitis in the GI tract has also been reported [171]. Animal models have shown that SARS-CoV-2 infection can impair intestinal stem cell function and epithelial repair [279] and damage the gastric epithelial and parietal cells through inflammatory, apoptotic and pyroptotic mechanisms [280].

The gut has been recognized as a long-term SARS-CoV-2 reservoir in numerous studies [145,281,282]. Changes to the GI tract microbiome have also been highlighted. Microbiome alterations can lead to dysbiosis, potentially contributing to multiple sequelae by promoting inflammation, affecting the integrity of the intestinal barrier, and altering immune and neuroendocrine pathways through the gut–lung and gut–brain axes [283–285]. Moreover, research on GI tissues carried out via multiple techniques, including but not limited to high-resolution microscopy and spatial transcriptomics on biopsy, has revealed evidence of long-term inflammatory conditions and tissue scarring in addition to viral persistence [286]. Damage to the epithelial barrier of the esophagus, with increased per-

meability and evidence of heartburn and acid reflux symptoms, has been identified on biopsy in a cohort of COVID-19 survivors months post hospital discharge [76]. Additional research would further clarify the underpinnings of GI sequelae following SARS-CoV-2 infection and support access to testing and any available treatment.

### 5.8. Hapatobiliary System

The hepatobiliary system, composed of liver, bile ducts and gallbladder, plays a key role in metabolism, digestion and excretion. It is a target of pathology in acute and Long COVID. Higher risk for hepatobiliary conditions has been reported in large-scale post COVID-19 cohorts as compared to uninfected controls [273,274]. Symptoms and signs include but are not limited to fatigue, skin changes, digestion problems and abdominal pain. Liver function anomalies can be indicated by abnormal levels of liver enzymes, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which are documented months to years following SARS-CoV-2 infection in some cohorts [287]. Different putative mechanisms of liver injury and dysfunction have been suggested, from direct viral infection of hepatic cells to secondary mechanisms involving immuno-mediated damage as well as inflammatory and vascular sequelae of infection, including the presence of vasculopathy, endotheliopathy and thrombosis in the liver [288–291]. A study using ultrasound shear wave elastography has suggested that SARS-CoV-2 infection is associated with increased liver stiffness, which could indicate persistent hepatic injury, including ongoing inflammation and fibrosis [292]. Cooper and colleagues reported different patterns of liver injury in a small sample of children with Long COVID, including necrosis and inflammation, with two infants requiring liver transplantation [72].

Damage to the bile ducts has also been noted. Liver organoids derived from bile duct cells have been reported to be susceptible to direct infection and viral replication by Lui and colleagues [293]. Cholangiopathy, a damage of the epithelial cells lining the bile ducts, has been occasionally documented, generally after severe COVID-19; the condition appears to present COVID-19-specific features distinguishing it from pre-pandemic cholangiopaties and can result in adverse outcomes such as transplantation [294,295]. The gallbladder is also a target of SARS-CoV-2 infection. For example, the presence of SARS-CoV-2 viral RNA has been reported in acute COVID-19 together with radiological pattern of cholecystitis, while the N protein was identified in gallbladder tissues of patients who underwent surgery after COVID-19 [296,297]. Gallbladder perforation, gangrene, thrombosis and inflammation have been documented days to weeks from infection and can result in life-threatening complications and surgical removal of the gallbladder [298]. A 2026 systematic review of 23 studies with heterogeneous study design identified post-COVID-19 cholangitis, cholecystitis and hepatitis among the hepatobiliary diseases following SARS-CoV-2 infection [299]. Given this evidence, further research is recommended to address hepatobiliary sequelae in Long COVID, including subclinical or less overt disease of liver, bile ducts and gallbladder.

### 5.9. Pancreas

The pancreas is an organ with critical functions in food digestion (exocrine function) and regulation of blood sugars (endocrine function). Research conducted in vitro, in vivo and on autopsy has shown the pancreas to be a key target of SARS-CoV-2 infection, with long-term sequelae including diabetogenic effects, endocrine impairment [300], hyperglycemia and potentially hypoglycemia [301]. Diabetes has been flagged as a sequel of SARS-CoV-2 infection [49], with ongoing discussion about prevalence, manifestations and pathogenesis [22]. A 2026 review summarized the molecular mechanisms and biomarkers of post-COVID-19 diabetes, including but not limited to profound β-cell defects, unique metabolic reprogramming, systemic inflammation, endothelial dysfunction, autoimmunity,

islet apoptosis and fibrosis, anomalous response to glucocorticoid therapy, severe hyperglycemia, significant rapid insulin loss, as well as frequent crises due to hyperglycemia and grave insulin deficiency, which, taken together, distinguish it from pre-pandemic type 2 diabetes (T2D) [302]. Pancreatitis, the inflammation of the pancreas, has also been documented during and following acute COVID-19 [303].

Pancreatic tissue in humans and non-human primates was found with thrombi, fibrotic changes and evidence of direct viral infection by Qadir and colleagues, with some patients in the study being diagnosed with new-onset diabetes [304]. SARS-CoV-2 has been reported to infect human pancreatic β cells, elicit β cell impairment and affect insulin levels [305], and promote altered β-cell proinsulin processing as well as β-cell degeneration and hyperstimulation (as seen in postmortem pancreatic tissues) [306]. Deng and colleagues found that SARS-CoV-2 infection can impair glucose metabolism and pancreatic function in a sample of non-human primates, with the virus directly infecting different types of pancreatic cells, including both exocrine and endocrine cells [307]. A study by Müller and co-authors also reported that SARS-CoV-2 can infect cells of the human exocrine and endocrine pancreas ex vivo and in vivo, with morphological, transcriptional and functional changes prospectively linked to the metabolic disorders observed following SARS-CoV-2 infection [308]. Andrade Barboza and colleagues found the SARS-CoV-2 S1 subunit to activate pericytes and constrict capillaries in the human islets, a critical endocrine miniorgan in the pancreas, with islet vascular dysfunction potentially contributing to dysglycemia following SARS-CoV-2 infection [309]. In young children with high genetic risk of type 1 diabetes (T1D), SARS-CoV-2 infection has been temporally associated with the development of islet autoantibodies, which would suggest the development of islet autoimmunity [310]. Further research is recommended to better elucidate the effects of SARS-CoV-2 infection on the pancreas. Evaluation of COVID-19 survivors for diabetes and broader endocrine and metabolic sequelae is critical.

### *5.10. Kidney*

The kidney emerged in early 2020 as a key target of SARS-CoV-2 infection, with patients, especially those with severe disease, being vulnerable to acute kidney injury (AKI) in the early phases of COVID-19 [311]. Injury to the kidney has been ascribed to direct viral effects and/or secondary effects such as immune and inflammatory responses as well vascular pathology, renal perfusion deficits, capillary thrombosis and endotheliitis, with such effects being documented on biopsy, autopsy, radiology and laboratory testing [71,312,313]. Research has highlighted the risk of developing chronic kidney disease (CKD) following SARS-CoV-2 infection, especially in those who presented with AKI in acute COVID-19 [71,314]. Long-term sequelae have been documented in multiple cohorts [315–318]. The presence and risk of gradual, long-term loss of renal function have been noted [315,316,319], with potential adverse outcomes such as renal failure and death especially in severe COVID-19 cohorts [315,316]. Loss of function can be initially asymptomatic and later associated with symptoms and signs such as fatigue, swelling of ankles and feet, proteinuria, excess of protein in urine, and changes in urine frequency [320], which remain to be better documented in the literature [314].

Substantial decline in estimated glomerular filtration rate (eGFR), a marker of kidney function, has been noted in multiple cohorts months to years post infection, especially in patients who survived severe COVID-19 [316,321,322]. Bowe and co-authors reported that survivors of COVID-19 beyond 30 days of disease showed higher risks of AKI, eGFR decline, end-stage renal disease (ESKD), major adverse kidney events (MAKE), and steeper longitudinal decline in eGFR than uninfected controls [315]. Adverse outcomes such as MAKE in COVID-19 survivors were also noted by Atiquzzaman and colleagues [316].

In a case report, Qin and co-authors reported the case of 34-year-old Asian man with pre-existing evidence of possible kidney disease, who was diagnosed with incident thrombotic microangiopathy (TMA) following SARS-CoV-2 infection, had endothelial manifestations identified on renal biopsy for TMA, showed evidence of viral pneumonia and pulmonary edema on CT scan, was diagnosed with acute left heart failure, developed acute renal failure, and remained on peritoneal dialysis over one year after infection [323]. On the other end, Li and colleagues described the case of a 30-year-old male who developed IgA vasculitis as a complication of COVID-19, had necrotizing IgA nephropathy seen on renal biopsy, but was stabilized by six weeks on medication [324]. A 2025 study focusing on the medical records of three million people diagnosed with COVID-19 and ten million who were not showed increased risk of long-term renal failure in hospitalized COVID-19 patients but not in milder cases; the risk persisted during the Omicron wave [325]. Further research and clinical evaluation is therefore needed to assess longer-term outcomes in Long COVID across the broader patient population, with particular attention to subclinical and asymptomatic pathology that might remain undiagnosed and undocumented in clinical records.

## 6. Patient and Public Involvement (PPI)

The author is a patient-researcher living with Long COVID and other chronic diseases.

## 7. Conclusions

Long COVID is a novel, heterogeneous disease entity triggered and potentially driven by SARS-CoV-2 infection. The condition results in biological abnormalities documented across all body systems, which can manifest with dozens of symptoms, clinical signs and sequelae. Some key mechanisms and manifestations of pathology have been described in this review, such as but not limited to viral persistence, immune dysfunction, autoimmunity, multi-organ involvement, vascular pathology, coagulation abnormalities, perfusion deficits, inflammation, parenchymal damage, as well as cellular and subcellular damage. Pathogenesis and symptomatology of Long COVID are complex and multifactorial. Manifestations are highly variable across the patient population and can evolve across the disease course. Outcomes range from apparent recovery—although subclinical pathology is attested in asymptomatic and minimally symptomatic individuals—to death. In addition, Long COVID can present with manifestations that might meet the case definition for conditions that already existed before the pandemic (e.g., diabetes, PE, vasculitis). However, research points to the existence of COVID-19-specific features for some of these conditions. Further research and clinical guidance, therefore, must address their natural history, outcomes, risk factors, response to treatment and need for tailored diagnostics [22].

A rich palette of biomarkers is available from numerous studies and can guide diagnosis, treatment and clinical trials. However, additional research is needed to validate findings based on small samples and animal models in larger and more diverse human cohorts. Moreover, not all patients will be positive for any specific biomarker, especially if less sensitive testing is given and subclinical pathology is present. Furthermore, a number of laboratory and imaging abnormalities identified in Long COVID, especially those from standard and less sensitive tests, are attested in other diseases, making diagnosis more challenging. Heterogeneity in manifestations, potential risk of death and the degree of disability in several disease subsets, however, call for timely diagnosis of each Long COVID type and a fuller understanding of their pathophysiological underpinnings. Further research is needed to better elucidate pathobiology while developing effective clinical trials as well as scalable treatments and biomarkers. Research addressing long-term sequelae in 2020–2021 cohorts is highly recommended, as studies covering Long COVID

five–six years from initial infection are generally lacking. Long COVID in cohorts who had access to vaccination and were infected after the emergence of Omicron needs further attention. Sequelae following infection with variants which emerged in the last few years, such as JN.1, deserve urgent research, as some studies have suggested variant-specific pathology [115,326]. The impact of reinfections needs urgent attention [31,327]. Sustained funding and education about the full spectrum and scope of Long COVID are necessary. The development of updated reviews and guidelines focusing on clinical management and therapeutics is critical. Prevention of infection is key. Access to tests, such as imaging, already able to identify pathology, and to existing treatments, is crucial. Access to disability benefits and adequate care is indispensable.

## 8. Addendum 1: Search Strategy

Articles were searched in PubMed, Google Scholar and LitCovid from January–March 2020 to February 2026, using terms such as (COVID-19 OR SARS-CoV-2 OR Coronavirus disease 2019 OR 2019-nCoV OR Long COVID OR post-COVID-19 condition OR PASC OR Post-acute sequelae of SARS-CoV-2 infection OR Post-COVID-19 conditions OR Long Haul COVID OR Post-COVID-19 syndrome OR post-COVID-19) AND (name of organ or body system OR name of test OR antibodies OR case definition OR prevalence OR incidence OR WHO OR NICE OR NASEM OR pathophysiology). Different versions of the same term could be searched, such as Long COVID OR Long Covid. No language restrictions were applied, but publications in English were vastly prevalent in the search. Grey literature such as preprints and posts, e.g., by the WHO, were searched when needed. Search, screening, selection and synthesis were conducted by the author. This review is part of a larger ongoing project by the author on COVID-19 and Long COVID, building upon the author's lived experience, advocacy and research [10,15]. Given the sheer amount of literature on COVID-19 and Long COVID, only some topics and publications could be discussed in this review.

## 9. Addendum 2: Summary of Terminology and Main Case Definitions

WHO case definition for post-COVID-19 condition or PCC (Long COVID): "post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis" [50]. Established by Delphi consensus, it focuses on symptoms but does not exclude sequelae and conditions.

NICE guidelines for the long-term effects of COVID-19: "two definitions of postacute COVID-19 are given: (1) ongoing symptomatic COVID-19 for people who still have symptoms between 4 and 12 weeks after the start of acute symptoms; and (2) post-COVID-19 syndrome [PCS] for people who still have symptoms for more than 12 weeks after the start of acute symptoms." [58]. The guidelines also mention and use the term Long COVID. They focus on symptoms but also acknowledge conditions such as PE.

US Government working definition for Long COVID or USG: in brief, it recognized broadly defined symptoms, signs and conditions that continue or develop after initial SARS-CoV-2 infection. The signs, symptoms, and conditions persist for four weeks or more after the initial phase of infection [22]. In theory, it is superseded by the 2024 NASEM definition, but it can still appear in publications [186]. A critical review is in Perego 2025 [22].

2024 NASEM definition of Long COVID: produced by a NASEM committee after extensive consultation with stakeholders, it is proposed as the current benchmark in the US [21]. In brief, it defines Long COVID as a "disease state" and an "infection-associated chronic condition" that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more

organ systems". It acknowledges the broader manifestations and sequelae of SARS-CoV-2 infection. A critical review is in Perego 2025 [22].

PASC or post-acute sequelae of SARS-CoV-2 infection: especially used in the US, it generally acknowledges the wider sequelae of COVID-19, although variability in usage and meaning remain [22,52]. It is often used as synonym for Long COVID, especially in the literature.

Post-COVID-19 conditions or PCC: it was defined as "a broad term that captures illness due to both the direct and indirect effects of the virus" and equivalent to Long COVID in the US [52]. It is now less commonly used, especially after the establishment of the USG and 2024 NASEM definitions.

Post COVID is a term and case definition from Spain to identify "a set of multi-organic symptoms that persist or fluctuate after acute COVID-19 infection and are not attributable to other causes" with a minimum duration of 3 months. Established by a modified eDelphi consensus among up to 333 patients and professionals, it was promoted by the Spanish Ministry of Health, Instituto de Salud Carlos III and CIBER consortium [328].

## 10. Addendum 3: Imaging and Testing

Imaging and other tests mentioned in this review can have limitations, including but not limited to: (i) false positives; (ii) false negatives; (iii) image artifacts (e.g., something seen on imaging that is not present in reality, but appears, e.g., due to inappropriate technical factors); (iv) costs, patient safety (e.g., contrast) and lack of accessibility; (v) limited resolution for some techniques; (vi) long acquisition time for some techniques; (vii) potential impact of patient motion on image acquisition [96–101].

In addition, specific limitations related to SARS-CoV-2 infection sequelae include but are not limited to: (i) reduced or no availability for COVID-19 and Long COVID patients specifically, for example because of a lack of tailored guidelines; (ii) use in research and pre-clinical studies, but not in clinical settings; (iii) application to small cohorts only, especially for the most sensitive and costly tests; (iv) inadequate approaches to testing for a novel disease entity. For example, more standard tests such as CT lung scans have limited value in identifying specific lung pathology in COVID-19 and Long COVID, such as micro-thrombi and microvascular dysfunction in sub-subsegmental vessels [136]; however, more useful tests such as V/Q SPECT-CT might be difficult to obtain in clinical settings.

**Funding:** No funding was received for this review.

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

**Informed Consent Statement:** Not applicable. No human subject was used for this review.

**Data Availability Statement:** No new data were created for this review.

**Conflicts of Interest:** E.P. is a patient-researcher suffering from Long COVID and other chronic diseases since childhood. She took part in advocacy and research about Long COVID. She provided evidence for several institutions seeking to define Long COVID and did not receive any compensation for these contributions. She was a Long COVID Kids champion for the charity Long COVID Kids, a volunteer, unpaid role for the recognition of pediatric Long COVID. She is a member of the international federation Long COVID Rise Up, a volunteer, unpaid role for the recognition of Long COVID.

## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| AKI | Acute kidney injury |
| BBB | Blood–brain barrier |

| | |
|---|---|
| CKD | Chronic kidney disease |
| COVID-19 | Coronavirus disease 2019 |
| CT | Computed tomography |
| DVP | Deep vein thrombosis |
| E | Envelope protein of SARS-CoV-2 |
| eGFR | Estimated glomerular filtration rate |
| GMC | Grey matter concentration |
| GI | Gastrointestinal |
| LitCovid | A literature hub for tracking up-to-date scientific information about the 2019 Novel Coronavirus https://www.ncbi.nlm.nih.gov/research/coronavirus/ (last accessed on 1 February 2026) |
| KD | Kawasaki disease |
| M | Membrane protein of SARS-CoV-2 |
| MAKE | Major adverse kidney events |
| ME/CFS | Myalgic encephalomyelitis/chronic fatigue syndrome |
| MIS-C | Multi-system inflammatory syndrome in children (following SARS-CoV-2 infection) |
| MPI | Myocardial perfusion imaging |
| MRI | Magnetic resonance imaging |
| N | Nucleocapside protein of SARS-CoV-2 |
| NASEM | US National Academies of Sciences, Engineering, and Medicine |
| NICE | National Institute for Health and Care Excellence (UK) |
| PASC | Post-acute sequelae of COVID-19 or SARS-CoV-2 infection |
| PCC | Post-COVID-19 condition |
| PCC | Post-COVID-19 conditions |
| PE | Pulmonary embolism |
| PET | Positron emission tomography |
| PNS | Peripheral nervous system |
| POTS | Postural orthostatic tachycardia syndrome |
| USG | US government working definition for Long COVID |
| S | Spike protein of SARS-CoV-2 |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SPECT-CT | Single-photon emission computed tomography |
| TMA | Thrombotic microangiopathy |
| Tregs | Regulatory T cells |
| VOC | Variant of concern |
| WHO | World Health Organization |

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