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Current Topics in Post-COVID Syndromes

Edited by Alfonso J. Rodriguez-Morales

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IntechOpen Book Series
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Aims and Scope of the Series

Public health is what we as a society do collectively to contribute to and ensure the health and social conditions for the enjoyment of health as a resource for life. It can also be defined as science and research that promotes health, prevents disease, and improves populations' well-being and quality of life. Its objective is to know the risk factors that determine and condition the populations' health levels at present. At the end of the 20th century and the beginning of the 21st century, it is unjustifiable and regrettable that morbimortality according to age plays a leading role when the causes are mostly well known and therefore preventable, such as obesity, AIDS, cirrhosis, diabetes mellitus, addictions and cancer associated with the consumption of tobacco and alcohol, etc. In short, public health is science based on epidemiology and biostatistics, and currently, new technologies and artificial intelligence must be incorporated to identify patterns and trends in what we do collectively as a society to ensure living conditions and prevent risk factors that affect individual and population health. For all these reasons, it is essential to scientifically investigate and act on the determinants that impede the well-being and quality of life related to the health of people, patients, and populations in general, given that to control the determinants of diseases, it is important to control the environment and genetics. Consequently, the current fight for public health must prioritize the control of the environment, such as atmospheric and biological pollution and environmental and social biodiversity, promoting the sensitivity and training of society and its individuals by empowering them to make free and appropriate decisions about these aspects to lead healthy lifestyles based on motivation and responsibility in the face of the challenges they cope with from an individual point of view, such as dealing with the addictions that exist in today's complex world. Public health also requires an ethical vision and incorporates strategies to reduce social inequality.

Meet the Series Editor

José Antonio Mirón Canelo is a physician, doctor, and professor of Preventive Medicine and Public Health at the Faculty of Medicine and Dentistry of the University of Salamanca with over 30 years of experience. He is the director of the USAL's Expert Degree in Health Management, currently in its 13th edition. Prof. Mirón Canelo directs a research group at the Research Institute of Biomedical Sciences (IBSAL) of the University of Salamanca focused on addressing the challenges and care needs of vulnerable people and patients such as the elderly with multiple pathologies and people with disabilities and dependence. As a teacher, he has been recognized for excellence in teaching three times in a period of five years.

Meet the Volume Editor

Dr. Alfonso J. Rodriguez-Morales received his MD from Universidad Central de Venezuela, Caracas, and his MSc in Protozoology/ Parasitology from Universidad de Los Andes, Trujillo, Venezuela. He received his Diploma in Tropical Medicine & Hygiene (DT-M&H) from Universidad Peruana Cayetano Heredia, Lima, Peru, and the University of Alabama at Birmingham, Alabama, USA. He also holds a DipEd. Dr. Rodriguez-Morales is a fellow of the Royal Society for Tropical Medicine & Hygiene (FRSTMH), London, United Kingdom; of the Faculty of Travel Medicine (FFTM) of the Royal College of Physicians and Surgeons of Glasgow (RCPSG), Glasgow, Scotland, United Kingdom; of the American College of Epidemiology (FACE), USA; and the International Society for Antimicrobial Chemotherapy (FISAC). He has a HonDSc from Universidad Privada Franz Tamayo (UniFranz), Cochabamba, Bolivia. He is the President of the Latin American Society for Travel Medicine (SLAMVI) (2023-2025) and the Past President of the Colombian Infectious Diseases Association (2021–2023). He is a member of the Council (2020-2026) of the International Society for Infectious Diseases (ISID). He is a senior researcher of Colciencias (2015–2027), and a professor at the Fundación Universitaria Autónoma de las Américas, Pereira, Risaralda, Colombia, and the Universidad Científica del Sur (UCSUR), Lima, Peru. He is a visiting professor at multiple national and international universities.

Contents

Preface

The global COVID-19 pandemic has left a lasting imprint on public health systems and the lives of millions who continue to grapple with its lingering effects. As the acute phase of the pandemic has waned, a growing body of clinical, epidemiological, and translational research has brought attention to the complex and multifaceted nature of post-COVID syndromes. These encompass many persistent symptoms and dysfunctions, ranging from fatigue, cognitive impairment, and respiratory issues to cardiovascular, neurological, and psychological sequelae that may endure for months or even years after the initial infection. *Current Topics in Post-COVID Syndromes* brings together leading experts and emerging voices to explore the evolving landscape of this critical area of medicine. This volume provides a timely synthesis of current knowledge, addresses gaps in understanding, and offers clinical insights to guide the diagnosis, management, and rehabilitation of affected individuals. By framing these conditions within broader contexts, such as public health, health systems readiness, and global disparities, this work aims to advance a more holistic and equitable approach to post-pandemic care. We hope this book serves as both a scientific resource and a catalyst for continued inquiry into one of the most urgent challenges of the post-COVID era.

Considering these issues, this book presents research and clinical topics related to what has been learned in the last five years regarding PCS. The book's ten chapters are organized into three major sections: "General Aspects and Epidemiology," "Clinical Aspects," and "Pediatric Implications."

Commissioning this book by IntechOpen is partly related to my long commitment to tropical and emerging diseases, mainly vector-borne, zoonotic, and neglected tropical diseases. I am a member of the Council of the International Society for Infectious Diseases (ISID) (2020-2026) and Past President of the Colombian Association of Infectious Diseases (Asociación Colombiana de Infectología, ACIN) (2021-2023), as well as of the Committee on Tropical Medicine, Zoonoses and Travel Medicine of the ACIN. During 2020, I founded the Latin American Network of Research on COVID-19 (LANCOVID). LANCOVID has made significant contributions to the research on SARS-CoV-2/COVID-19 in Latin America. Since 2024, I have been a member of the World Health Organization (WHO) Guideline Development Group for

Clinical Management of post-COVID-19 condition (2024-2025).

Following the same philosophy we used for my twelve previous books with IntechOpen, this book is not intended to be an exhaustive compilation. Research in SARS-CoV-29/COVID-19 has become highly dynamic and changing, requiring consulting the most recent available evidence for appropriate diagnostic and special decisions.

I want to give a very special thanks to IntechOpen, particularly Maja Bozicevic, Publishing Process Manager, and Iva Simcic Mance, Senior Commissioning Editor, for the opportunity to edit this fascinating and important book and for their constant support.

I would like to take a moment to dedicate this book to my beloved family, who are spread geographically across Venezuela, Chile, and Colombia, although physically distant, they are close in our hearts (Aurora, Alfonso José, Alejandro, and Andrea, the neurologist). Katterine, my loving wife, soul, and passion, makes every day special and cares about every aspect of my life. I love her more than anything, and I am happy to have her lovely presence in our lives with our canine kids, Antonieta and Jazz. I love you more and more every day.

I would also like to thank my friends, undergraduate and postgraduate students, in Colombia, Venezuela, and Latin America. In 2019, I began working at the Fundación Universitaria Autónoma de las Américas in Pereira, Risaralda, Colombia, a new "home" that provides me with support and trust in my new endeavors in research and teaching. I would like to extend special thanks to Drs. Maria Monica Murillo, our dean at the Faculty of Medicine, and our former School of Medicine Director, Dr. Jaime Cardona-Ospina, a long-time friend and fellow, is now a PhD student in the United States of America. I would also like to thank the significant support of Dr. Jose Antonio Suárez, "Tony" (Venezuela/Panama), who has become very special to me over time, and to my friend Dr. Alberto Paniz-Mondolfi (Venezuela/USA).

Finally, I hope our readers enjoy this publication as much as I enjoyed putting it together with my talented and knowledgeable collaborators.

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Section 1

General Aspects and Epidemiology

Chapter 1

Introductory Chapter: Learning and Recognizing the Post-COVID Syndromes

Alfonso J. Rodriguez-Morales, Carmen Salazar, Luisa Sánchez, María Alejandra Ávila, Sofia Rendón, Viviana Contreras, Juan Camilo Gómez and Wilmer E. Villamil-Gómez

1. Introduction

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has profoundly reshaped global health, economies, and societies. While the acute phase of COVID-19 garnered immediate and intense medical focus, a growing body of evidence has highlighted a significant subset of individuals who continue to experience a wide range of symptoms and complications well beyond the resolution of the initial infection. These lingering or delayed manifestations have collectively been termed post-COVID-19 syndromes, also referred to as long COVID, post-acute sequelae of SARS-CoV-2 infection (PASC), or post-acute COVID-19 syndrome (PACS) [1, 2].

Post-COVID syndromes (PCS) encompass a heterogeneous spectrum of clinical manifestations that may affect virtually every organ system. Symptoms are often multi-systemic, including persistent fatigue, dyspnea, cognitive impairment ("brain fog"), neuropsychiatric disturbances, autonomic dysfunction, and musculoskeletal pain, among others [3, 4]. Importantly, these symptoms may arise following mild, moderate, or severe acute COVID-19 and are reported across all age groups, including children and adolescents [2]. The onset may be continuous or relapsing-remitting, sometimes fluctuating in intensity, which complicates diagnosis and management [3, 4].

Recognition of post-COVID conditions has evolved, driven by both patient-led initiatives and academic research. Long COVID advocacy groups, mainly composed of affected individuals, were instrumental in bringing attention to these prolonged health issues early in the pandemic. Subsequently, scientific inquiry has validated many of these patient experiences, leading to broader acknowledgment by health authorities such as the World Health Organization (WHO), the U.S. Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH). Still, significant challenges remain in standardizing definitions, diagnostic criteria, and therapeutic approaches [5].

Understanding the pathophysiology of post-COVID syndromes is a rapidly advancing area of investigation. Current hypotheses implicate immune dysregulation, viral persistence, microvascular injury, and dysautonomia as key mechanisms. Comorbidities, host genetics, and the impact of different viral variants and vaccination status may also modulate the risk and severity of these syndromes. Importantly, the interplay between physical and psychological domains must be carefully considered in both research and clinical care [6, 7].

This chapter aims to provide an updated, integrative overview of post-COVID syndromes, emphasizing their clinical recognition, underlying mechanisms, epidemiology, and evolving management strategies. It is essential that healthcare professionals, researchers, and policy makers remain vigilant and informed about this emerging facet of the pandemic's legacy. The long-term consequences of COVID-19 will likely shape healthcare systems for years to come, reinforcing the need for sustained research, surveillance, and multidisciplinary care approaches [8].

2. Epidemiology of post-COVID-19 syndromes

The epidemiology of post-COVID-19 syndromes remains complex and evolving, commonly referred to as long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC). Early studies and meta-analyses suggest that a substantial proportion of individuals infected with SARS-CoV-2 continue to experience symptoms beyond the acute phase, often lasting for weeks to months. A systematic review by Lopez-Leon et al. [7] estimated that up to 80% of COVID-19 survivors develop one or more persistent symptoms, with fatigue (58%), headache (44%), attention disorders (27%), hair loss (25%), and dyspnea (24%) being among the most frequently reported [2, 7, 8].

The definition of long COVID varies across studies and institutions, ranging from symptom persistence beyond 4 weeks to more than 12 weeks post-infection. Such variability complicates prevalence estimates. Nonetheless, consistent findings across global cohorts have confirmed the widespread nature of the syndrome. A European study found that over 50 long-term effects could persist for months after initial infection, emphasizing the syndrome's multisystemic impact [5].

Demographic and clinical predictors of long COVID include female sex, advanced age, high body mass index (BMI), presence of comorbidities, and severity of the initial infection. Reinfection with SARS-CoV-2 has also been associated with an increased risk of long COVID manifestations. Notably, long COVID is not restricted to hospitalized or severely ill patients; individuals with initially mild or even asymptomatic disease may later report significant sequelae [9, 10].

Children and adolescents are also affected, though data in pediatric populations remain more limited. Reported symptoms in younger age groups include fatigue, headaches, abdominal pain, and difficulty concentrating. These may interfere with school performance and social development, posing additional diagnostic and management challenges [2, 5, 7, 8].

Genetic factors may also influence susceptibility to post-COVID-19 syndromes. Specific genetic variants, such as those located in the LZTFL1 and IL10RB genes, have been associated with increased risk of persistent symptoms. Furthermore, psychosocial factors—such as anxiety, depression, and previous somatic complaints—may not only influence the manifestation of symptoms but also modulate recovery trajectories [11, 12].

The epidemiological burden of long COVID is significant, contributing to increased healthcare utilization, economic losses due to work incapacity, and reduced quality of life. As new variants of SARS-CoV-2 emerge and vaccine-mediated immunity alters infection patterns, ongoing surveillance and robust epidemiological studies are essential to inform public health strategies and guide clinical responses to this enduring global health challenge.

3. Main clinical aspects of PCS

Post-COVID-19 syndromes (PCS), or long COVID, represent a constellation of symptoms that persist or emerge after the acute phase of SARS-CoV-2 infection, typically beyond 4–12 weeks. PCS is a multi-organ, multifaceted condition that affects both previously hospitalized and non-hospitalized individuals across all age groups. The heterogeneity of clinical manifestations and their fluctuating nature make PCS a diagnostic and therapeutic challenge for clinicians worldwide (**Table 1**) [5, 8].

Organ system	Main clinical findings	Related laboratory findings	Imaging findings
General	Fatigue, malaise, post-exertional symptom exacerbation	Non-specific; elevated inflammatory markers (CRP, ESR), mild leukocytosis	Not routinely used; often normal
Respiratory	Dyspnea, chronic cough, reduced exercise tolerance	Hypoxia, abnormal pulmonary function tests (PFTs), elevated D-dimer	Ground-glass opacities or fibrotic changes on chest CT, abnormal chest X-ray
Cardiovascular	Chest pain, palpitations, tachycardia, postural orthostatic tachycardia syndrome (POTS)	Elevated troponins, NT-proBNP, abnormal ECG/ holter findings	Echocardiography: reduced LVEF, pericardial effusion; cardiac MRI: myocarditis
Neurological	Brain fog, headaches, dizziness, paresthesias, seizures	Normal or elevated inflammatory markers, and autoantibodies in some cases	Brain MRI usually normal; occasional white matter lesions or perfusion changes
Neuropsychiatric	Anxiety, depression, insomnia, PTSD	Elevated cortisol, abnormal thyroid function tests, and elevated CRP in some cases	Brain imaging typically unremarkable
Gastrointestinal	Diarrhea, nausea, abdominal pain, and appetite loss	Occasional mild transaminase elevations, abnormal stool tests	Abdominal ultrasound is often normal; mild bowel wall thickening in some cases
Hepatic	Elevated liver enzymes, right upper quadrant discomfort	Mild-to-moderate transaminase elevation (ALT, AST), elevated bilirubin	Ultrasound or CT may show hepatomegaly or steatosis
Musculoskeletal	Myalgia, arthralgia, joint stiffness	Elevated creatine kinase (CK), lactate, and inflammatory markers	Joint X-rays are usually normal; MRI may show soft tissue inflammation
Dermatologic	Hair loss (telogen effluvium), skin rashes	None specific; occasionally abnormal ANA or inflammatory markers	Dermatologic imaging is not typically used
Endocrine and metabolic	New-onset diabetes, menstrual irregularities, thyroid dysfunction, weight changes	Elevated fasting glucose, HbA1c, abnormal TSH, low vitamin D	Thyroid ultrasound may reveal inflammation; pancreatic imaging is rarely needed
Renal	Mild proteinuria, altered renal function (less common)	Increased creatinine, mild proteinuria	Renal ultrasound is usually routine; CT scan if AKI suspected
Pediatric specific	Fatigue, attention deficit, school difficulties, abdominal pain, mood changes	Often normal; inflammatory markers occasionally elevated	Chest imaging may show subtle changes; brain MRI is rarely abnormal

Table 1.
Main clinical, laboratory, and imaging findings of PCS by organs and systems.

3.1 Multisystemic symptomatology

PCS commonly affects multiple organ systems, with symptoms that may be continuous, relapsing, or waxing and waning. Fatigue is the most frequently reported symptom, affecting over half of patients in several studies. This fatigue is often profound, disproportionate to activity, and may worsen with exertion, resembling myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [13, 14].

Respiratory symptoms, particularly dyspnea and persistent cough, are prominent even in those with mild initial disease. These may result from lingering pulmonary inflammation, interstitial changes, or reduced respiratory muscle strength. Some individuals present with exertional hypoxia, requiring prolonged oxygen therapy or pulmonary rehabilitation [15, 16].

Cardiovascular complaints include chest pain, palpitations, and postural tachycardia syndrome (POTS), suggestive of autonomic nervous system dysregulation. Myocardial inflammation and arrhythmias have also been documented on imaging and telemetry, even in asymptomatic individuals [17, 18].

3.2 Neurocognitive and neuropsychiatric symptoms

Cognitive dysfunction—or "brain fog"—is a hallmark feature, characterized by impaired concentration, memory deficits, and slowed thinking. This may significantly impact daily functioning and work productivity. Neuropsychiatric symptoms such as anxiety, depression, insomnia, and post-traumatic stress disorder (PTSD) are common, particularly among previously hospitalized patients, including those who required intensive care [19, 20].

Headache and dizziness are also frequent, and in some cases, more severe neurological complications such as peripheral neuropathy, encephalopathy, and seizures have been described. These manifestations highlight the neurotropic potential of SARS-CoV-2 and possible immune-mediated mechanisms contributing to long-term neurological sequelae [21, 22].

3.3 Gastrointestinal and hepatic involvement

Patients with PCS may experience gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, and loss of appetite. Liver enzyme abnormalities, although often mild, may persist for months, reflecting ongoing hepatic inflammation or drug-related injury during acute illness. Alterations in gut microbiota ("dysbiosis") have also been postulated as contributing to chronic gastrointestinal complaints [23, 24].

3.4 Musculoskeletal and dermatologic manifestations

Myalgia, arthralgia, and generalized musculoskeletal pain are prevalent and often debilitating. These symptoms may mimic fibromyalgia and are commonly associated with fatigue and sleep disturbances. Hair loss (telogen effluvium) is another frequent complaint. It often appears weeks after infection and is linked to the physiological stress of illness rather than direct viral effects [25, 26].

3.5 Endocrine and metabolic effects

New-onset or worsening of diabetes mellitus, menstrual irregularities, and thyroid dysfunction have been observed in PCS. The exact mechanisms remain under investigation but may involve direct viral injury to endocrine organs, autoimmunity, or systemic inflammatory responses. Weight fluctuations and dysregulated appetite are also frequently reported [27, 28].

3.6 Pediatric considerations

Although manifestations differ from adults, children and adolescents may also develop PCS. Fatigue, difficulty concentrating, abdominal pain, and mood changes are among the most reported symptoms. While most children recover fully, some experience significant disruption to school attendance and developmental milestones, underscoring the importance of pediatric-specific diagnostic and support strategies [29, 30].

3.7 Clustering and phenotyping of PCS

Recent studies have proposed symptom clustering to characterize the syndrome better. For instance, four main clusters have been described: [1] low symptom burden, [2] high symptom burden, [3] respiratory and anosmia-related symptoms, and [4] neurocognitive and psychosocial symptoms. Identifying such clusters can help personalize management approaches and facilitate targeted research [31, 32].

3.8 Impact on quality of life

The chronicity, unpredictability, and multiplicity of PCS symptoms significantly impact patients' quality of life, functional capacity, and psychological well-being. Many patients report difficulty returning to work or resuming normal activities, leading to social and economic consequences. The burden on healthcare systems is considerable, with increasing demand for rehabilitation, mental health services, and multidisciplinary care [33, 34].

4. Research challenges on PCS

Despite growing awareness and scientific interest, the research landscape surrounding post-COVID-19 syndromes (PCS) faces numerous challenges that hinder comprehensive understanding and effective response. These obstacles span definitions, methodologies, population heterogeneity, and resource allocation, all of which complicate generating robust, generalizable evidence [2, 4, 5, 34].

One of the most fundamental limitations in PCS research is the absence of universally accepted diagnostic criteria. Variability in definitions—from symptom persistence beyond 4 weeks to more than 12 weeks—makes it difficult to compare studies and synthesize findings across cohorts. Moreover, "long COVID" lacks clinical specificity, and many studies rely on self-reported symptoms without objective diagnostic tools or biomarkers [35, 36].

PCS is characterized by a highly heterogeneous symptom profile, affecting multiple systems with variable onset and duration. This diversity complicates patient stratification, recruitment for clinical trials, and interpretation of outcomes. Furthermore, symptoms can overlap with other post-viral syndromes or pre-existing conditions, creating diagnostic ambiguity [36, 37].

Many early studies were limited to hospitalized patients in high-income countries, neglecting community cases, low- and middle-income populations, and pediatric groups. This restricts the generalizability of findings and may underrepresent the actual burden of PCS. There is also a paucity of large-scale, longitudinal cohort studies that follow individuals beyond 1-year post-infection to understand the natural history and resolution patterns of symptoms [38, 39].

The underlying mechanisms of PCS remain largely speculative, involving hypotheses such as viral persistence, immune dysregulation, microvascular dysfunction, and autonomic imbalance. However, definitive evidence is lacking due to the absence of validated biomarkers and limited access to tissue samples or advanced imaging. This knowledge gap impedes the development of targeted therapies and diagnostic tests [40, 41].

The global research response to PCS has been uneven. While some nations have launched dedicated initiatives, such as the NIH's RECOVER program, many others lack coordinated strategies or funding. Multidisciplinary collaboration across clinical, translational, and public health domains is essential, yet often limited by siloed approaches and bureaucratic barriers [42].

Overcoming these research challenges is critical to advancing knowledge, improving patient outcomes, and preparing for future post-viral syndromes. Harmonized definitions, inclusive and longitudinal studies, and global collaboration are indispensable for building a comprehensive understanding of PCS.

5. Conclusions

Post-COVID-19 syndromes (PCS), or long COVID, have emerged as one of the most complex and enduring public health challenges following the global SARS-CoV-2 pandemic. While the world has made significant progress in reducing acute COVID-19 morbidity and mortality through vaccination, antiviral therapies, and public health interventions, the long-term consequences of infection continue to affect millions of individuals across diverse populations. PCS encapsulates a broad and heterogeneous spectrum of symptoms that persist or appear after the acute phase of infection, often impairing quality of life and functional capacity for weeks or months.

The clinical presentation of PCS is multifaceted, involving fatigue, dyspnea, neurocognitive disturbances, musculoskeletal pain, autonomic dysfunction, and neuropsychiatric symptoms. These manifestations can vary in intensity, duration, and trajectory, challenging diagnosis and management. Notably, PCS is not restricted to those who experienced severe acute COVID-19; it also affects individuals with mild or asymptomatic infections. Furthermore, the syndrome does not discriminate by age, and children, adolescents, and adults can all be affected, albeit with different clinical patterns and implications.

Epidemiological data indicate a substantial global burden of PCS, with prevalence estimates ranging widely depending on the population studied, the definition applied, and the duration of follow-up. Evidence suggests that risk factors for PCS include female sex, higher body mass index, comorbidities, reinfection, and the severity of the initial infection. However, many cases occur in previously healthy individuals, underlining the need for continued vigilance and surveillance in all patient groups.

From a pathophysiological standpoint, the mechanisms underlying PCS remain incompletely understood. Hypotheses include viral persistence, immune dysregulation, autoimmunity, endothelial dysfunction, and alterations in the microbiome, among others. These diverse pathways may interact complexly, explaining the wide variability in clinical manifestations. Ongoing research efforts are crucial to identifying specific biomarkers and mechanistic targets for diagnosis and therapy.

Despite increasing attention, PCS research faces significant challenges, including inconsistent definitions, methodological heterogeneity, underrepresentation of vulnerable populations, and limited longitudinal data. The lack of standardized diagnostic criteria and objective testing tools hampers clinical care and scientific progress. Coordinated, multidisciplinary efforts—both nationally and internationally—are essential to overcome these barriers and develop evidence-based approaches for diagnosis, treatment, and rehabilitation.

Equally important is the need for healthcare systems to adapt and respond to the long-term care requirements of individuals with PCS. This includes training for healthcare professionals, integrating multidisciplinary teams, establishing post-COVID care units, and developing patient-centered rehabilitation strategies. Public health responses must also include education, destigmatization, and support for affected individuals to reduce the psychosocial and economic burden of long COVID.

In conclusion, PCS represents a significant, multifactorial, evolving public health issue that demands sustained attention, research, and healthcare innovation. Learning to recognize and manage these post-infectious syndromes is critical for current patients and preparing for future pandemics where long-term sequelae may similarly emerge. The lessons learned from PCS will undoubtedly shape the future of infectious disease care, chronic illness management, and interdisciplinary research for years to come.

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Chapter 2

Perspective Chapter: What Happens When You Don't Recover from COVID-19?

Raj Kamal Choudhary

Abstract

The immense impact of COVID-19 would not have been anticipated by 7.5 billion people worldwide a few years ago. According to the World Health Organization (WHO), the initial detectable instance of COVID-19 was identified in the Wuhan province of China in December 2019. Subsequently, on January 30, 2020, WHO declared the disease a global emergency. Others, however, contended that the virus had been unnoticedly disseminated across the region for several months prior to the pandemic. The single-stranded RNA virus has the potential to induce severe respiratory complications and is transmitted via aerosol droplets. According to the initial investigations conducted by the CDC, the infectivity (R0) of the novel strain of the Coronavirus is estimated to be 2.5. This indicates that, on average, one infected individual could transmit the virus to 2.5 noninfected individuals. The annual aR0 for the prevalent influenza virus is less than one. Due to the absence of effective treatment and the prospect of the vaccine in 2021, the global community has been subjected to the catastrophic effects of COVID-19. Based on the statistical data regarding the pandemic that was published by Johns Hopkins University in the United States as of 30 June 2020, the global cumulative number of fatalities accounted for 502,123, while the confirmed cases numbered 10,245,217. To date, the COVID-19 pandemic remains a significant threat to worldwide public health and safety while exerting a considerable influence on socioeconomic progress on a global scale.

Keywords: thromboembolism, myocarditis, ischemic heart disease, acute kidney failure, pyrexia of unknown origin

1. Introduction

The immense impact of COVID-19 would not have been anticipated by 7.5 billion people worldwide a few years ago. According to the World Health Organization (WHO), the initial detectable instance of COVID-19 was identified in the Wuhan province of China in December 2019. Subsequently, on January 30, 2020, WHO declared the disease a global emergency. Others, however, contended that the virus had been unnoticedly disseminated across the region for several months prior to the pandemic [1]. The single-stranded RNA virus has the potential to induce severe respiratory complications and is transmitted via aerosol droplets. According to the initial investigations conducted by the CDC, the infectivity (R0) of the novel strain of the coronavirus is estimated to be 2.5. This indicates that, on average, one infected individual could transmit the virus to 2.5 noninfected individuals [2]. The annual aR0 for the prevalent influenza virus is less than one. Due to the absence of effective treatment and the prospect of the vaccine in 2021, the global community has been subjected to the catastrophic effects of COVID-19. Based on the statistical data regarding the pandemic that was published by Johns Hopkins University in the United States as of 30 June 2020, the global cumulative number of fatalities accounted for 502,123, while the confirmed cases numbered 10,245,217. To date, the COVID-19 pandemic remains a significant threat to worldwide public health and safety while exerting a considerable influence on socioeconomic progress on a global scale [1–5].

The clinical manifestations of COVID-19 are diverse, spanning from asymptomatic to severe. This is due to the complexity of the disease. The cardiovascular, respiratory, gastrointestinal, neurological, hematological, and immune systems are all affected by the disease, which is classified as a systematic infection [6–8]. The documented mortality rate varies from 1 to 7% [9]; respiratory failure, septic shock, multiorgan failure, and cardiac arrest were regarded as the primary causes of death [10, 11]. Acute respiratory distress syndrome (ARDS) was observed in 41.8% of patients infected with COVID-19; this proportion is highest among those who have chronic kidney injury, diabetes mellitus, hypertension, or cardiovascular disease [12]. The occurrence of severe cases of COVID-19, such as myocardial injury (acute coronary syndrome, myocarditis, heart failure, hypertension, shock, and sepsis), is significantly correlated with mortality. This correlation has been elucidated by the cytokine storm generated subsequent to SARS-Cov-2 infection and the presence of Angiotension - Convertign Enzyme 2 (ACE2) in myocardial cells [11, 13, 14]. Additionally, disseminated intravascular coagulation and thrombotic macroangiopathy are coagulation abnormalities associated with COVID-19 that result from inflammation-induced endothelial cell injury and a massive release of plasminogen activators [15]. Additional complications associated with COVID-19 have been documented, including AKI, coinfection with another pathogen, thromboembolism, and multiorgan failure [12].

The widespread, profound effect of the COVID-19 pandemic has prompted a demand for international collaborative research on mental health, encompassing psychological assessment as well as an awareness of the influence of recurrent health massaging and media exposure in relation to the virus and pandemic [16]. Psychological repercussions have been observed on a global scale throughout the course of the pandemic. They may have an enduring impact on the well-being of communities and individuals, in addition to the impending response to the COVID-19 pandemic, by affecting comprehension, attention, and decision-making ability. The COVID-19 pandemic has consistently been associated with elevated levels of tension, anxiety, and depression in different nations, according to the recent research. A review of four Chinese studies revealed that 16–20% of respondents exhibited symptoms of anxiety and depression [17].

A study conducted in Germany, which included more than 6000 participants, revealed that more than 50% of the respondents reported experiencing anxiety and distress in relation to the COVID-19 pandemic [18]. Results regarding mental tension levels that are similarly correlated were also documented in Italy and Spain [19, 20]. Additional results obtained from a survey carried out in Bangladesh revealed that more than 85% of the respondents experienced stress related to COVID-19; this stress manifested as sleep disturbance, irritability, and hormonal disorder in females [21]. One month subsequent to the issuance of a state of emergency in the United States of America (USA), a document elevated rates of anxiety and depression, specifically 45.4 and 43.3%, respectively [22].

The long-term consequences of COVID-19, which are interchangeably known as a post-COVID sequel, long COVUD, post-acute COVID-19, and post-COVID condition, are an undetermined duration inflammatory or host response to the virus that develops around 4 weeks after the initial infection. The US Center for Disease Control and Prevention estimate, based on the Census Bureau Household Pulse Survey, that less than 6% of adults in the United States experience the emergence of new symptoms more than three months after COVID-19. 87% of those individuals report that their newly developed symptoms significantly impede their capacity to perform routine tasks, while 26% indicated that their activity level is significantly restricted. The annual economic toll of PASC in the US is estimated to be around $743 billion, taking into account factors such as diminished quality of life, decreased wages, and increased medical expenditures [23].

The objective of the review is to provide clinicians with current information on the systematic effects of long-term COVID-19 infections, including prevalence, possible causes, pathophysiology, long COVID subtypes, clinical predictors and risk factors, mental health impacts, economic and societal impact, unanswered questions, and future directions. This information is intended to assist clinicians in managing long-haul COVID-19 cases.

2. Post-acute sequel of COVID-19

A subgroup of SARS-CoV-2-infected patients get additional symptoms or further effects that take months or years for full recovery. This condition is referred to as a post-acute sequel of COVID-19 (PASC) or long COVID. While the majority of the individuals recover rapidly from the acute disease, a subgroup may experience prolonged symptoms or the development of new symptoms following the initial disease [24, 25]. There have been reports of risk factors for severe disease and the possibility that severe disease is associated with chronic sequelae [26, 27]; this is consistent with previous studies that have documented the symptomatic persistence of other coronavirus infections [28–30]. Initially, the condition was referred to as long COVID-19 or post-COVID-19, which encompasses symptoms that persisted long after individuals had recovered from the acute infection. The terminology has been updated more recently.

The term "post-COVID-19" condition has been revised to mean a state of being that endures for a minimum of two months and three months after the initiation of the symptoms. The syndrome of persistent symptoms, termed "post-acute sequelae of COVID-19" (PASC), typically persists for over four weeks following recovery from acute COVID-19 [31]. Patients with PASC typically have either vague symptoms like exhaustion and dyspnea or severe single or multisystem consequences such as heart problems, thrombosis of blood, kidney problems, psychological problems, and neurological problems [32]. An initial study reported up to 76% of patients discharged from the hospital had at least one remaining symptom 6 months after the onset of COVID-19, with more women affected than men. A recent study showed that just 65% of persons had returned to their usual state of health 14–21 days after a positive COVID-19 test. An initial study found that six months after the onset of COVID-19, up to 76% of hospital discharged patients still have at least one symptom, with a higher proportion of women affected compared to men. Only 65% of individuals had returned to their normal stage of health within 14–21 days of a COVID-19 test, according to a recent study for SARS-CoV-2.

Tissue biopsy studies, studies from SARS-CoV-2 patients in plasma, and studies inferring the presence of SARS-CoV-2 reservoir in tissue based on the characteristics of the adaptive immune response provide the majority of the evidence for the existence of a SARS-CoV-2 in PASC. A tissue biopsy study on endoscopy-undergoing individuals with inflammatory bowel disease [33]. Seven months after COVID-19, despite experiencing modest acute infections, 70% of the patients still had SARS-CoV-2 RNA in intestinal mucosal tissue, and 52% had nucleocapsid (N) protein in the intestinal epithelium. Persistence of viral RNA and protein was associated with PASC symptoms, but it was unrelated to the severity of acute COVID-19 or immunosuppressive therapy.

In colorectal tissue taken from five patients who developed PASC between 158 and 676 days after their first COVID-19 infection, another researcher discovered RNA encoding the SARS-CoV-2 spike protein. A large group of individuals with higher T-cell activation in the spinal cord and gut, as shown by whole-body PET imaging, were included in a questionnaire. The activation was different from that of patients who had recovered effectively from COVID-19 and pre-pandemic control individuals [34]. In the skin, appendix, and breast tissues of two patients who had PASC symptoms 163 and 426 days following acute COVID-19 infection, SARS-CoV2 RNA and N protein have been found [35]. Three patients with negative findings for nasopharyngeal swab PCR using reverse transcription (RT_PCR) but persistent anosmia also had SARS-CoV-2 RNA and protein found in olfactory mucosa samples 110–196 days after the onset of symptoms [36]. Many investigations have shown SARS-CoV-2 proteins in PASC plasma months or even more than a year following acute COVID-19 infection. The protein "leaks" into the bloodstream, whereas it may be detected, but it most likely originated from PASC tissue reservoir locations. Schult heiß et al. found SARS-CoV-2 S1 protein in the plasma of around 64% of PASC study participants recruited at a median of 8 months (range 1–17 months) after acute COVID-19, but only in 35% of convalescent control patients in a study limited to unvaccinated individuals [36].

Swank et al. detected spike protein S1 or N protein in around 65% of plasma samples taken from PASC patients a few months following SARS-CoV-2 infection using an enhanced ultrasensitive single-molecular array (Simoa) technique [37]. In 60% of PASC participants up to 12 months after COVID-19 onset, a rise was seen; in COVID-19 convalescent control patients, no spike protein was found. Out of the 37 PASC participants, twelve had multiple viral protein detections at different time points, from which the researchers had gathered longitudinal samples. Furthermore, in a different post-acute cohort that included PAC and fully recovered individuals, additional Simoa analysis revealed that 24% of all post-acute participants had at least one detectable SARS-CoV-2 protein in plasma at least once up to 16 months after COVID-19 [34]. However, the majority of data were collected prior to participants receiving any SARS-CoV-2 vaccine, which could have been a confounding factor in these analyses [38]. The more severe initial infection was linked to the existence of persistent protein; the highest proportion of protein persistence was found in the most symptomatic individuals (35% of those with nine or more symptoms). Remarkably, a portion of recuperating control patients (18%) who declared complete recuperation additionally exhibited detectable viral protein in their bloodstream.

3. Long COVID subtypes

New studies are currently underway to evaluate whether distinct SARS-CoV-2 subtypes or certain pandemic waves are linked to the post-COVID-19 infection and maybe to other subtypes. Research has employed PCR variant testing at various times (e.g., pandemic waves) as a stand-in for distinct variations. In published prospective cohort research from Norway, almost 35,000 participants with verified diagnoses (based on genetic testing) of the Delta and Omicron variants were compared using data from a national registry [39]. According to the research, individuals with either variation in fatigue or shortness of breath are more frequent than those without COVID-19 infection. However, the study found no statistically significant changes in the kind of frequency of commonly reported post-COVID-19 symptoms between the two genotypes [39]. A case-control study was conducted to assess the chances of acquiring long COVID, which is defined as new or continuous symptoms lasting at least four weeks between two COVID-19 waves. The study used the data from the COVID symptoms research [40].

Researchers identified two time periods in which over 70% of instances were consistent with either the Omicron or Delta variants [41]. According to the study, individuals with Omicron variant infection had a lower likelihood of having a long COVID-19 than those with a Delta variant infection, with an odds ratio ranging from 0.24 to 0.50 [41]. The study indicated that various variants could be linked to distinct risk profiles, even though it did not evaluate if the clinical characteristics of individuals who acquired protracted COVID differed between the two variants. The National Institute of Health and Care Excellence's classifications of extended COVID (symptoms lasting more than 4 weeks) and post-COVID (symptoms lasting more than 12 weeks) were compared in the study's clinical manifestation. A clustering study showed that the wild-type, Alpha, and Delta variants had varying numbers of symptom clusters. These clusters varied in severity and impacted several distinct organ systems [42]. But out of all the variants that were taken into consideration, the three most prevalent clusters were the systematic/inflammatory clusters (which was prevalent in all variants but at a lower frequency), the cardiorespiratory cluster (which was more prominent in the wild type of variant), and the central neurologic cluster (which was prominent in the Alpha and Delta variants) [42]. People with the Delta variants were more likely to experience neurologic symptoms (such as headache, anosmia, and ageusia), according to Spanish research looking at hospital survivors who were infected with the same three variants [43].

4. Prevalence and risk factor

Estimating the real prevalence of long-term COVID has been difficult due to the wide range of people's experiences. Some people experience many continuous symptoms that alter over time, while others only have one chronic condition. The symptoms might vary in degree and duration. The risk factors for acute COVID-19 and PASC are still being investigated. They are primarily genetic, gender differences, age, co-morbid conditions, and environmental, behavioral, and lifestyle variables.

5. Genetic factors

5.1 HLA types

The Human Leukocyte Antigen (HLA) system promotes immunological control by presenting processed peptide antigens to T-cells. Certain HLA haplotypes have been linked to a genetic predisposition to COVID-19 and may affect illness outcomes. The HLA-B46:01114 haplotype contains fewer binding sites for SARS-CoV-2, but the HLA-B15:03 haplotype can provide more conserved SARS-CoV-2 peptides. Individuals with the HLA-B*46:01114 haplotype may have a greater risk of severe illness due to reduced immune system exposure to SARS-CoV-2 peptides. A kind of HLA's ability to generate immunological responses may also influence the course of COVID-19 and PASC. In patients with systemic lupus erythematosus (SLE), for instance, DRB1*15:01–DRB5*01:01–DQA1*01:02–DQB1*06:02 are overrepresented, whereas HLA-DRB1*03, HLA-DRB1*15, and HLA-DRB1*04 are overrepresented and determine the type of auto-antibodies and SLE symptoms.

Remarkably, at 8 months, PASC patients' levels of highly activated CD38 + HLA-DR+ myeloid cells are higher than those of controls [44]. HLA-B*35 has also been linked to post-COVID subacute thyroiditis. Furthermore, distinct SARS-CoV-2 peptides may be more or less immunogenic at different HLAs; the most immunogenic ligands are those supplied by HLA-B*40:01. To find out whether HLA haplotypes can more accurately predict PASC in specific individuals, more study is required.

5.2 Sex differences

According to research, having biological intercourse increases your chance of contracting COVID-19. Male-to-female physiological variations that impact the intensity of infection and autoimmune reactions are probably the cause of this [45–48].

5.3 Studies in males

According to one study, the risk of in-hospital mortality from COVID-19 is eighteen times greater in men, indicating a higher likelihood of hospitalization and death [49]. Over 89.8% of male hospital patients had low testosterone levels, according to another study [50]. The data linking acute COVID-19 susceptibility to testosterone has been debatable nonetheless. For instance, compared to patients without androgen deprivation treatment (ADT), patients with prostate cancer who had ADT had a considerably lower incidence of COVID-19 [51]. Conversely, larger levels of free testosterone were linked to more severe COVID-19 in males [52].

A correlation has been seen between male libido reduction and erectile dysfunction in PASC [53, 54]. However, at this point, it is unknown if the symptoms seen in males with PASC are caused by male sex, hypogonadism (caused by direct gonadal or hypothalamus SARS-CoV-2 damage resulting in low testosterone), or other variables (such as stress, depression, or immunological dysregulation). Clarifying male-specific risk factors for acute COVID-19 and PASC, such as hormones and hereditary vs. environmental hazards, would require more investigation.

5.4 Studies in females

In a 4:1 female:male ratio, females seem to be more prone to PASC, even while men may be more susceptible to acute COVID-19 [55, 56].

It is noteworthy that the hormonal condition of females might influence their susceptibility to acute COVID-19 and PASC. For instance, estrogen augmentation was linked to a lower risk of mortality from acute COVID-19 in postmenopausal women, and menopause has been linked to an increased risk for severe acute COVID-19 illness [57, 58]. Similarly, compared to women before menopause, postmenopausal women had a greater incidence of acute COVID-19 infections, which suggests that estrogen may have an impact on the severity of acute COVID-19 illness [59].

Sex differences in COVID-19 results have been linked to genes on the X chromosome. Notably, the X chromosome is home to angiotensin converting enzyme 2 (ACE2), the primary receptor for SARS-CoV-2 entrance into cells [60]. Compared to males, females have lower levels of ACE2 expression in their lungs, and estrogen suppresses this expression [61, 62]. The reduced severity of acute COVID-19 and lesser viral entry may thus be explained by decreased ACE2 expression in females. Moreover, another X chromosome immune gene is Toll-like receptor 7 (TLR7), which controls the synthesis of interferon (IFN) [63]. According to Souyris et al. [64], there is evidence that higher TLR7 expression levels correlate with increased IFN signaling in acute COVID-19 cases and better viral clearance in females. However, sustained IFN signaling may also result in excessive immune activation and chronic inflammation, which could put females at risk for autoimmunity and PASC. To completely comprehend the function of sex chromosomal genes and hormones in male vs. female-specific hazards in acute COVID-19 and PASC, more study is required.

5.5 Age in PASC

The significance of age in PASC has been debated, with some studies suggesting age to be a major predictor of PASC, with incidence rates ranging from 9.9% in 18–49 year old patients to 21.9% in those over 70 [65]. Research suggests that women aged 40–60 had a higher risk of PASC [66, 67]. In contrast, several studies discovered that PASC risk declines with age or has no connection [68, 69]. Further study is needed to discover if specific age groups are more prone to PASC, as it is unclear whether age is an independent risk factor.

6. Environmental, behavioral, and lifestyle risk factors of acute SARS-CoV-2 infection and PASC

Environmental and behavioral risk factors have been shown to impact disease outcomes. In this part, we will look at the reactivation of Epstein-Barr Virus (EBV), gut microbiota, and lifestyle variables in acute SARS-CoV-2 infection and PASC.

6.1 EBV reactivation in PASC

Gold et al. first observed that in PASC, early antigen-diffuse immunoglobulin G antibody titers were positively correlated with the frequency of PASC-related symptoms, with 66.7% of PASC patients and only 10% of the controls testing positive for EBV reactivation [70]. Su et al. examined the link between EBV viremia and SARS-CoV-2 RNAemia and PASC and discovered that measures of both at the time of acute COVID-19 diagnosis were substantially correlated with memory issues associated to PASC later on [71]. Interestingly, it is interesting to note that sputum production and weariness were exclusive to EBV viremia in PASC patients. Additionally, Peluso et al. have shown that EBV reaction is especially related to tiredness and neurologic symptoms, suggesting that it may be a major role in PASC [34].

Treatments for reactivated EBV in the absence of COVID-19 may also be helpful to look into as therapy to address EBV reactivation in acute COVID-19 and PASC, given the documented EBV reactivation in acute SARS-CoV-2 infection and PASC.

For instance, rituximab, an anti-CD20 monoclonal antibody, has been used to treat reactivated EBV following hematopoietic cell transplantation [72]. Acyclovir, ganciclovir, and vidarabine are examples of other antiviral medications that have been used to treat chronic active EBV; however, they have not been proven to be useful in treating chronic non-active EBV [73]. Another possible treatment is the infusion of immunoglobulins (IVIG), which has been used effectively in a few critically ill patients who did not have SARS-CoV-2 infection and may help with acute COVID-19 or PASC [74]. To find out if the therapies for EBV reactivation unrelated to SARS-CoV-2 are also helpful in treating acute COVID-19 and PASC, more study is required.

6.2 Diet in PASC

Balanced diets high in whole grains, veggies high in polyphenols, and foods high in omega-3 fatty acids may lessen inflammation and weariness in autoimmune illnesses [75]. There are now over twenty trials registered on clinicaltrials.gov that explore the possibility of treating PASC patients, who are believed to have immunological dysregulation, with an anti-inflammatory diet or supplements. However, an antihistamine diet is one such diet gaining traction with patients, as PASC may be influenced by mast cell overactivation and histamine production [76, 77]. Diamine oxidase deficiency that results in mast cell activation syndrome may be linked to histamine intolerance in PASC [78]. Blue fish and fermented foods such as cheeses, sausages, wine, beer, sauerkraut, and fermented soy derivatives are foods rich in histamine [79]. A low-histamine diet might include avoiding certain items, but there is not much study on this at the moment [80].

Increasing the amount of salt, water, and electrolytes consumed may help reduce tiredness due to PASC, which is primarily caused by autonomic dysfunction in POTS (Postural Orthostatic Tachycardia Syndrome) [81]. Meals should be smaller and more often; diets high in fiber and probiotics may help with GI issues associated with POTS. It was recently discovered that a high-quality diet (above 40% of the Alternate Healthy Eating Index-2010 score) was protective against PASC; however, given the variability of PASC clinical presentations, more research is required to ascertain whether particular dietary interventions can treat various PASC symptoms [82].

6.3 Alcohol in PASC

Excessive alcohol consumption alters many pathophysiological processes through the elevation of proinflammatory cytokine levels, interference with alveolar macrophage functions in the lungs, and desensitization of respiratory ciliated cells [83]. Persistent high-dose alcohol use may worsen inflammation by upregulating cytokines, as persistent inflammation is one of the features of PASC. How alcohol interacts with or causes PASC is yet unknown, though. Further investigations, including the NIH RECOVER experiment, are presently being conducted addressing alcohol and susceptibility to PASC in light of the discrepancy in existing research and the considerable rise in alcohol sales during the pandemic [84].

6.4 Smoking in PASC

According to recent findings, smoking may raise the risk of PASC [85]. In particular, smokers had a higher risk of tachycardia and/or elevated blood pressure.

But much like with alcohol, research on the effects of smoking on PASC patients is still ongoing, and more investigation is required to establish a causal connection.

7. Symptoms and complications

7.1 Chronic fatigue

Similar to central sensitization syndrome with chronic tiredness or chronic fatigue syndrome, some people have persistent weariness. Investigating and, if feasible, correcting additional potential reasons, such as dietary inadequacies, is advised. The treatment of patients with myalgia, exhaustion, and exercise intolerance is poorly documented. Some interdisciplinary hospitals, like the Mayo Clinic, have put in place programs for cognitive behavioral therapy to help patients get well from these symptoms.

7.2 Cardiovascular complications

Patients with COVID-19 frequently exhibit symptoms of myocardial damage, such as myocarditis and heart failure, as well as an aggravation of pre-existing cardiovascular illness, as shown by higher brain natriuretic peptide (BNP) and troponin T (TnT) levels [86]. Potential mechanisms of injury include the following:

- elevated pulmonary vascular resistance, which leads to right heart failure and pulmonary hypertension.

- excessive stimulation of the renin-angiotensin system (RAS), which can cause hypokalemia and cardiac arrhythmias as well as other harmful effects on the cardiovascular system, including secondary hyperaldosteronism [87].

- proinflammatory cytokines cause the rupture of atherosclerotic plaque, which in turn causes an infarction, particularly when coronary artery disorders are already present [88].

- myocardial oxygen supply/demand mismatch from the combination of reduced venous return and severe hypoxemia owing to ARDS, leading to myocardial ischemia/necrosis.

- ACE-2-mediated viral invasion of cardiomyocytes culminating in myocarditis.

- Potential cardiotoxicity of anti-COVID agents includes the macrolide antibiotic azithromycin, which has been correlated to a prolonged QT interval [89]; the conduction defect-inducing agent chloroquine/hydroxychloroquine; the cholesterol-raising agent tocilizumab [90]; and the protease inhibitors lopinavir/ritonavir, which may cause an extension of the PR and QT intervals and impede CYP3A4 activity, which affects metabolite [91].

Myocardial injury is characterized by a remodeling process that encompasses fibrosis and hypertrophy of the left ventricular wall. This results in diminished contractility and impaired global function [92]. TGF-β, being the primary profibrotic cytokine, plays a significant role in this remodeling process. Although it may be premature to forecast the long-term cardiac ramifications of COVID-19, extrapolation from SARS-CoV-1 patients is feasible due to the genetic resemblances between the two viruses. Specifically, 40% of SARS-CoV-1 patients exhibited cardiovascular abnormalities after 12 years of follow-up [93].

In addition to atrial fibrillation induced by hypoxia, severe and persistent disease may result from underlying cardiovascular conditions. Acute myocardial infarction is the most common cardiovascular complication of COVID-19, affecting 8–12% of patients [94, 95]. Persisting cardiovascular PASC disorders consist of pericarditis, fibrosis, myocarditis, and scarring [96]. 15% of the patients in a study of twenty-six competitive collegiate athletes with moderate to asymptomatic disease and cardiac magnetic resonance imaging (MRI) revealed myocarditis. Interestingly, 30.8% of the patients also exhibited signs of prior myocardial infarction [97].

An estimated 20% of patients with pre-existing heart disease experience myocardial infarction, congestive heart failure, cardiomyopathy, or arrhythmias [96, 97]. Angiocardial MRI data indicates that myocardial inflammation could reach 60% or more more than sixty days after an infection diagnosis. At sixty days post-infection, twenty percent of patients have reported chest discomfort.

7.3 Pulmonary fibrosis and dysfunction

Although mild or asymptomatic symptoms characterize the majority of COVID-19 cases, an estimated 5–8% of infected individuals progress to adult respiratory distress syndrome (ARDS). This condition is distinguished by symptoms such as decreased lung compliance, bilateral pulmonary infiltrates resulting from non-cardiogenic pulmonary edema, and hypoxemia. Mechanical ventilation is frequently necessary in ARDS [98]. It is hypothesized that the pathological progression of ARDS comprises three phases that overlap: exudative, proliferative, and fibrotic [99]. During the exudative phase, proinflammatory cytokines including IL-1β, TNF, and IL-6 are released, neutrophils influx, and the endothelia-lepithelial barrier is disrupted. These events collectively contribute to respiratory distress and alveolar inundation [100]. Following the exudative phase, a fibroproliferative phase ensues, characterized by the accumulation of fibrocytes, fibroblasts, and myofibroblasts in the alveolar compartment. This accumulation results in an overabundance of matrix components such as fibronectin, collagen I, and collagen III [101]. Mechanical ventilation is a factor in the development of a fibroproliferative response in acute respiratory distress syndrome (ARDS), as shear forces stimulate collagen synthesis and inhibit collagenase production in addition to inducing the secretion of transforming growth factor β1 [102]. A subset of individuals who have survived acute respiratory distress syndrome (ARDS) and, by extension, patients infected with COVID-19 develop pulmonary fibrosis. This condition is characterized by persistent dry cough and exercise-induced dyspnea, and its management primarily involves supportive measures such as pulmonary rehabilitation, supplemental oxygen administration, and vaccination against Streptococcus pneumoniae and influenza [103]. Although not curative, nintedanib and pirfenidone, two medications approved by the FDA, have been shown to impede the progression of pulmonary fibrosis [104]. Up to five years after ARDS, these patients, whose mortality risk is elevated, may continue to exhibit exercise limitations and diminished quality of life [105].

7.4 Neurologic complications

SARS-CoV-2 has been identified in the cerebrospinal fluid and brain tissue of infected patients upon autopsy, according to numerous investigations [106]. During their illness, more than 80 percent of hospitalized patients will experience neurologic symptoms [107–109]. Neurological manifestations may impact the skeletal musculature, peripheral nervous system, or central nervous system. Patients have been diagnosed with neurologic symptoms such as meningitis, hypoxic encephalopathy (caused by impaired cardiac or pulmonary function), ischemic or hemorrhagic stroke (resulting from coagulation disorders or depressed cardiac function), seizures, and neuromuscular weakness, which may endure beyond the resolution of the acute disease [110, 111].

Autoimmune/para-infectious processes can result in Guillain-Barre, transverse myelitis, acute inflammatory demyelinating polyneuropathy, and autoimmune encephalitis [108, 111–113]. Movement disorders including Parkinsonism, myoclonus, and ataxia are possible [113]. Headache and vertigo are the most frequently observed symptoms [111]. Nearly 70% of intensive care unit (ICU) patients have been reported to have encephalopathy or delirium, which may lead to chronic cognitive decline or cerebral fog [111]. Brain confusion following COVID-19 can also be induced by deconditioning, post-traumatic stress disorder, and dysautonomia. Cognitive dysfunction is observed in around 88% of individuals diagnosed with PASC. A reported incidence of 30–40% among COVID-19 survivors is associated with psychiatric disorders, including but not limited to psychosis, obsessive-compulsive disorder (OCD), anxiety, melancholy, post-traumatic stress disorder (PTSD), and sleep disturbances [114].

Although the actual frequency of post-COVID headaches is unclear, estimates range from 14–43%. Possible causes include medication overuse headaches, exacerbation of pre-existing migraine headaches, and daily persistent headaches in the absence of a previous history of headaches. Bifrontal, holocranial, frequently lasting longer than twenty-four hours, worsening in the evening, exacerbated by respiration and exercise, and associated with photophobia and phonophobia are characteristics of COVID-associated migraines. Trigeminal symptoms are reported in 1% of patients [115].

7.5 Digestive involvement

Heartburn, gastrointestinal disorders, constipation, appetite loss, and abdominal pain are the most prevalent gastrointestinal symptoms of protracted COVID [116–119]. Even seven months after infection, 20.5% of participants with long COVID experienced persistent diarrhea, and 13.7% of long COVID patients experienced loss of appetite, according to an online survey of individuals from fifty-six countries. Approximately 29% of the 749 COVID-19 survivors who participated in a prospective study reported experiencing gastrointestinal symptoms six months after the onset of viral infection [120]. According to Blackett et al. [120], the most common digestive symptoms among them were reflux/heartburn (16.3% of cases), constipation (11.1% of cases), diarrhea (9.6% of cases), stomach pain (9.4% of cases), and nausea/vomiting (7.1% of cases). Therefore, it is impossible to ignore how symptoms of the digestive system affect the patients' quality of life when they have a protracted COVID.

The two most likely theories for the processes underlying gastrointestinal symptoms are changes in the gut microbiota and the presence of an active or persistent virus. Numerous investigations conducted to confirm the presence of persistent SARS-CoV-2 in the gastrointestinal system discovered that viral RNAs and proteins may be isolated in feces and gut tissue for up to a year following diagnosis [33, 37, 121]. An endoscopic investigation revealed that even seven months after the initial infection, a considerable proportion of patients still maintained detectable quantities of the SARS-CoV-2 nucleocapsid protein in the intestinal epithelium [33]. Additionally, it was shown that the majority of patients who exhibited antigen persistence had lengthy COVID-19, a condition that did not manifest in those who did not possess persistent antigens [33].

According to Weersma et al. [122], the gut microbiota is thought to be a complex ecosystem that has a significant impact on human health and a range of illnesses. Additionally, recent research has demonstrated that the gut flora plays a crucial role in the gastrointestinal symptoms associated with prolonged COVID [123]. Long COVID patients have a microbiome that is characterized by higher amounts of Ruminococcus gnavus and Bacteroides vulgatus and lower levels of Faecalibacterium prausnitzii, which may help with the digestive aspects of long COVID. Interestingly, it has recently been confirmed that the gut microbiome may be predictive. Respiratory symptoms are associated with opportunistic gut infections; neuropsychiatric symptoms may be caused by nosocomial pathogens such as Actinomyces naeslundii and Clostridium innocuum; and protracted COVID is inversely associated with butyrate-producing bacteria. Similarly, individuals who experience a continuous decline in their ability to diffuse carbon monoxide via their lungs have a changed composition of their gut microbiota. This is evidenced by the decreased prevalence of several bacterial taxa and the elevated levels of various Veillonella-related taxa [124]. Consequently, a promising area of study to clarify the processes of extended COVID across other systems other than the digestive system is the gut microbiota.

8. Conclusion

Multiple organ systems are affected by the effects of long-term COVID-19, necessitating continued medical care even after the acute sickness has subsided. In the majority of situations, a multidisciplinary approach is necessary for adequate therapy. Although a lot of study has been done on PASC, more is still required to look into the self-reported phenomenon of PASC and lessen the burden of sickness and medical treatment for these people. This will advance the delivery of patient-centered, evidence-based treatment by professionals. However, it is challenging to determine whether a COVID-19 diagnosis and subsequent morbidity are causally related. This is because both chronic illness and persistent post-COVID syndrome (PPCS) may have similar risk factors and antecedents, such as advanced age, diabetes, smoking, obesity or malnutrition, immunosuppression, and hypertension, which indicate a widespread susceptibility to these pathologies. Additional elements that might make diagnosis and treatment more challenging include.

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Chapter 3

Perspective Chapter: Epidemiology of Post-COVID Syndrome in Indian Subcontinent

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Abstract

Post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, also known as long-COVID (LC) or post-COVID syndrome (PCS), became a significant public health concern after the initial COVID-19 outbreaks. PCS refers to symptoms that persist beyond the weeks- and months-long acute phase of the infection. Prioritizing the management of acute instances to lower the mortality rate led to the initial neglect of cases of such extended duration, until it was discovered that many of the patients continued to experience symptoms long after they had recovered. "Long COVID" describes a group of persistent symptoms that are detectable and identified, often four weeks following the acute sickness. PCS can be diagnosed based on a patient's history and physical results after other diagnoses have been ruled out due to the lack of a conclusive test. The complicated interplay between the virus and host factors causes COVID-19 to change from acute to post-acute sequelae. The high absolute number of COVID-19 patients and the healthcare system's variability contribute to the varying prevalence of PCS throughout the Indian subcontinent. This chapter explores the epidemiology of post-COVID syndrome in the Indian subcontinent, focusing on its prevalence, pathogenesis, and clinical manifestations and the implications for policy health systems, society, and culture for effective PCS management.

Keywords: post-COVID syndrome, long-COVID, epidemiology, prevalence, risk factors

1. Introduction

Post-COVID syndrome (PCS), also known as long-COVID, has emerged as a pressing public health concern in the wake of the initial COVID-19 outbreaks. This syndrome encompasses a wide range of symptoms that persist for an extended period, extending beyond the initial phase of SARS-CoV-2 infection by weeks or even months. Initially, PCS did not garner much attention, focusing primarily on managing severe COVID-19 cases and reducing mortality rates. However, as the pandemic progressed, it became clear that many individuals were experiencing persistent symptoms long after their initial recovery, underscoring the importance of understanding and addressing this condition.

2. Historical context and emergence of COVID-19

In the late 1960s, a significant breakthrough in virology occurred when Tyrrell studied infectious bronchitis virus, mouse hepatitis virus, and transmissible gastroenteritis virus of swine. These viruses shared the same structure when viewed under an electron microscope. They were subsequently classified as coronaviruses due to their crown-like surface projections. The SARS outbreak in 2002–2003 affected 29 countries across North America, South America, Europe, and Asia, with a total of 8098 diagnosed cases and 774 deaths. Understanding this global context is crucial for comprehending the origins of COVID-19 and its impact on global health [1]. Another publication noted that SARS, a novel respiratory illness, first appeared in the autumn of 2002 in Guangdong Province, China, before spreading to 29 nations [2].

3. Naming the virus and disease: why do the virus and the disease have different names?

Various procedures and objectives exist for the nomenclature of viruses and diseases. Viruses are assigned names according to their genetic structure to aid in developing diagnostic tests, vaccinations, and medications. Virologists and other scientific community members, including you, are responsible for this task, whereby viruses are designated names by the International Committee on Taxonomy of Viruses (ICTV). Diseases are assigned names to facilitate discussions regarding illness prevention, transmission, transmissibility, severity, and treatment. The World Health Organization (WHO), in which you play a crucial role, is responsible for the readiness and response to human diseases. As part of this responsibility, the WHO formally names diseases in the International Classification of Diseases (ICD). The International Committee on Taxonomy of Viruses (ICTV) officially designated the name "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" for the novel virus on February 11, 2020. The name was selected due to the genetic similarity between the virus and the coronavirus that caused the SARS epidemic in 2003. Although they are related, the two viruses are distinct. The World Health Organization (WHO) officially designated the name "COVID-19" for this novel illness on February 11, 2020. This decision was made following established procedures developed in collaboration with the World Organization for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO) [3].

4. "Long COVID" or "Post COVID condition" or "long COVID-19" or "long haulers"

Long-COVID refers to a diverse array of novel, recurring, or persistent health issues that individuals encounter following infection with the COVID-19 virus. The majority of individuals infected with COVID-19 experience a recovery period ranging from a few days to a few weeks. Therefore, the initial identification of Long-COVID might occur at least 4 weeks following infection. Long-COVID can be experienced by everyone who has been infected. The majority of individuals with Long-COVID developed symptoms shortly after being diagnosed with COVID-19. However, there are cases when individuals who later experienced Long-COVID were unaware of the exact time they were infected. There is currently no diagnostic test available to definitively determine whether your symptoms or condition are caused by COVID-19. Long-COVID encompasses a range of illnesses. A diagnosis of Long-COVID is determined by a healthcare provider through an assessment of your medical history, which includes whether you have previously tested positive for COVID-19, experienced symptoms, or had exposure to the virus. Additionally, a physical examination is conducted to evaluate health condition further [4]. The Centre for Disease Control (CDC) in the United States employs the term "Post-COVID Conditions" (PCC) to encompass the diverse array of health outcomes that may manifest four or more weeks following infection with SARS-CoV-2, the virus responsible for COVID-19 [5].

4.1 Other terms

The individuals who experience ongoing symptoms after recovering from COVID-19 are commonly called "long haulers." This clinical condition is known as post-COVID or "long COVID" [6].

4.2 Case definition

A clinical case definition of post-COVID-19 condition arrived at by a Delphi consensus by the World Health Organization (WHO) is mentioned as follows: "Post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time" [7].

5. The transition from acute COVID-19 to post-COVID syndrome

The progression from acute COVID-19 to post-COVID syndrome (PCS) is influenced by factors, such as the initial infection's intensity, pre-existing health issues, and individual immune responses. These factors interact in a complicated manner during the transition. Given that moderate illness is shown in up to 81% of all SARS-CoV-2-infected patients, it is likely that a greater number of individuals will be affected by PCS than originally anticipated. This will result in significant medical, societal, and economic issues [8].

5.1 Pathophysiology of post-COVID syndrome/long-COVID (LC)

With COVID-19 transforming from a pandemic to an endemic disease, it is indisputable that cases of LC will persist for many years. Therefore, it is imperative to thoroughly comprehend the underlying cause(s) of LC and post-viral disorders. The pathogenic mechanism of LC is likely not a singular factor but rather a complex interaction between the virus and the host. This interaction can vary in different patients and may influence the amount and severity of the resulting complications.

SARS-CoV-2 can exhibit two forms of persistence—ongoing reproduction of the infectious virus and the presence of virus macromolecules such as RNA and proteins. Both types of viral persistence are expected to elicit distinct levels of immune system activation compared to acute infection. The existing data supporting the idea of extended SARS-CoV-2 viral replication playing a functional role in the development of LC are based on finding viral genomic particles in bodily fluids taken from infected individuals after they have partially recovered from the initial acute infection [9]. The proposal suggests that a deficient immunological response in the host contributes to developing SARS-CoV-2 variations, allowing the virus to persist by evading the immune system more effectively [10]. In addition, specific antigens of the SARS-CoV-2 virus can function as superantigens, which means they can activate T cells through nonspecific interactions with T cell receptors. This leads to excessive immune stimulation and the release of excessive cytokines, reducing the ability to clear the virus effectively. This creates a negative cycle where the immune system becomes exhausted or inhibited, allowing the virus to persist unintentionally [11].

5.2 Burden of post-COVID syndrome (PCS)

The prevalence of PCS in the Indian subcontinent has been notably significant due to the substantial number of COVID-19 cases and the diverse degrees of healthcare facilities throughout the region. As a result, healthcare authorities have acknowledged PCS as a significant public health concern and have devised measures to address its long-term consequences effectively. Research published in 2021 in the "Archives of Medical Research" reveals that the occurrence of post-COVID syndrome was estimated to be between 10 and 35%. However, for patients who were hospitalized, this percentage might potentially rise as high as 85% [12]. The findings of a separate review article demonstrated a significant disparity in the occurrence of extended COVID, ranging from 2% in Ghana to 86% in Egypt [13]. During a study conducted in Thailand, it was observed that out of 390 patients, 77.7% experienced symptoms associated with long-COVID [14]. A cohort research revealed that out of the 280 patients analyzed, 71.43% were found to have post-COVID-19 syndrome, with a greater percentage observed in males (53%) [15]. According to the World Health Organization (WHO), most individuals who contract COVID-19 experience a complete recovery. However, existing information indicates that around 10–20% of individuals encounter a range of medium- and long-term consequences following their recovery from the initial disease [16]. A systematic review and meta-analysis published in the Journal of Infection (2023) revealed that the occurrence rate of post-COVID symptoms stands at 30% after a two-year period following COVID-19 [17]. A study conducted in Maharashtra, India, revealed that of the 617 COVID-19 cases confirmed in the laboratory, 82.97% were attributed to the Omicron variant, while the remaining 17.03% were associated with the Delta variant. The average duration of follow-up for Delta and Omicron patients was 78.05 and 21.56 weeks, respectively. Out of the total cases, 40 individuals (6.48%) experienced ongoing symptoms during the follow-up period. The persistent symptoms were higher among those infected with the Delta variant (12.38%) than the Omicron variant (5.27%) [18].

In general, the high occurrence of PCS emphasizes the necessity for continuous monitoring and investigation to comprehend the complete scope of the disease and to create efficient strategies for managing it customized to the requirements of various populations.

5.3 Clinical manifestations and risk factors

Long-haul COVID or post-COVID sequelae can affect the health and quality of life of affected individuals. Hence, knowing the burden and potential risk factors is crucial in managing such post-viral illnesses.

5.3.1 Indian subcontinent

Different studies mostly reported the incidence at 4, 6, and 12 months. The overall incidence of long-haul COVID, as reported by various studies, ranges from 24 to 27.3% at 12 months of follow-up [19, 20]. A study from eastern India reported the incidence of self-reported long-COVID with a median follow-up of 73 days to be 8% [21].

The most common systems involved were respiratory, musculoskeletal, cardiovascular, neuropsychiatric, gastrointestinal tract (GIT), ear, nose, throat (ENT), and eye.

5.3.1.1 Respiratory system

The most common system affected by long-COVID was the respiratory system. This can be possible because respiratory illnesses are already prevalent in the nation, and a superadded effect of viral illness can worsen the situation. Cough and breathing difficulty were the most commonly reported symptoms. A study from north India showed that cough was a significant persistent system [22]. A multicentric study with a follow-up of 12 months reported persistent shortness of breath among 17% of the subjects and persistent cough among 8.6% [20]. A study from the north India reported the prevalence of cough at 3 months of follow-up to be 2.1% [23]. In contrast, a study from central India at 6 months of follow-up reported the prevalence of cough at 17.1% [24]. Other studies from south and central India reported the prevalence of cough to be 0.2% [25], 13.4% [26], and 8.6% [20]. The prevalence of breathing difficulty was 16.9% at 4 weeks, which increased to 28.6% at 6 months [24]. Areekal et al. [26] reported persistent symptoms after 28 days and showed that dyspnea was present in 23% of subjects, cough among 13%, and sputum production in 2.7%. Nair et al. [25], at 12 weeks of follow-up, reported the presence of dyspnea among 1.9% of subjects.

5.3.1.2 Cardiovascular system

Cardiovascular complications range from chest pain to palpitations. Arjun et al. [24] reported the prevalence of chest pain to be 8.4% at 4 weeks of follow-up, which decreased to 5.7% at 6 months. Other studies reported the persistence of chest pain in 1.2% [23] and 2.7% [26] of the individuals beyond 4 weeks of COVID-19 infection. Similarly, another study with a 12-month follow-up reported chest pain in 2.7% of subjects [20].

5.3.1.3 ENT and eye

Around 6% of the COVID survivors reported anosmia, sore throat, and vertigo, each by 1.5% [26].

5.3.1.4 Central nervous system (CNS)

Anxiety and depression were reported to be 2.9 and 11.4%, respectively, at 6 months of follow-up [24]. Evidence suggests that neuropsychiatric symptoms persist even beyond 12 months. A pan-India study reported persistence of confusion among 6.8%, sleep disturbances in 5.4%, and headache in 6.1% [20]. Budhiraja et al. [19] reported the persistence of neuropsychiatric symptoms in 9% of the subjects at 12 months of follow-up. Mood disturbances were found in 0.2% of subjects at 12 weeks of follow-up [25].

5.3.1.5 Musculoskeletal system

Eleven percent of the subjects complained about myalgia and 8.4% about joint pain [26]. A study from South India also reported the presence of myalgia and paresthesia among 0.5% of the subjects at 12 weeks of follow-up [25]. Conversely, at 12 months of follow-up, persistent muscle pain was reported by 14.7%, joint pain by 12.6%, and muscle weakness by 10.4% [20].

5.3.1.6 Gastrointestinal system

The most common symptoms reported from the GIT system were dyspepsia, diarrhea, constipation, loss of appetite, etc. At the 12-week follow-up, dyspepsia was complained of by 2.7% of the subjects [25]. Diarrhea was reported by 1.8% and dyspepsia by 6.3% of the subjects at the 28-day follow-up [26].

5.3.1.7 Constitutional symptoms

The studies reported many vague symptoms that are difficult to categorize into any system. Fatigue, one of the most common complaints, was reported by 32.5% of the subjects after 28 days of infection [26]. Another study reported the persistence of fatigue among 18.1% of the subjects at 6 weeks, which decreased to 4.6% at 12 weeks [25]. A study from north India reported persistence of fatigue, even at 12 months among 12.5% subjects.

5.3.1.8 Identified risk factors

1. Pre-existing medical conditions: Subjects with any pre-existing medical conditions were twice more prone to having long-haul symptoms (adjusted odds ratio (AOR): 2, p value: 0.01) [24]. The odds of developing long-haul symptoms were 4 times higher in subjects having hypothyroidism (p value<0.001). Also, type 2 DM (type 2 diabetes mellitus) (AOR: 3.6, p value<0.001), hypertension (AOR: 6.6, p value<0.001), and dyslipidemia (AOR: 4.0, p value<0.001) were also significantly linked with developing long-COVID in future [25].

2. Also, the number of COVID-19 symptoms in the acute phase (AOR: 6.88, p value<0.001) and severity of illness (AOR: 5.7, p value<0.001) [24] were also the identified risk factors. Naik et al. also reported that having moderate or severe disease was significantly associated with the development of long-haul symptoms (AOR: 1.7, p value = 0.012) [23].

Study and year	Region	Incidence
Shah et al. [27]	Nepal	59%
Fatima et al. [28]	Pakistan	20% (among vaccinated) 37.9% (among unvaccinated)
Jayasekera et al. [29]	Sri Lanka	16.3%
Afroze et al. [30]	Bangladesh	76%
Hossain et al. [31]	Bangladesh	16.1%

Table 1.
Incidence of Long-COVID reported by different studies conducted in South Asian region.

3. Hospitalization status: The appearance of long-COVID symptoms was 2.9 times more common among hospitalized patients in the acute phase as compared to nonhospitalized ones (p value: 0.006) [23].

4. Age: Subjects who were > 65 years of age were 6 times more likely to develop long-COVID (p value<0.001) [25].

5.3.2 Other countries of the south Asian region

We searched PubMed and Google Scholar for published articles on Long-COVID and could find studies from Pakistan, Bangladesh, Sri Lanka, and Nepal regions (**Table 1**).

6. Health system and sociocultural impacts

6.1 Healthcare infrastructure and challenges

The COVID-19 pandemic has exposed the vulnerabilities of healthcare systems in various countries and placed an unprecedented strain on the global healthcare delivery system.

6.1.1 Weakness of our healthcare system

In addition to the persistent lack of healthcare personnel in India, there were substantial deficits in various healthcare services, and logistical factors determined them. There is a significant lack of modern infection prevention and control facilities in healthcare facilities, which are necessary for containing infected patients and preventing the spread of COVID-19 and the Post-COVID Syndrome [32]. These facilities have major shortcomings in infection control methods. In 2010, the Government of India developed national guidelines for controlling airborne infections in healthcare institutions, with a particular emphasis on preventing tuberculosis transmission [33]. Newly updated in the year 2020, the comprehensive national recommendations for infection control were recently modified by the Indian health authorities [32]. Nevertheless, the infection control procedures implemented across the various primary healthcare institutions in Indian regions were generally inadequate, particularly regarding airborne infections. During the COVID-19 pandemic, the scarcity of measures was limited to the measures designed to control infections; nevertheless, it also extended to the personal protective equipment (PPE) intended to protect the workforce from infection [34]. According to reports, there is a recurrent lack of personal protective equipment (PPE) in two private hospitals in Mumbai [35]. According to reports from several regions across India, medical professionals frequently treat patients suspected of having severe acute respiratory syndrome coronavirus 2 infection without using masks or surgical masks that offer less protection. This contrasts with the NK95 masks advised for use by healthcare practitioners [36]. Unfortunately, due to a lack of personal protective equipment (PPE) and excessive demand, healthcare professionals have been forced to reuse or extend the usage of PPE, which increases the likelihood that they will contract COVID-19 [37]. The behavior described above, albeit expected, demonstrates a lack of appropriate understanding and training about infection control measures, the utilization of personal protective equipment (PPE), and the correct disposal of these items. It is one of the rights of healthcare personnel to receive proper training before being exposed to patients who have COVID-19 [38]. It has been alleged that many South Asian countries, notably India, do not provide their healthcare staff with the necessary training [39]. On the other hand, Raj et al. [40] found that a little less than half of the healthcare personnel in Kerala, India, had received training on the appropriate procedures for infection control techniques.

6.1.2 Health system responses in post-COVID times

When it comes to addressing the issues that are posed by PCS, innovations in public health measures are vital. The construction of post-COVID care centers is a noteworthy innovation that has been implemented. Physical therapy, mental health assistance, and dietary counseling are all services that are provided by these clinics, which provide a comprehensive solution for patients who are experiencing post-traumatic stress disorder (PCS). These facilities have been established in several different regions across the Indian subcontinent, and there have been reports of positive outcomes in terms of the satisfaction of patients and the improvement of their health. [(i) COVID Care Center with isolation beds for mild or pre-symptomatic cases; (ii) Dedicated COVID Health Center (DCHC) with oxygen-supported isolation beds for moderate cases; and (iii) Dedicated COVID Hospital (DCH) with intensive care unit (ICU) beds for severe cases] is the three-tier arrangement of health facilities that has been brought into place to provide appropriate management of COVID-19 cases. Concerning case management, tertiary care hospitals that fall under the purview of Employees' State Insurance Corporation (ESIC), the Defense Department, Railways, paramilitary forces, and the Steel Ministry have been utilized [41].

6.2 Digital innovations for fighting the COVID-19 as well as post-COVID syndrome

To a significant degree, COVID has played the role of a catalyst in the rapid adoption of digital healthcare technologies, despite the fact that regulation has not been implemented. The way in which public health systems function, the way in which patients seek care, and the way in which healthcare practitioners offer care are all being transformed by digital health tools and technologies. The most important digital health trends that were observed in the public sector included illness surveillance, safeguarding continuity of care during times of crisis caused by COVID, and making it possible for human resources to be utilized for health purposes. Incorporating

Geo-Fencing and Interactive Voice Response Service (IVRS) functions on mobile phones as steps for containment is yet another important technique that has been undertaken by the Ministry of Electronics and Information Technology (MEITY). In addition, India undertook the enormous task of vaccinating its population of 1.3 billion people against the virus with the assistance of an in-house digital application known as Company Win. There was a positive reaction from the general population to COWIN, with a total of 95,20,99,713 registrations up till January 7, 2022 [42].

7. Cultural perspectives on illness and recovery

Cultural background greatly influences perceptions of disease and healing, particularly among the different nations of the Indian subcontinent. This section examines the influence of cultural beliefs, practices, and societal attitudes on managing and recovering post-COVID syndrome (PCS) in India, Nepal, Bangladesh, Pakistan, Bhutan, Sri Lanka, and the Maldives.

7.1 Community responses and stigma associated with PCS

Different Indian subcontinent communities react to PCS in somewhat different ways. Many areas have the stigma connected with COVID-19 extending to persons with PCS [43]. As a consequence of the disease's persistent symptoms, patients frequently experience social exclusion. It has been established that individuals with inadequately understood and managed health conditions, such as long-COVID, experience stigma in three primary forms: anticipated stigma, internalized stigma, and enacted stigma [44]. The emotional well-being, health-seeking behavior, and overall quality of life can all be impacted by this [45]. For instance, in rural India, individuals with PCS may be perceived with suspicion, resulting in social isolation and a reluctance to seek medical care. According to a study conducted in the United Kingdom, 95.4% of individuals reported experiencing stigma at least occasionally [46].

7.2 Traditional vs. modern medical practices in treatment

Conventional medical techniques are vital in treating PCS in the Indian subcontinent. Ayurveda, Unani, and traditional Tibetan medicine are frequently employed in conjunction with or as alternatives to contemporary medical interventions. In India, Ayurveda practitioners have devised specialized protocols to address PCS symptoms effectively. These protocols primarily focus on utilizing herbal remedies, making dietary adjustments, and incorporating yoga practices [47]. Similarly, in Bhutan, the government healthcare system incorporates traditional Tibetan medicine, which encompasses herbal treatments and spiritual healing methods to tackle PCS. Nevertheless, dependence on conventional methods can occasionally hinder the acceptance of scientifically validated therapies. The difficulty lies in combining these conventional approaches with evidence-based medical therapies to offer comprehensive care. Healthcare systems in the Indian subcontinent have modified their practices to accommodate the cultural requirements of their populations. The AYUSH ministry in India has implemented initiatives to integrate traditional and contemporary healthcare approaches. In addition, including Ayurveda therapy alongside standard medical care has demonstrated improved treatment outcomes and reduced disease progression, ultimately resulting in a lower incidence of post-COVID syndrome [48]. In Sri Lanka, mental health support services are being customized to suit the distinct cultural context, including integrating traditional healing techniques and community-based initiatives to diminish the stigma linked to post-COVID syndrome (PCS). Understanding the cultural perspectives on illness and recovery is crucial for effectively managing PCS in the Indian subcontinent. By acknowledging and integrating traditional practices and addressing the stigma associated with PCS, healthcare providers can offer more culturally sensitive and effective care. This approach improves patient outcomes and enhances the overall resilience of healthcare systems in the region.

8. Policy implications and future directions

8.1 Readiness and response to future pandemics

Understanding the genesis and spread of the COVID-19 pandemic and its unexplained aftermath (long-COVID) is critical for both current and future outlooks. Dr. Simon Williams, a behavioral scientist, stated that the long-COVID may not be an acute crisis, but rather a continuing chronic crisis. The COVID-19 pandemic has highlighted the importance of being prepared and having effective response mechanisms in place to manage future pandemics. Effective preparedness requires a multidimensional approach that includes surveillance, healthcare infrastructure, worker training, and community involvement.

Strengthening and integrating the healthcare staff is an important part of pandemic preparation. Governments should invest in the training and retention of healthcare workers to ensure that there is enough personnel to respond to health emergencies. This group consists of doctors, nurses, public health professionals, epidemiologists, and laboratory technicians.

Infrastructure enhancements are required to strengthen the resilience of healthcare systems. This includes improving healthcare facilities, assuring the availability of critical medical supplies, and building surge capacity to accommodate increasing patient loads during pandemics. Policymakers should prioritize the construction of multidisciplinary clinics to provide a more complete care [49]. Governments should also invest in Research and Development (R&D) to help with the quick manufacture and distribution of vaccinations and therapies.

Community engagement is critical for a successful pandemic response. Public health officials should collaborate with communities to increase health literacy and support adherence to public health policies. Transparent communication regarding the risks and benefits of interventions, as well as dealing with misinformation that might undermine public health efforts, is critical [50].

Furthermore, worldwide collaboration is required for pandemic preparedness. The COVID-19 pandemic has demonstrated that no country can handle a pandemic alone. Global health institutions, such as the World Health Organization (WHO), play an important role in coordinating efforts, providing technical help, and promoting information and resource exchange. Collaborations can speed up progress while also ensuring consistent care standards around the world [51].

8.2 Lessons learned and improvements in health system preparedness

The COVID-19 pandemic has taught us vital lessons about improving healthcare system preparedness. One important takeaway is the value of flexibility and adaptability in healthcare systems. Health systems that could quickly adjust to the shifting dynamics of the pandemic, such as reallocating resources and revising care protocols, fared better in crisis management.

Another lesson is the importance of strong supply chains for medical supplies and personal protective equipment (PPE). Many countries had faced serious supply shortages during the epidemic, emphasizing the significance of keeping strategic stocks and improving domestic manufacturing capacities.

The pandemic has also highlighted the critical need to incorporate mental health services into pandemic response plans. The epidemic has had a severe psychological impact, and addressing mental health issues is critical to providing full treatment. Health systems should make mental health services available and teach healthcare providers to recognize and manage mental health concerns [52].

8.3 Research needs and policy recommendations

Research is critical for comprehending PCS and generating appropriate management plans. Priority areas for research include PCS pathogenesis, long-term health consequences, and establishing diagnostic criteria and treatment guidelines. Understanding the molecular pathways that drive PCS is critical for creating targeted treatments. Research should aim to develop biomarkers that can help with PCS diagnosis and monitoring. Furthermore, investigations should look into the involvement of the immune system and any genetic variables that may predispose people to PCS.

Longitudinal studies are required to determine the long-term health effects of PCS. These investigations can illuminate the syndrome's natural history and uncover risk factors for recovery or chronic symptoms. Data from this research can help to shape rehabilitation programs and other therapies for PCS patients [53]. Creating uniform diagnostic criteria and treatment protocols is also a goal. Research should develop evidence-based guidelines that healthcare providers around the world can follow. These guidelines should address several areas of PCS care, including symptom management, mental health assistance, and rehabilitation. Policy recommendations should center on improving healthcare delivery, funding research, and boosting public health initiatives. Governments should ensure that healthcare systems are prepared to provide complete care for PCS patients, such as building dedicated post-COVID care centers and utilizing telehealth to increase access to care.

Furthermore, legislators should fund PCS research to improve our understanding of the illness and create appropriate treatments. Collaborative research activities should be supported to combine resources and skills. Public health efforts should be launched to increase awareness about PCS and minimize stigma. These efforts can inform the public about the signs of PCS, the significance of obtaining medical attention, and accessible support resources. International cooperation is also critical in tackling PCS. Global health organizations can help low- and middle-income nations by sharing knowledge and best practices, providing technical assistance, and supporting capacity-building activities.

8.4 Prioritizing areas for future research

Future research should prioritize the following areas to improve our understanding and management of PCS:

8.4.1 Pathophysiology and biomarkers

Identifying the biological mechanisms and biomarkers associated with PCS to aid in diagnosis and treatment development.

8.4.2 Epidemiology and risk factors

Understanding the prevalence and risk factors for PCS across different populations and regions to inform targeted interventions.

8.4.3 Long-term health impacts

Assessing the long-term physical, mental, and social impacts of PCS to develop comprehensive care strategies.

8.4.4 Intervention effectiveness

Evaluating the effectiveness of various interventions, including pharmacological treatments, rehabilitation programs, and mental health support.

8.4.5 Health system integration

Exploring ways to integrate PCS management into existing health systems, including the use of telehealth and community-based approaches.

8.4.6 Policy interventions to mitigate PCS impacts

Policy interventions are essential for mitigating the impacts of PCS on individuals and health systems. These interventions should focus on enhancing healthcare delivery, supporting research, and promoting public health measures.

8.4.7 Healthcare delivery

Governments should ensure that healthcare systems are equipped to provide comprehensive care for PCS patients. This includes establishing dedicated post-COVID care centers, integrating mental health services, and leveraging telehealth to improve access to care.

8.4.8 Research support

Policymakers should fund PCS research to advance our understanding of the syndrome and develop effective treatments. Collaborative research initiatives should be encouraged to pool resources and expertise.

8.4.9 Public health measures

Public health campaigns should be implemented to raise awareness about PCS and reduce stigma. These campaigns can educate the public about the symptoms of PCS, the importance of seeking medical care, and the available support services.

8.4.10 International collaboration

Global cooperation is crucial for addressing PCS. International organizations can facilitate the sharing of knowledge and best practices, provide technical assistance, and support capacity-building efforts in low- and middle-income countries.

9. Conclusions

Addressing the challenges posed by PCS requires a concerted effort from policymakers, healthcare providers, researchers, and the community. By enhancing healthcare delivery, supporting research, and promoting public health initiatives, we can mitigate the long-term impacts of PCS and improve the quality of life for affected individuals. The lessons learned from the COVID-19 pandemic underscore the importance of flexibility in healthcare systems, robust supply chains, and the integration of mental health services. Ongoing research is vital to uncover the mechanisms of PCS, identify biomarkers for diagnosis, and develop targeted treatments. Longitudinal studies will provide insights into the long-term impacts of PCS and inform the development of comprehensive care strategies.

Conflict of interest

The author declares no conflict of interest.

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Section 2

Clinical Aspects

Chapter 4

Perspective Chapter: Exploring Cognitive Impairment in Long COVID – Insights and Therapeutic Progress

Chanchal Sonkar, Shailendra Chauhan and Charu Sonkar

Abstract

Coronavirus disease 2019 (COVID-19) was caused by a novel severe acute respiratory syndrome related coronavirus (SARS-CoV-2) that occurred in late 2019 and soon emerged as a global pandemic. Even after recovering from the initial infection, approximately 45% of patients experience persistent symptoms, known as post-COVID syndromes or long COVID, which can endure for weeks to months. Among the prominent lingering symptoms are fatigue, cognitive impairment (commonly referred to as brain fog), and musculoskeletal disorders. Brain fog manifests as confusion, difficulty focusing, and memory loss. Although the exact cause of cognitive deficits induced by SARS-CoV-2 remains unclear, it is speculated that persistent chronic inflammation resulting from residual virus remnants in the body's reservoirs and stress-released peptides may play a significant role. This chapter aims to delve into the etiology and recent advancements in treating brain fog associated with COVID-19, shedding light on our understanding of this complex phenomenon and potential therapeutic strategies.

Keywords: coronavirus, long COVID, SARS-CoV-2, cognitive impairment, brain fog, co-infection, therapeutics

1. Introduction

With the emergence of the first case recorded in Wuhan, China, in December 2019, the COVID-19 disease has disseminated globally. According to the World Health Organization's report, there have been approximately 670 million cases worldwide recorded in January 2023, with about 70 million deaths [1]. The patterns of disease intensity can vary from asymptomatic to fatal. The sustained symptoms of this disease can pose severe medical conditions. According to a study, around 80% of SARS-CoV-2-infected patients suffer with one or more persistent symptoms. Additionally, around 70% of patients with persistent symptoms having a low risk of COVID-19-related mortality have dysfunction in one or more organs 4 months post-infection [2, 3]. Some individuals suffering from acute SARS-CoV-2 infection experience sustained symptoms for weeks, months, or years. This sequela is known as

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long COVID (LC), which encompasses all the individuals that experience prolonged symptoms post-acute COVID-19 infection [4]. The most frequent symptom includes pyrexia, cough, fatigue, and olfactory impairment. With approximately 85% of infected patients having hyposmia and gustation. About 37% of patients experience some kind of neurological complications like headaches or impaired alertness during hospitalization. Additionally, in COVID-19 patients, the virus is considered to enter the Central Nervous System (CNS), resulting in evident neurological symptoms. Patients with persistent symptoms or those who have recovered from the infection too face prolonged cognitive impairment [5].

Cognition is the approach-based evaluation system of data, which is important for gaining knowledge and the delivery of the desired response. This system incorporates the collection of data, sorting out important information, comprehending it, and retaining it in the memory, leading to behavior control. Post-COVID-19 conditions (PCC) of infected patients usually show fatigue, memory impairment, problems in decision-making and focus, and arthralgia as a common neurological complication in the disease [6, 7]. Many patients have also reported a slight impairment in their behavior and cognitive abilities that was difficult to define. These features are usually characterized as 'brain fog' or 'mental clouding' or 'cognitive impairment' [8]. Cognitive impairment or psychiatric problems may remain even after months of infection. Considering the sustained neurological implications, PCC have reported the onset of neurodegenerative disease in patients without any prior history, such as Guillain-Barré syndrome (GBS), encephalopathy, and Alzheimer's disease (AD) [9, 10]. Additionally, myalgia and hyposmia were also detected in infected patients. Irrespective of the physical or clinical complexities of the infection, over 75% of patients have faced some sort of dysfunction in executive function or sensorimotor integration (psychomotor coordination) [11]. It poses difficulty in patients' daily function, jobs, and ability to work efficiently, resulting in a significant increase in disease load. Clinical syndromes of PCC and health conditions of infected patients are intricate and poorly understood [12]. Hence a more thorough investigation is required for its proper characterization, as numerous mechanisms are proposed for cognitive dysfunctions mediated by LC. These include deterioration of the blood-brain barrier (BBB), synaptic impairment, improper neurotransmitter emission, neurodegeneration, and neurological inflammation. Addressing these mechanisms holds promise for potential treatments of long-COVID-related problems [13].

Currently in PCC, there has been an increase in the occurrence and severity of invasive infections, particularly in children, resulting in a high disease burden. Infections caused by bacteria such as Group A Streptococcus (GAS) are associated not necessarily with the incidence or severity of the disease but with a lack of immunity [14]. GAS infections include necrotizing fasciitis, toxic shock syndrome, and pneumonia, and they also increase susceptibility to infection by *Streptococcus pyogenes* [15]. Additionally, the reactivation of lymphotropic and neurotropic herpesviruses, such as Epstein-Barr virus (EBV) (gamma herpesvirus) and Varicella-zoster virus (VZV) (alpha herpesvirus), is well established in PCC. These viruses tend to remain dormant until reactivated by a stressor, such as the SARS-CoV-2 virus [16, 17]. Therefore, a detailed study of co-infection is necessary for the accurate treatment of patients suffering from LC. Previous knowledge of mechanisms and therapies from the pre-pandemic era can aid in managing patients with neurological and cognitive dysfunction. However, there is a significant need to comprehend current mechanisms and develop therapies specifically targeting these neurological manifestations of the disease [18].

Given the global impact of LC and its uncertain persistent symptoms, this chapter summarizes the current detrimental effects of LC on cognitive function, their underlying mechanisms, any co-infections involved, and probable therapeutic treatments, which are of primary importance.

2. Clinical syndromes associated with COVID-19-related cognitive impairment

A wide range of tenacious symptoms occurs in patients with a history of COVID-19 infection. Among these, persistent cognitive traits are particularly troubling. Studies have revealed that patients infected with ancestral strains of the virus exhibit emerging neurological health concerns with the infected individuals. Based on a meta-analysis of approximately forty studies involving 10,000 subjects, it was found that about 25% of individuals infected with mild SARS-CoV-2 infection had cognitive impairment. Additionally, approximately 70% of infected individuals continued to show at least one symptom even after 2 months of infection [19]. Similarly, based on neuropsychometric analysis, one study found that approximately 75% of patients experienced at least one cognitive impairment even 3 months after contracting COVID-19. These impairments encompassed functions such as sensorimotor integration, learning, memory, cognition, information processing, impaired thinking (brain fog), and executive function [11]. Using the same neuropsychometric technique, another study revealed cognitive impairments in attention, information processing speed, memory consolidation, and cognitive control among patients with mild, moderate, and severe infections [20].

Even 12 months after contracting COVID-19, patients are observed to have an increased risk of neurological disorders such as GBS, encephalopathy, and AD. Cognitive dysfunction was noted across all subgroups, regardless of gender, age, or history of diabetes, smoking, and hyperlipidemia [21, 22]. A retrospective study indicated that this impairment may persist for up to 2 years following COVID-19 infection. Conversely, the likelihood of heightened anxiety levels and mood disorders stabilized within 60 days. However, these patients still exhibited an elevated risk of cognitive dysfunction and sleep disorders. In contrast to adults, children showed a faster recovery from cognitive impairment, typically within approximately 490 days [23].

A cognitive disorder can significantly impact individuals who experience even a mild infection of SARS-CoV-2. A study conducted on participants from the UK Biobank provided longitudinal assessment data before and after SARS-CoV-2 infection. This study revealed evidence that even mild infections could lead to a decline in cognitive ability compared to their pre-COVID-19 baseline. Importantly, this decline persisted even after excluding patients hospitalized due to infection from the analysis [24]. The probable contributors to this dysfunction include unmeasurable neural abnormalities, sleep disorders, and psychological factors [25]. These impairments may affect mild and acutely infected patients, and they tend to increase in patients with severe SARS-CoV-2 infection, often leading to hospitalization [26].

The most common cognitive impairments occurring post-COVID-19 are psychomotor synchronization, sleep disorders, memory, brain fog, psychological factors cognition, learning, information processing, and executive function, and neurological disorders such as Alzheimer's disease and insomnia. Each of them is now discussed sequentially.

2.1 Sensorimotor integration

Sensorimotor integration, or psychomotor synchronization, is a neurological process by which sensory and motor systems collaborate to facilitate the execution of voluntary motor action in response to certain environmental requirements. This process is also involved in intricate neural operations that coordinate sensory input with motor output [27]. Simply, sensorimotor integration is the brain's capability to integrate the sensor information with movement commands to produce coordinated actions [28].

One of the studies observed a difference in sensorimotor integration between LC-19 and the control group. This suggested that the infected patient may suffer from problems in coordination of sensory input and motor output. COVID-19 infection may impact differently in different stages of the somatosensory system, impacting different stages of sensory processing [29]. Additionally, post-COVID-19, a significant elevation was observed in frontal N30 potential post-infection. N30 is the negative peak in the median nerve of somatosensory potentials. Frontal potential N30 is connected with the functioning of the motor system, precisely as a thalamo-corticobasal ganglia circuit. This circuit is responsible for motor planning and its execution. This circuit consists of interconnected brain regions (such as primary motor cortex, prefrontal cortex, premotor cortex, and supplementary motor area) for motor planning and execution [30]. Any changes in N30 would result in problems in accurate and coordinated movement. Hence, an increase in N30 may disrupt the proper functioning of various brain parts that control motor responses, such as the thalamus, basal ganglia, primary cortes for the motor system, and premotor area [31].

LC-19 changes have also been observed in sensory processing and transmission in patients. SARS-CoV-2 infection has shown elevated amplitude of brainstem P14 and spinal N13, suggesting changes in sensory processing and transmission. These changes affect the integration of sensory information, resulting in disruption in its processing in the brain. The infection also leads to alteration in N20 and P27, causing problems in the interaction of sensory and motor systems. Although the precise mechanism is still under exploration, these findings suggest the direct impact of viruses on nervous systems, leading to detrimental consequences (**Figure 1**) [28, 32].

2.2 Sleep disorders

Sleep disturbances are a common symptom in post-COVID-19 conditions. According to an online survey, the prevalence of sleep disturbances was found to be up to approximately 78% after a seven-month follow-up. These disturbances include sleeplessness, sleep-disordered breathing, nighttime sweating, and restless leg syndrome. Post-COVID-19 symptoms are intricate, and no clear pathological explanation is currently available. Neuroinflammation caused by the immune response can be a potential cause of sleep disturbances. Some intestinal cells and gut bacteria alter neurotransmitters or metabolites, leading to elevated levels of pro-inflammatory proteins such as C-reactive protein (CRP), Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 (IL-1), and Interleukin-6 (IL-6). Increased intestinal permeability can cause a cytokine surge in infected patients, resulting in neuroinflammation that ultimately affects the sleep cycle [33]. Several factors affect sleep disorders, including age, gender, loneliness, distorted sleep-wake cycles, disease severity, and psychological issues such as depression, anxiety, stress, and fear. These disorders, in turn, lead

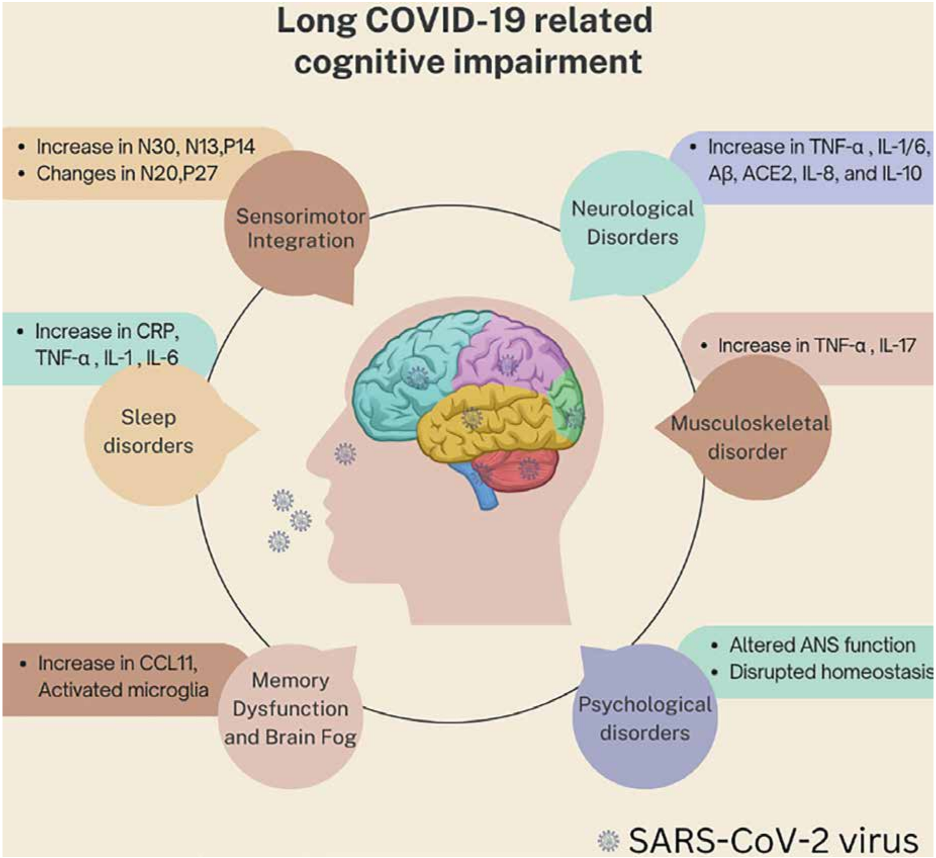

Figure 1.
Clinical syndromes associated with COVID-19-related cognitive impairment.

to various aftereffects, such as a decline in efficiency, increased health problems, and higher healthcare costs. Therefore, it is important to address and treat sleep-related problems (**Figure 1**) [34].

2.3 Memory dysfunction and brain fog

Within 4 weeks of the onset of acute COVID-19 syndrome, about 25% of ICU (intensive care unit) patients experienced cognitive problems. Additionally, patients who required oxygen showed declines in memory, focus, and functional performance [35, 36]. After 12 weeks, ICU patients continued to have memory dysfunction, difficulty focusing, and anxiety [37]. Moreover, approximately 60% of patients suffered from some form of neurological problem, with impairments observed even 6 months post-infection. Severe cases reported reduced attention spans, episodic memory issues, and decreased spatial cognition [38].

"Brain fog," also known as "COVID fog," is a term recently coined to describe cognitive impairments such as focus issues, information retention problems, speech difficulties, and executive dysfunction. Researchers have noticed a striking similarity between "COVID fog" and "chemo brain," a condition of neural inflammation experienced by patients undergoing radiation or cytotoxic therapy. In the chemo brain, elevated neurodegenerative cytokines and activated microglia lead to a series of multicellular events causing changes in both gray and white matter [39]. Applying this understanding, cytokines and microglia were evaluated in SARS-CoV-2 infections. Similar to chemo brain, increased levels of cytokines were found in the white matter of the hippocampus, specifically 7 weeks post-infection, with elevated levels of CCL11. Additionally, activated microglia levels were increased in the white matter of LC-19 patients [40]. Elevated activated microglia suppress neurogenesis and oligodendrocyte-mediated myelination. Neurogenesis is crucial for the creation and maintenance of hippocampus-dependent memories. Reduced axonal myelination may also impair cognitive function, as myelination controls neural processing. Overall, brain fog is typically the result of a reduced number of neurons, dysregulation of oligodendrocytes, and elevated levels of pro-inflammatory cytokines and activated microglia (**Figure 1**) [41].

2.4 Psychological disorders

Primary research suggests a connection between mood disorders and neuropsychological changes following COVID-19 recovery [36]. A study examining patients 30 to 35 days post-COVID-19 found elevated stress and mental disorders (anxiety and depression) among the patients. Both conditions involve impaired focus as their main diagnostic criteria. Additionally, depression is associated with several other disorders, such as episodic memory impairment, cognitive deficits, lack of focus, and poor memory [42].

Statistically, around 50% of COVID-19 patients experience anxiety and depression. Even after 6 months of diagnosis, patients remain at elevated risk of mood disorders, psychotic disorders, and anxiety. Moreover, post-traumatic stress disorder (PTSD) can be added to this list, with its presence observed in more than 6% of patients within 2 months of a COVID-19 diagnosis [23, 43, 44]. Particularly, invasive memories and elevated arousal symptoms were frequent among severe ICU patients admitted for COVID-19 treatment. These symptoms can be grouped into three categories: avoidance, intrusion, and hyperarousal. Additionally, PTSD occurs in patients with abnormal personalities, such as emotional instabilities and antisocial tendencies. Interestingly, women suffer more from LC-19 symptoms compared to men. They have an elevated risk of developing sleep problems, pain, fatigue, visual impairment, and psychological distress [45, 46]. One of the significant traits of PTSD is a lack of clarity in physiological and psychological states, making it difficult for patients to handle environmental stress.

Specifically, these subjects suffer from abnormal functioning of the autonomic nervous system (ANS). Normally, the ANS is responsible for biological responses to stress, such as the fight-or-flight response and relaxation. However, in PTSD patients, these responses become erratic, ranging from extreme combat behavior to complete isolation, dissociation, or withdrawal. This dysfunctional ANS reaction to any external stimulus is a central feature of PTSD, putting PTSD subjects at elevated risk of various diseases, including diabetes and cardiovascular disease [47].

Some characteristic personality traits, such as emotional instability and antisocial behavior, are speculated to predict the development of post-traumatic stress disorder (PTSD) after COVID-19 recovery. These traits were also found to be elevated in patients experiencing post-COVID-19 symptoms [48].

Particularly, the personality trait known as antipathy, commonly associated with antagonism, can increase the potential for developing long-lasting symptoms of LC.

Individuals with this trait exhibit extreme feelings of self-importance and have high expectations of special treatment. Consequently, they may resist adhering to COVID-19 preventive protocols and vaccination recommendations, ultimately complicating their treatment [49].

Another psychological disorder known as alexithymia has been observed to increase in post-COVID-19 patients. Alexithymia is characterized by difficulties in recognizing and expressing emotions. It has been implicated as a causative factor in multiple organ dysfunction, respiratory problems, and cognitive impairment among post-COVID-19 patients [50, 51]. Alexithymia is also speculated to play a role in the early detection of various pathological conditions. Several hypotheses propose four pathways for detecting alexithymia: somatic, behavioral, cerebral, and societal [52]. A characteristic trait of individuals suffering from alexithymia is a loss of emotional control, which results in changes in several bodily systems, including the autonomic, endocrine, and immune systems. These changes disrupt the body's homeostasis, leading to pathological conditions. As alexithymia patients struggle to adapt and cope with stress, they may be prone to adopting unhealthy lifestyles, such as substance abuse. Their difficulty in identifying their physiological state and mental condition makes it challenging to diagnose the disease [53]. Furthermore, their inability to understand their own emotions hinders their ability to seek positive social support, exacerbating their stress levels. Consequently, alexithymia significantly contributes to the trauma faced by COVID-19 patients, ultimately compromising their homeostasis and contributing to the persistence of symptoms (**Figure 1**) [54].

Overall, this highlights the need for meticulous psychological evaluation of patients to understand symptoms specific to each disorder. Additionally, gender-specific treatment considerations are essential, given the differences between men and women.

2.5 Mucoskeletal disorder

Reports related to LC have consistently highlighted fatigue and myalgia as common symptoms of the disease. In fact, at least 87% of recovered COVID-19 patients from hospitals in Italy have reported fatigue as a persistent symptom. These patients also experienced a decrease in the volume of the femoris muscle, as well as reduced strength in their quadriceps and biceps. When compared to healthy individuals, recovered COVID-19 patients who were discharged 3 months ago were found to have weaker grip strength and a reduction in the distance traveled in 6 minutes [55–57]. Additionally, these patients face challenges in returning to their daily lives and exhibit resistance toward physical movements. Fatigue can manifest as mental, emotional, and physical exhaustion, and therefore, it should be researched along with specific characteristics of the disease [58, 59].

Myalgia is pain of muscle, whereas arthralgia is pain in joints. This symptom is either present at the beginning of the disease or as a symptom of LC. A study has reported that patients who have not reported arthralgia as a symptom on onset of COVID-19, around 13 and 21% of them reported it about a month and 2 months post-discharge, respectively. Additionally, myalgia was reported as one of the prolonged symptoms of COVID-19, which is found in the patients half a year after their discharge [60, 61]. LC-19 also causes initial phase inflammatory arthritis and Reiter's syndrome 1 month post-its diagnosis [62]. Cytokine storm is considered the primary reason for the majority of all these musculoskeletal manifestations in long-COVID patients, specifically those patients who were prone to ICU admission [63].

These patients have also been diagnosed with low Bone Mineral Density (BMD), which is characterized by an increase in bone fragility and a decrease in bone strength. The cytokine; Interleukin-17 (IL-17) and TNF-α restrict osteoblast proliferation and induce osteoclast differentiation, resulting in bone fragility [64]. The technique used to diagnose BMD is known as computed tomography. During follow-up, in LC patients, BMD decreased by a mean of 8.6%, resulting in doubling the rate of osteoporosis. Additionally, an animal study using the golden hamster model to study the effect of the SARS-CoV-2 virus revealed a multifocal trabeculae loss in long bones and vertebrae of infected hamsters. A similar impact is expected to be replicated in humans as well [65]. A similar experiment was conducted in mouse models, whose results indicate approximately quarter loss of bone mass and 60% elevation in osteoclast proliferation in infected mice post-14 days of infection (**Figure 1**) [66].

2.6 Neurological disorders

The SARS-CoV-2 virus affects not only the respiratory system but also the nervous system, leading to various neurological manifestations. One such manifestation is GBS. GBS is a rare condition where the immune system launches an attack on the peripheral nervous system, causing neuronal inflammation. Antibodies mistakenly target proteins on the myelin sheath of neurons, resulting in muscle weakness. In severe cases, respiratory muscles weaken, necessitating mechanical ventilation in approximately 15% of patients [67].

Additionally, COVID-19 can lead to seizures due to its invasion of the central nervous system (CNS). A study involving over 3700 COVID-19 patients under 18 years old found that 1% experienced neurological problems. Among them, 0.3% had seizures of varying intensity. These seizures, known as status epilepticus, can also occur due to low blood oxygen levels resulting from acute pneumonia. Metabolic changes and sepsis-induced brain disorders are common in these patients [68]. Prognosis for patients with a history of status epilepticus is challenging. Despite having a lower seizure threshold, they may experience a high number and intensity of seizures [69]. The hypothesized mechanism involves virus-induced CNS invasion triggering neuro-inflammatory reactions, depolarization of neurons, and subsequent molecular and cellular alterations associated with epiletogenesis. Severe COVID-19 cases exhibit metabolic discrepancies, reduced oxygen levels, and inflammatory cascades, all contributing to the occurrence of seizures [70]. To manage this disorder effectively, maintaining molecular and electrolyte balance, avoiding hypoxia, and engaging in regular respiratory exercises are crucial.

In the same study conducted by Panda et al. in 2021, 0.7% of total infected patients developed encephalopathy. They also had an increased mortality rate and a decreased prognosis of the disease. The proposed mechanism involves ACE2 and SARS-CoV-2 interaction on either the vascular endothelial or neuronal layer, resulting in neural damage. This triggers an immune response, increasing levels of interleukins such as IL-6, IL-8, and IL-10. Approximately 33% of COVID-19-infected patients experience consciousness dysfunction during acute encephalopathy, which can also lead to a state of coma, limiting the operational ability of an individual. Therefore, early prognosis and accurate treatment are important in such conditions to prevent the development of multi-organ failure or irreversible organ damage [71, 72].

Considering the degree of severity of the encephalopathy and its neurological impact, patients can undergo therapies that can activate neuroplasticity, such as music, behavioral and physical therapies, as well as mobility training. To achieve this, multidisciplinary studies including biomechanics, biomedical engineering, and neurophysiology can be conducted [73].

It has been reported that patients already diagnosed with AD have a five-fold higher mortality rate when infected with the SARS-CoV-2 virus. These two conditions (AD and LC) are correlated through similarities in cellular pathways, mechanisms, and outcomes of medical imaging. AD is a neurodegenerative disorder caused by the accumulation of amyloid beta and hyperphosphorylation of tau proteins. Amyloid beta protein accumulates between synapses, limiting signal transfer from one neuron to another, while hyperphosphorylation of tau proteins blocks nutrient transfer within neurons for nourishment. Their presence may stimulate an immune response leading to chronic inflammation, resulting in a reduction in brain volume [74]. AD is a prominent cause of dementia, cognitive impairments, mood fluctuations, and personality alterations, symptoms similar to those of LC-19 patients. Even neuropathological damages and biomarkers are found to be either similar or overlapping in both diseases [75]. Biomarkers such as APOE4, the apolipoprotein E type 4 allele (APOE ε4), which are significant risk factors in AD, are considered biomarkers for COVID-19. APOE ε4 homozygotes are more prone to severe COVID-19 infection. Moreover, the protein products of the APOE gene act as receptors for the SARS-CoV-2 virus [74, 76]. Additionally, biomarkers such as TNF, IL-1/6, and complement proteins are referred to as predictive biomarkers for both diseases. It has also been hypothesized that virus-mediated neuro-invasion may increase Aβ, which facilitates amyloid beta deposition. Increased angiotensin-converting enzyme 2 receptor (ACE2), which is considered the receptor for the SARS-CoV-2 virus, is also a characteristic feature of AD [77, 78]. Medical imaging has shown a reduction in brain volume and size and reduced metabolism in the thalamus, parahippocampal gyrus, and cingulate cortex. There are similarities in molecular pathways, including dysregulation of folate-mediated one-carbon metabolism, pathological microglia, and reduction in ubiquinone. Despite the many similarities found between LC and AD, rigorous studies are still required to validate their importance and usefulness in the medical field (**Figure 1**) [79].

3. Exploring neuroimmune interactions in LC-related brain fog

COVID-19 has been found to alter the cognitive regions of the brain, resulting in functional changes and leading to several psychiatric conditions [80]. Recent reports also suggest that the CNS is directly or indirectly affected by COVID-19 disease. Consequently, this disease is associated with several long-term mental or cognitive impairments, including a condition known as 'brain fog' [81]. The term brain fog is collectively refers to symptoms such as mental fatigue, dizziness, confusion, anxiety, poor concentration, lowered mental and cognitive abilities, and short- and long-term memory loss [82]. Neuropathy patients have also shown the symptoms of brain fog, which are now considered early indications of various diseases such as AD, autism disorder, and mild cognitive impairment [83]. Additionally, the brain fog symptoms are associated with patients suffering from mast cell activation and systemic mastocytosis [84, 85].

It is well established that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes COVID-19 disease, which primarily affects respiratory, cardiovascular, gastrointestinal, and CNS [20, 86]. As the viral load increases in the body, the SARS-CoV-2 may hijack mitochondrial machinery for its replication and survival, consequently leading to mitochondrial dysfunction [87, 88]. This impairment of mitochondrial metabolism results from the virus targeting the oxygen availability and utilization by the SARS-CoV-2, causing hypoxia in the microenvironment. Hypoxic conditions develop in certain cerebral areas due to mitochondrial dysfunction. Cerebral tissues have a high metabolism, owing to which there is a constant and immediate oxygen requirement in the cerebral areas. However, these hypoxic conditions damage these high metabolism-requiring neurons, thereby resulting in cognitive impairment [89].

This hypoxic microenvironment generates oxidative stress, which activates mitochondria to initiate the pro-inflammatory response. This response may lead to several neurodegenerative and mental disorders [90, 91]. Additionally, the viral genome manipulations of the host mitochondrial leads to the release of mitochondrial DNA (mtDNA) into the cytoplasm. This mtDNA release triggers mtDNA-induced inflammasome and suppresses the innate and adaptive immunity, consequently leading to an increased spread of viral infection [92].

Currently, the mechanisms underlying brain fog following COVID-19 are still in the early stages of research. However, current hypotheses suggest that brain fog may be caused by factors such as neuroinflammation, psychological disorders, immune reactions, and microvascular injury (**Figure 2**) [93, 94].

3.1 COVID-19 and brain interaction

SARS-CoV-2 primarily infects the body by targeting ACE2 receptors on respiratory cells. This interaction activates the immune response, triggering the release of cytokines that affect the vascular system. The resulting damage to endothelial cells can lead to blood clots, inflammation, and brain damage [94, 95]. The pro-inflammatory response from the immune cells and activation of the innate immune response lead to the decrease production of monoamines (serotonin, norepinephrine, and dopamine),

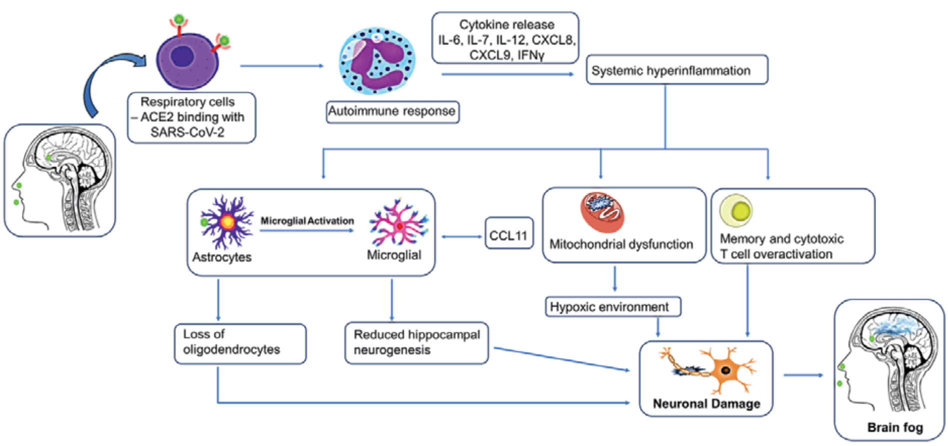

Figure 2.
Systemic and immune response: SARS-CoV-2 infects the body by binding to the ACE2 receptors of respiratory cells. This interaction triggers an immune response against the virus. However, prolonged antigen presentation and cytokine storms caused by an abnormal immune response led to systemic inflammation, causing astrocyte damage and microglial activation, which in turn resulted in neuronal damage. Systemic inflammation also causes mitochondrial damage, creating a hypoxic environment that further damages neurons. Additionally, this inflammation overactivates memory and cytotoxic T cells, leading to a pro-inflammatory response and subsequent neuronal damage. These mechanisms collectively result in neuronal dysfunction, ultimately causing cognitive impairment and brain fog.

trophic factors, and activation of microglial cells, which enhances the production of glutamate and N-methyl-D-aspartate (NMDA) receptors. This overproduction of aforementioned receptors leads to neuronal damage and brain dysfunction [96].

The SARS-CoV-2 can invade the brain through numerous mechanisms, leading to severe neurological disorders. This virus penetrates the olfactory mucosa, causing the loss of smell and taste in the patients suffering from COVID-19 diseases. However, this virus can penetrate the brain through the cribriform plate of the olfactory pathway or vagus pathway. The cytokine response generated by the immune system against the virus can destabilize the blood-brain barrier (BBB) or monocytes, leading to the increased permeability of the BBB and facilitating the movement of the viruses across the membrane [97]. The viruses can also reach the brain through circumventricular structures, which are the midline structures beside the ventricles that monitor blood and cerebrospinal fluid. These organs have capillaries that lack the tight junction proteins typically found in the BBB, making them more permeable [98]. Thus, COVID-19 can cause neuropathological disorders either by direct virus injury, neuroinflammation, or autoimmune consequences caused by critical illness.

3.2 Neurologic and systemic immunological response

The immunological response to SARS-CoV-2 infection consists of a spectrum of immune cells, chemokines, cytokines, and inflammatory molecules, which makes them a center of attraction for investigating the neuropathological disorders associated with LC 19 [99]. The pro-inflammatory response generated by the immune cells leads to persistent systemic inflammation, causing the expansion of monocyte subsets and T cell dysregulation, which are associated with damaged BBB and neuronal dysfunction.

3.2.1 Astrocyte activation

The pathogenesis of brain fog due to COVID-19 is currently unknown, but several hypotheses have been proposed to determine the mechanism. SARS-CoV-2 enters the CNS by attaching its viral spike-neuropilin-1 (NRP-1) protein to the ACE2 receptor expressed on astrocytes and neurons, subsequently passing through the olfactory bulb and hypothalamus [100]. Astrocytes are the most abundant cells in the CNS and play a crucial role in maintaining CNS homeostasis and immune modulation. Aerobic glycolysis is the metabolic process that occurs in astrocytes and provides energy to the neurons in the CNS; however, this metabolic process makes it a vulnerable site for the multiplication of viral agents [101–104].

Astrocytes glycolysis is activated by neuronal excitation, consuming a large amount of glucose and increasing lactate production. The pentose phosphate pathway (PPP) in astrocytes protects the neurons from oxidative stress by providing a reduced form of glutathione, which is necessary for the removal of reactive oxygen species [104]. Increased oxidative stress and mitochondrial dysfunction impair astrocyte glycolysis and the PPP pathway, causing significant neuronal damage. When astrocytes are infected with SARS-CoV-2, neurotransmitter biosynthesis, neuronal proteins, and energy metabolism are modified, potentially leading to changes in brain structure and causing neurological and neuropsychiatric symptoms [105].

Astrocytes are considered immunomodulators of the CNS; they release cytokines, modulate the immune response, and activate microglial cells following neuronal injury. Astrocytes activation remains crucial for virus control and clearance during acute infection. However, prolonged activation of astrocytes may support viral replication and cause significant neuronal damage [106, 107].

3.2.2 Persistent inflammatory response

The SARS-CoV-2 infection leads to the activation of a variety of immune cells, generating a robust immune response against the virus. However, this dysregulation in the peripheral immune system can persist for several months after the infection, causing the neurological dysfunction. COVID-19 patients exhibit changes in the population of innate immune cells, including natural killer cells, macrophage chemokine receptors, and mast cells, as well as cells for adaptive immune cells such as T helper cells and regulatory T cells [108].

These immune cells tend to secrete chemokines or cytokines, such as interferon β (IFN-β), IFN-λ1, IFN-γ, C-X-C motif chemokine ligand 8 (CXCL8), (CXCL9), CXCL10, interleukin 2 (IL-2), IL-6, and IL-17. The elevated levels of these chemokines further activate the immune system, leading to the prolonged neurological symptoms [109]. Previous reports have indicated that the symptoms of LC and mast cell activation syndrome are quite similar. Mast cells are abundantly present in the tissue microenvironment and often get triggered by viral infections to produce large amounts of inflammatory mediators such as cytokines, histamines, prostaglandins, leukotrienes, and proteases [110]. These elevated inflammatory mediators can cause persistent systemic inflammation, leading to microvascular injury and activation of microglia, thereby damaging CNS [111].

Prolonged cytokine release activates various cell populations, such as non-classical and intermediate monocytes, fibroblast, and myeloid cells. The non-classical monocytes stimulate the complement system and mediate antibody-dependent phagocytosis of viral particles. These monocytes, located on the luminal side of the vascular endothelium, contribute to the BBB integrity. Increased levels of macrophage scavenger receptor 1 (MSR-1) in COVID-19 patients indicate enhanced macrophage activation, which can damage the BBB integrity and CNS functionality. Similarly, the activation of intermediate monocytes leads to increased antigen presentation and release of pro-inflammatory cytokines [110, 111]. Additionally, Th2 cell activation results in the production of CCL11 cytokine, which activates the microglia, further enhancing the production of CCL11, ultimately causing neuroinflammation. This microglial activation leads to reduced hippocampal neurogenesis, loss of oligodendrocyte precursors, and subcortical white matter demyelination [112]. These systemic inflammation mechanisms have been strongly associated with cognitive impairment and neuropsychiatric disorders.

Impaired pro-inflammatory response and redox homeostasis are pivotal mechanisms in affecting the neurological disorder progression in COVID-19 patients. The genetic variation of antioxidant enzymes such as GSTO1 and GSTP1AB influences the extent of SARS-CoV-2 infection in the patients. Moreover, the GSTM1-null/GPX1LeuLeu genotype increases the persistent brain fog in patients if the NRF2 A allele is also associated. Such findings can also open a new avenue for the correlation of LC-associated brain fog with genetic susceptibility [113].

3.2.3 T cell dysregulation

It is well established that the presence of T cells is crucial for the clearance of viral infections. Both $CD4^+$ and $CD8^+$ T cells have been found to recognize the spike proteins of SARS-CoV-2 in 100 and 70% of COVID-19 patients, respectively [112]. However, chronic stimulation of T cells by viral antigens can lead to elevated levels of inhibitory transcription and decreased effector activities, a process known as T cell exhaustion. This phenomenon is particularly common in CD8+ T cells, leading to defects in functional responsiveness in clearing chronic infections [114].

Additionally, previous reports indicate the presence of memory T cells that are cross-reactive to the SARS-CoV-2 nucleocapsid even 17 years after exposure to the SARS-CoV. In LC patients, serum samples have shown an increase in memory $CD8^+$ T with higher expression of cytolytic granules but with reduced activation by specific antigens [26, 28]. Despite the increased number of memory $CD8^+$ T cells and elevated production of cytolytic enzymes, IL-6 and IFN-γ specific for viral nucleocapsid, these T cells lack polyfunctionality and effective responses, leading to various neuropsychiatric symptoms [112].

These T cells, producing higher cytolytic granzymes, are localized in the microglia nodules, which are the hotspots for immunological responses [115]. The cytotoxic T cells situated near the vasculature produce cytokines, resulting in BBB damage and neuroinflammation, consequently causing several neurological disorders [115, 116]. Additionally, the presence of an increased number of exhausted $CD4^+$ and $CD8^+$ T cells, along with decreased memory $CD4^+$ T cells with reduced executive functions, indicates toward atypical immunological engagement [117].

Thus, abnormal T cell function may lead to neuroinflammation. T cell dysfunction can cause the production of large amounts of pro-inflammatory cytokines, damaging the BBB and neurological function, resulting in various cognitive disorders.

3.2.4 Generation of autoimmune responses

The virus-induced abnormal stimulation of immune responses and inflammatory cascades in the body may lead to the production of autoantibodies. SARS-CoV-2 directly infects cells, producing enormous amounts of inflammatory cytokines, chemokines, spike protein receptor T cells, and autoantibodies, which damage the cells through oxidative stress [118]. These autoantibodies are found to enter the CNS through damaged BBB. Autoantibodies detected in the serum of COVID-19 patients can target extracellular, cell membrane, and intracellular components, including immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies against cytokines, angiotensin-converting enzyme 2 (anti-ACE2), and anti-nuclear proteins (ANA), respectively [119–121].

The IgA and IgG antibodies, which are secreted following the activation of peripheral B cells immune response and inflammatory cascade, cause cytokine dysfunction and damage endothelial integrity. The ACE-2 antibodies are found to upregulate the renin-angiotensin pathway, which can elicit the thrombo-inflammatory responses and cause hypertension-related ischemia, associating with chronic fatigue and myelitis [122]. Persistent autoreactivity of ANA is associated with several LC nineteen symptoms, such as fatigue, dyspnea, and brain fog [123]. These autoantibodies are linked to various autoimmune diseases, including encephalitis, vasculitis, GBS, *etc.* [124].

Researchers have discovered that the viruses can induce the autoimmunity through mechanisms such as molecular mimicry, transient immunosuppression, T cell bystander activation, and inflammation, potentially leading to post-COVID autoimmunity [125]. SARS-CoV-2 may cause autoimmunity due to the mimicry of human molecular chaperone proteins by viral proteins. It has been reported that brainstem respiratory pacemaker neurons (namely DABI, SURF1, and AIFM) share similar antigenic epitopes with SARS-CoV-2. This molecular mimicry may cause damage in brainstem respiratory neurons, leading to respiratory failure in COVID-19 patients [126, 127]. Recent experiments using bioinformatics prediction tools to identify immunogenic epitopes have found that seventeen molecular chaperones share significant peptide similarities with viral proteins, making them likely targets for immune system recognition and autoimmune responses [126]. However, the direct correlation between brain fog and autoimmunity remains unclear, necessitating further research to understand the disease pathogenesis.

4. Viral co-infection

SARS-CoV-2 infection may directly or indirectly impact the CNS, resulting in cognitive impairment and psychiatric conditions. Symptoms can include diverse manifestations such as "brain fog"—forgetfulness, mental fatigue, lack of motivation, and a tendency to be easily distracted. Further, infections with other viruses, including Human Immunodeficiency Virus (HIV), Epstein-Barr Virus (EBV), and Human Herpesvirus 6 (HHV-6), Cytomegalovirus (CMV), dramatically affect the cognitive symptoms in COVID-19 patients. A study revealed that LC-19 neurocognitive (LC) symptoms are more robust and prevalent in people with an underlying HIV infection than others [128]. A recent case study involved a 62-year-old man with a pre-existing history of HIV since 1991 who developed SARS-CoV-2 infection in February 2020. The man experienced several new post-COVID effects like atrial fibrillation, mental cloudiness, rolling brain waves, a sense of general body weariness, and dyspnea on minimal exertion. The man also faced trouble while driving a car on a familiar route he has driven two dozen times, resulting in poor decisions while behind the wheel and early morning waking without having had more than 2–3 hours of sleep [129]. The elevated rates probably result from the combined effects of immune dysregulation and chronic inflammation present in both HIV and COVID-19. Additionally, the reactivation of opportunistic viral infections such as EBV, HHV-6, and CMV has been linked to more severe COVID-19 symptoms and longer recovery time. EBV has the ability to infect human B cells and evade the host immune system by establishing latency after infection. Hence, making EBV a latent immunotropic like HHV-6, which is also capable of doing these things. On the other hand, the reactivation of EBV in COVID-19 has the potential to induce sequelae connected to EBV, which may make cognitive results even worse [130–132].

Although there is no particular information on Varicella-Zoster virus (VZV) and Hepatitis B and C virus (HBV/HCV) co-infections in COVID-19, similar immune system evasion and inflammation mechanisms might worsen the cognitive symptoms. Reports have also suggested that viral co-infections (such as HIV, VZV, HBV/HCV, and EBV) may intensify these cognitive symptoms by selectively impacting CD4+ and CD8+ T cell populations. These cells play a key role in producing a higher transforming growth factor (TGF)-β to interferon (IFN)-γ ratio. This potential imbalance can lead to an overproduction of bradykinin, which in turn leads to increased blood-brain barrier permeability and greater degrees of malfunction, especially for people who have conditions like AD or Parkinson's disease (PD). This could start our plunge into the dementia era, which is rapidly spreading today [133]. Furthermore, co-infections such as infection by IAV (influenza A virus) showed just how much SARS-CoV-2 is being amplified by these other viruses, resulting in higher infectious doses and more pronounced subsequent lung pathology—which may indirectly contribute toward producing even worse neurocognitive disorders. This example of a co-infection highlights the importance of preventing the co-occurrence of flu season and the COVID-19 pandemic, resulting in further enhanced health risk. It can cause hypoxia in specific areas of the brain due to other viral infections, compromising the neuronal energy metabolism and mitochondrial function, aggravating cognitive processes and physiological sceneries, and contributing to the viral spread. Secondly, co-infection with viruses that trigger or exacerbate autoimmune disorders, including a primary concern with an invasion of the brain and damage to the central nervous system [8, 134, 135]. Furthermore, the long-term cognitive sequelae of COVID-19 are not just dependent on the severity of the initial illness; they are also impacted by other long-term COVID symptoms, such as respiratory problems, sleep deprivation, and social isolation, which might potentially be severe in situations of co-infections. As a consequence of this, the interaction between SARS-CoV-2 and other viral illnesses can significantly improve cognitive results. This highlights the necessity of developing comprehensive diagnostic and treatment procedures to properly engage with these complex relationships.

4.1 Bacterial co-infection

Bacterial co-infections are frequently reported in COVID-19 patients with certain pathogens such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*, which further complicates diagnosis, intervention, and prognosis [136]. It has been shown in previous studies that infection with *Clostridium difficile* bacteria might make the results of COVID-19 worse, leading to a more severe illness and a greater fatality rate [137]. Bacterial co-infections are present in those with more severe disease courses with higher rates of in-hospital mortality and the need for more intensive therapies. Studies also found that bacterial co-infection was present in 51% of COVID-19 patients and associated with increased in-hospital mortality rates [138]. Moreover, broad-spectrum antibiotic therapy, frequently administered due to presumptive bacterial co-infections, was not associated with survival, thus underscoring the need to mitigate dispensable antibiotic use to reduce the propagation of multi-resistant bacteria. In addition, the occurrence of multi-drug-resistant (MDR) organisms can prolong hospitalization and worsen outcomes among patients with COVID-19 and concomitant bacterial co-infections [139, 140]. Brain fog symptoms ranging from mild disorientation to more severe dyscognition, memory, or concentration can result from the systemic inflammation and immune response elicited by co-infections. The acute COVID-19 state makes the complement system hyperactive, leading to secondary hypocomplementemia for a broad range of opportunistic bacterial infections, including those causing brain fog [141]. There is a possibility that this might contribute to increased inflammation and immunological dysregulation, which would speed up the course of the disease and perhaps result in brain fog. In the case of patients who had a bacterial bloodstream infection (BSI), for instance, there was a correlation between the presence of greater neurological symptoms and a higher white blood cell count, which was associated with poor outcomes and an increased death rate [142]. Reports have suggested that the respiratory infection caused by *Streptococcus pneumoniae* results in consequential complications like encephalitis and brain abscesses, which in turn cause neurological sequelae. Immunocompromised individuals are more prone to such problems [143]. It is common for severe cases of COVID-19 to be accompanied by a secondary infection known as *Staphylococcus aureus*. Its presence is associated with poor complement-mediated bacterial killing and perhaps a more complex clinical course resulting in cognitive deficits. *Klebsiella pneumoniae*, especially carbapenem-resistant strains, appears to be a serious risk because of multi-drug resistance and the correlation with major infections in COVID-19 patients such as those in the intensive care unit (ICU) [141, 144]. Furthermore, the existence of bacterial co-infections might make the symptoms worse and delay therapy in patients who have co-infections such as influenza viruses and mycobacteria, which can result in severe respiratory and systemic symptoms [145]. Additionally, immunosuppressive therapies used for COVID-19 management are known to increase the susceptibility of bacterial co-infections; hence they must be promptly diagnosed, monitored closely, and appropriate antimicrobial therapy instituted to prevent deleterious outcomes [146]. Collectively, the existence of COVID-19 and many other bacterial illnesses necessitates conducting comprehensive diagnostic screenings and developing individualized antibiotic regimens to prevent significant repercussions.

4.2 Fungal co-infection

COVID-19 patients with fungal co-infections make the disease much worse and thus lead to severe complications. Patients with severe COVID-19 are at high risk for invasive fungal infections because of immune dysregulation, comorbidities, administration of corticosteroids, and other types of immunomodulatory treatment. Aspergillus, Candida, and Mucor species are the most common fungal pathogens of COVID-19 infection, which are associated with higher morbidity and mortality [147, 148]. Aspergillus and Mucor spp. invade the airway epithelium that has been damaged by SARS-CoV-2, causing acute respiratory distress and potentially systemic infections that may also impact the CNS. Candida species, the most common fungal pathogen found in COVID-19 patients, can indirectly contribute to cognitive impairments due to prolonged critical illness, extended ICU treatments, and higher mortality rates [149, 150]. In critically ill or immunosuppressed patients, angioinvasive infections, such as COVID-19-associated pulmonary aspergillosis (CAPA) and COVID-19-associated mucormycosis (CAM), are common, leading to severe complications and increased mortality [151]. The risk of these fungal co-infections can be further augmented by the use of immunosuppressive drugs, such as corticosteroids, leading to invasive fungal infections (IFIs) that can target CNS, thereby contributing to symptoms of cognitive impairment. In addition, COVID-19-associated inflammatory responses and immune dysregulation propounded with direct effects caused by the fungal pathogens may further enhance the severity of neurological symptoms. Such infections can result in systemic inflammation, increased immune suppression, and a potential aggravation of the neurological symptomatology. Reports indicate that SARS-CoV2 patients with fungal co-infections have higher levels of inflammatory markers such as CRP and ferritin. These are also associated with cognitive disorders [152, 153]. The high mortality associated with fungal co-infections and the low sensitivity and specificity of established fungal biomarkers required better early diagnostic methods. Especially in the case of multispecies fungal infections such as Aspergillus and Mucor, which result in severe complications, it's important to establish accurate and effective diagnosis and treatment. Moreover, the antifungal treatments should be managed to avoid side effects and drug interactions causing further complications. Conclusively, fungal co-infections with COVID-19 may enhance the severity of disease, leading to widespread and severe cases of brain fog. Therefore, it is critical to develop accurate diagnostic tools and effective therapeutics to manage these challenging patients.

4.3 Immunopathologies of LC-19 co-infection

LC, or post-acute sequelae of SARS-CoV-2 infection (PASC), the post-infection syndrome includes a variety of chronically persistent symptoms and immunopathologies that can impact multiple organ systems, particularly in the case of co-infection with other viruses or bacteria. One of the most intriguing and least understood aspects of LC is its highly immunological pathophysiology, characterized by an unpredictable degree of host immune response dysregulation and the presence of both an excessive antiviral response as well as chronic inflammatory responses. LC is associated with systemic inflammation, immune dysregulation, and prolonged immune activation in some individuals, with a unique, allostatic phenotype very different from its acute phase counterpart. This includes an aberrant expansion of exhausted SARS-CoV-2-specific CD8+ T cells, along with evident mis-coordination of T and B cell responses and skewed T cell subset distribution [99, 154, 155]. In these patients, the hyperactivated immune system activates tissue injury mechanisms such as NETosis-induced microthrombofibrosis, microbial translocation, complement deposition, and the formation of autoantibodies [156]. Novel strategies to manage PASC are required despite widespread vaccination programs that have decreased the COVID-19 severity and mortality in many cases due to breakthrough infections and the emergence of new variants [157, 158]. Chronic slow-grade inflammation, driven by dysregulated cytokine production and signaling pathways (e.g., P38 MAP kinase), perpetuates neuroinflammation and associated symptoms such as fatigue, brain fog, and dysautonomias. [159, 160]. Additionally, patients with long COVID exhibit significant increases in pro-inflammatory cytokines, activated mast cells, and microemboli, resulting in reduced tissue perfusion and ischemia [161]. This is further complicated by the presence of persistent SARS-CoV-2 antigens and autoimmunity, evidenced by elevated anti-nuclear antibody (ANA) titers [162]. Interestingly, spike-reactive B cells have been observed to proliferate in response to non-SARS-CoV-2 antigens (e.g., EBV, CMV), particularly in patients with LC, to give rise to antibody-secreting B cells against non-SARS-CoV-2 antigens, arising as potential biomarkers. Immune dysregulation in LC implicates multiple facets of adaptive immunity accompanied by persistent viral reservoirs [117]. Autoantibodies target various cytokines and chemokines, such as interferon-α and interleukin-6. This in turn adds complexity to the immune milieu, thus leading to neurotoxicity and blood-brain barrier permeability issues culminating in neurological sequelae [163]. Regardless of the severity of immunopathologies, some LC effects, such as post-COVID lung fibrosis, are reversible, giving importance to targeted therapies that restore optimal immune function and ameliorate chronic inflammation. Elucidation of these mechanisms is an important step forward in the development of precision therapies to mitigate long-term damage to the life quality of LC patients.

5. Intervention and therapeutic progress in COVID-19-mediated brain fog

5.1 Potential intervention modalities for brain fog

Cognitive training, mindfulness meditation, and pharmacological treatments are among the effective modalities for addressing brain fog. A cognitive rehabilitation program called “Coping with Brain Fog” has been well-received by young adults with cancer, significantly improving their cognitive and emotional well-being. [164]. Multidisciplinary rehabilitation programs incorporating cognitive therapy, exercise, and diet, combined with personalized neuropsychological therapy, were effective in enhancing cognition. It has also been demonstrated that there is significant improvement in Montreal Cognitive Assessment (MoCA) scores in PACS compared with controls [165, 166]. Cognitive complaints and processing speed, meditation, especially mindfulness-based cognitive therapy (MBCT), has been helpful for patients with multiple sclerosis (MS) [167]. Pharmacological interventions like antihistamines, statins, and glucocorticosteroids reduce chronic neuroinflammation and therefore have therapeutic potential to reduce pro-inflammatory cytokine production and stabilize mast cells, which are essential triggers of brain fog [168]. Non-pharmacological strategies like repetitive transcranial magnetic stimulation (rTMS) and photobiomodulation (PBM) have shown increased alpha band power in EEG and cognitive enhancement [169]. Moreover, natural flavonoids, which have been proven to be anti-inflammatory and neuroprotective, such as luteolin, have also been suggested as potential treatments for neuropsychiatric disorders and brain fog [170].

Considering the overlap between LC and MCS, neurostimulation therapies like transcranial magnetic stimulation (TMS) and transcutaneous vagal nerve stimulation (tVNS) can be used for the development of symptom-specific neurotherapeutics and treat neurological symptoms in LC patients [171, 172]. A study found that photobiomodulation (PBM) effectively improved cognitive testing in a common type of brain fog, suggesting it could be an alternative or additional treatment to CBT [173]. Despite that, the efficacy of these interventions depends on patient characteristics and cognitive domains. For instance, combined domain cognitive training and moderate-frequency training have demonstrated clinical utility in treating attention deficit hyperactivity disorder (ADHD) in children [157]. These interventions provide a comprehensive approach to addressing brain fog by targeting the neuroinflammatory pathways and cognitive impairments induced by underlying biological factors. Although promising, challenges such as patient adherence and the development of personalized intervention strategies still need to be addressed.

5.2 Therapeutic treatments for brain fog (focusing on pharmacological progress)

Therapeutic strategies for brain fog, especially post-COVID-19 brain fog, consist of numerous pharmacological as well as non-pharmacological treatments. Pharmacologically, antihistamines, statins, non-steroidal anti-inflammatory drugs, antibiotics, and antihypertensives have been shown to significantly attenuate neuro-inflammation by inhibiting Kv1 channels and stabilizing mast cells, which are involved in the development of brain fog [168]. Furthermore, the combination of guanfacine, an α2A-adrenoceptor agonist, and N-acetylcysteine (NAC) has been reported to enhance cognitive abilities in patients by strengthening prefrontal connectivity and protecting mitochondria [174]. Bupropion, a dopamine and norepinephrine reuptake inhibitor, blocked hippocampal cell loss, reduced pro-inflammatory cytokines, and was effective for brain fog symptoms [175]. Non-pharmacological interventions such as PBM therapy, which involves the use of transcranial/whole-body PBM devices, have been reported to lead to meaningful improvements in cognitive tests and brain functional systems [173]. Acupoint target-specific electroacupuncture has been successful in improving memory and concentrating power as well as overall cerebral function in most patients suffering from depression

[176]. Additionally, several natural flavonoids, such as luteolin, that can exert anti-inflammatory and neuroprotective properties have been found to inhibit microglia activation, thereby reducing neuroinflammation, potentially indicating their use in the treatment of brain fog [177]. Medhya Drugs is a Sanskrit word to denote a group of drugs that can improve cognitive functions. These (Nootropic) are widely employed in Ayurveda and have shown antioxidant, acetylcholine esterase inhibition, antiamnesic, and neuroprotective properties [178]. Palmitoylethanolamide (PEA) was found to restore cognitive deficits and synaptic dysfunction by controlling levels of monoamines and enhancing neurogenesis, indicating a potential application of PEA as an adjuvant therapy for brain fog [179]. Anvifen (a nootropic GABAergic drug with anxiolytic effect) was greatly effective in lowering anxiety and cognitive complaints in the after-CVIs group in comparison with the control group. Additionally, the BBB poses a significant challenge for pharmacological drugs to reach the brain. However, novel approaches, including colloidal drug carrier systems, nerf, natal foreign drug, direct interstitial drug delivery, and techniques like focused ultrasound and pulsed electrical field-induced BBB disruption, have been developed to improve drug delivery to the brain [180, 181]. More generally in the field of neuropsychiatric disorders, pharmacological treatments for cognitive dysfunction in conditions such as attention deficit hyperactivity disorder (ADHD), schizophrenia, and depression have been proposed, and a proportion have been found to be effective in clinical trials [182]. Cholinesterase inhibitors and other cholinergic treatments have been the most studied in dementia, with ongoing research in growth factors and drugs acting on amyloid processing [142]. While there are no current treatments that can specifically target the mechanisms of neuroinflammation, such pharmacological advances are encouraging for treating brain fog and other associated cognitive deficits.

6. Conclusions

Research indicates that LC patients face an elevated risk of cognitive impairment, even in mild cases where hospitalization was not necessary. Common cognitive impairments associated with LC include issues with sensorimotor integration, sleep disturbances, memory dysfunction, decision-making difficulties, and executive function deficits. Mechanisms such as immune responses, microvascular injury, and neuroinflammation can impact the central nervous system (CNS), leading to neurological damage that affects cognition. However, whether these disorders directly result from CNS involvement requires further investigation. Additionally, the chapter explores potential co-infections or mechanisms that may worsen LC effects. Furthermore, it briefly discusses therapeutic progress and recent interventions for COVID-19-related brain fog. Understanding the full scope of neurological implications in LC is crucial for patient prognosis and care. This comprehensive chapter sheds light on clinical syndromes, mechanisms, co-infections, and therapeutics related to LC-mediated cognitive impairment advancements.

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Conflict of interest

All authors declare no conflict of interest.

Acronyms and abbreviations

COVID-19	coronavirus disease 2019
SARS-CoV-2	severe acute respiratory syndrome related coronavirus
CNS	central nervous system
PCC	Post-COVID-19 conditions
GBS	Guillain-Barré syndrome
AD	Alzheimer's disease
BBB	blood-brain barrier
GAS	Group A Streptococcus
EBV	Epstein-Barr virus
VZV	Varicella-Zoster virus
CRP	C-reactive protein
TNF-α	tumor necrosis factor-alpha
IL-1	interleukin-1
IL-6	interleukin-6
PTSD	post-traumatic stress disorder
ANS	autonomic nervous system
BMD	bone mineral density
APOE ε4	apolipoprotein E type 4 allele
ACE2	angiotensin-converting enzyme 2 receptor
mt DNA	mitochondrial DNA
NMDA	N-methyl-D-aspartate
NRP-1	neuropilin-1
PPP	pentose phosphate pathway
IFN-β	interferon β
IL-2	interleukin 2
MSR-1	macrophage scavenger receptor 1
IgG	immunoglobulin G
IgA	immunoglobulin A
anti-ACE2	angiotensin-converting enzyme 2
ANA	anti-nuclear proteins

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Chapter 5

Perspective Chapter: The Cardiovascular Impact of COVID-19

Rachel Anne Xuereb, Caroline J. Magri and Stephen Fava

Abstract

While it is well-known that subjects with underlying cardiovascular disease as well as those with associated comorbidities have an increased susceptibility to worse outcomes during acute COVID-19 infection, the long-term cardiovascular impact of COVID-19 is still to be unravelled. A subset of patients continues to present with cardiopulmonary symptoms, mainly shortness of breath, chest pain and palpitations, months and even years after the acute infection. Furthermore, studies have revealed that a minority of patients have residual left and/or right ventricular dysfunction at follow-up, as well as deranged cardiac markers, mainly troponin and NT-proBNP levels. The chapter will explore the current evidence with regard to endothelial and myocardial dysfunction following COVID-19, discuss possible underlying pathophysiology, and suggest the management of patients with persistent cardiovascular symptomatology.

Keywords: long COVID-19 syndrome, troponin, NT-proBNP, endothelial dysfunction, ventricular dysfunction

1. Introduction

The long COVID-19 syndrome refers to the persistence of symptoms after COVID-19 infection. It has also been referred to by various other names such as post-acute sequelae of SARS-CoV-2 infection (PASC), post-acute COVID-19 syndrome (PACS) and post-COVID-19 syndrome. It has been defined by the National Institute for Health and Care Excellence (NICE) of the UK as a set of persistent physical, cognitive, and/or psychological symptoms that continue for more than 12 weeks following the acute illness and which are not explained by an alternative diagnosis [1]. Using a Delphi process amongst an international panel of 265 patients, clinicians, researchers and WHO staff, the World Health Organisation has suggested a definition of the presence of symptoms that last for at least 2 months and which cannot be explained by an alternative diagnosis in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 [2].

The long COVID-19 syndrome is common [3–7]. Its prevalence has been estimated to range from 10 to 65.7%, depending on multiple factors including patient characteristics and length of follow-up. Its risk increases with increasing age, female sex, white ethnicity, poor pre-pandemic general and mental health, overweight/obesity, and asthma [7]. Shortness of breath is one of the most common symptoms of long COVID-19 syndrome [3, 8, 9].

Of major concern is the possibility of long-term cardiovascular complications. Data from the US Department of Veterans Affairs national healthcare databases has shown increased cerebrovascular disorders, dysrhythmias, ischaemic and non-ischaemic heart disease, pericarditis, myocarditis, heart failure and thromboembolic disease at 1-year post-COVID-19 in a population of individuals in their 60's [10].

The effects in the longer term are, as yet, unknown, but persistent endothelial and myocardial abnormalities raise the possibility of long-term cardiovascular sequelae after recovery from COVID-19. The chapter will explore these potential long-term complications. The possible post-vaccination effects are outside the scope of this chapter.

2. Inflammation and endothelial dysfunction

Endothelial dysfunction can persist after recovery from acute COVID-19, as evidenced by decreased flow-mediated dilatation [11–13] and increased L-selectin and P-selectin [14]. Another manifestation of endothelial dysfunction is reduced retinal venular flicker-induced dilation [15]. Increased endothelial-colony forming cells (an indication of vascular damage) have been reported at different time points after COVID-19, even up to 1 year [16, 17]. Endothelial dysfunction has even been reported in children 3–6 months after COVID-19 [18]. Charfeddine et al. reported that non-respiratory symptoms after COVID-19 are related to endothelial dysfunction. Furthermore, Berentschot et al. [19] have reported increased inflammatory gene expression in monocytes and increased serum pro-inflammatory cytokines 3–6 months after COVID-19. Possible reasons for the gender difference include hormonal influence on the perpetuation of inflammation [20, 21], as well as enhanced IgG antibody response [22], which may contribute to the gender difference in the prevalence of the long COVID-19 syndrome.

SARS-CoV2 can infect endothelial cells [23, 24], resulting in endotheliitis [25–27] and endothelial dysfunction [28]. It has also been shown to infect coronary vessels, inducing plaque inflammation [29]. There is evidence that SARS-CoV2 can persist in body fluids and cells [30–32], causing long-term endothelial dysfunction. T4 lymphocyte apoptosis during the acute phase might predispose to viral persistence [33]. There is also evidence of ongoing systemic inflammation months after recovery from COVID-19 [3]. This can also contribute to endothelial dysfunction. Indeed, Stahl et al. [34] have reported ongoing endotheliitis despite the absence of viral RNA in endothelial cells. A small study has reported the persistence of circulating viral spike proteins in patients up to 1 year after COVID-19, especially in those with long COVID-19 [35], which can contribute to ongoing inflammation. We also found a positive correlation of hsCRP with time, implying ongoing inflammation post-COVID-19 [3]. This has been confirmed by others [16, 36] but not all [37] authors. The reasons for these differences are unclear but might be related to different selection criteria, population differences, vaccination status, or the length of follow-up. Increased levels of other inflammatory markers such as tumour necrosis factor-α, interferon-γ, interleukins 2 and 6, platelet factor 4 and serum amyloid A have also been reported in patients with persistent symptoms after COVID-19 [36, 38]. Animal studies suggest that the complement alternative pathway may exacerbate endothelial injury and inflammation [39].

The findings of higher white cell count and lower haemoglobin in subjects with shortness of breath at follow-up suggest that persistent systemic inflammation may be greater in those with more severe disease or in those with slower recovery [3].

COVID-19 can also induce the formation of autoantibodies targeted against the catalytic domain of angiotensin-converting enzyme 2 (ACE2) [40], probably because ACE2 is the receptor for SARS-CoV2. These autoantibodies may persist after recovery from COVID-19 [41]. ACE2 catalyses the conversion of angiotensin II to angiotensin(1–7). Angiotensin II has vasoconstrictor, pro-fibrotic, and pro-inflammatory properties, whilst angiotensin(1–7) has opposite effects [42]. ACE2, therefore, favourably alters the balance between angiotensin II and angiotensin(1–7) and has been shown to improve endothelial function, to reduce oxidative stress and have anti-atherosclerotic properties [43, 44]. Indeed, genetic variants associated with increased ACE2 activity have been reported to confer cardiovascular protection [45]. The blocking autoantibodies directed against ACE2 after COVID-19 would therefore be expected to increase cardiovascular risk. Diminished ACE2 activity can also impair the reparative function of endothelial progenitor cells [46]. Arterial stiffness, which is known to be associated with increased cardiovascular risk [47], is also increased in patients with the long COVID-19 syndrome [48, 49].

Interestingly, sulodexide, a mixture of glycosaminoglycans with known beneficial effects on the fibrinolytic system, platelets, endothelial cells, and inflammation [50], has been reported to improve endothelial function and to alleviate chest pain and palpitations in patients with long COVID-19 syndrome [51]. Rajewska-Tabor et al. have reported that N-acetylcysteine and sulodexide reduced the synthesis of interleukin-6 and of von Willebrand factor in cultured coronary endothelial cells after exposure to the serum collected after 4 ± 1 months from coronavirus infection [52].

3. Metabolic derangements

Metabolic derangements including higher blood glucose, triglycerides and lower high-density lipoprotein cholesterol (HDL) have also been described in the long COVID-19 syndrome, especially in those with more severe COVID-19 requiring hospitalisation [8]. The mechanisms underlying such derangements are outlined in **Figure 1**. SARS-CoV2 has been reported to infect pancreatic β-cells [53] and to cause their apoptosis [54]. On the other hand, the ongoing inflammation leads to insulin resistance [55]. COVID-19 survivors also exhibit a decrease in lean mass [56]. Furthermore, SARS-CoV2 can infect and cause apoptosis of hepatocytes [57]. The decrease in muscle mass and in liver function both contribute to insulin resistance, which is known to be associated with increased cardiovascular risk [58, 59]. SARS-CoV2-induced endoplasmic reticulum stress may also increase hepatic lipogenesis [60] contributing to the increased circulating triglyceride levels and inducing hepatic steatosis.

The decrease in pancreatic β-cell mass coupled with insulin resistance predisposes to dysglycaemia. The decrease in ACE2 activity described above may also contribute

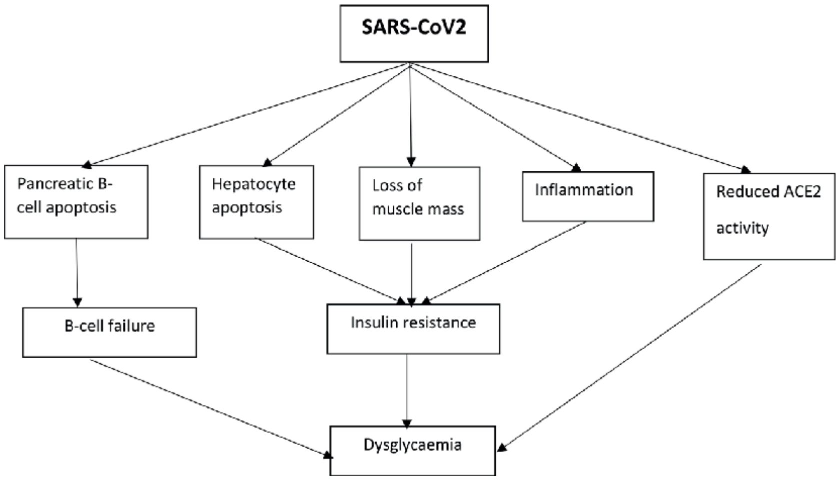

Figure 1.
Metabolic derangements following SARS-CoV2.

to the increased risk of dysglycaemia since ACE2 has been shown to improve glycaemic control in diabetic mice [61]. New onset diabetes after COVID-19 has been described by various authors [62–64]. New onset diabetes has also been linked to a specific microRNA (miR-34a) in circulating extracellular vesicles released by endothelial cells [65]. Diabetes is, of course, a major cardiovascular risk factor. However, even smaller degrees of elevation in blood glucose (remaining within the normal range) can contribute to increased cardiovascular risk. It is important to note that these changes have occurred in the background of increases in body weight, total fat and truncal fat in the general population as well as in COVID-19 survivors, probably as a result of lockdown-related behavioural changes [56], which also induce similar metabolic changes and increased cardiovascular risk.

Furthermore, there is evidence of impaired mitochondrial fatty acid oxidation post-COVID-19 [66, 67] which may result in an ischaemia equivalent and increased circulating free fatty acids which are known to be pro-inflammatory and to cause endothelial dysfunction. Finally, Grote et al. [68] have reported dysfunctional HDL post-COVID.

4. Thrombophilia and microclots

Fogarty et al. [69] have reported a pro-coagulant state after a median of 68 days after COVID-19. Various factors contribute to this (**Table 1**). Elevated levels of

↑ D-dimer
↓ Kallikrein
↑ Platelet factor 4
↑ von Willebrand factor
↑ α-2 antiplasmin
↑ PECAM-1

Table 1.
Causes of increased thrombophilia.

D-dimer have been reported 2–4 months after COVID-19 [70, 71]. Other abnormalities include decreased plasma kallikrein compared to controls, an increased level of platelet factor 4 (PF4), von Willebrand factor (VWF), and a marginally increased level of α-2 antiplasmin (α-2-AP) [72]. Likewise, Turner et al. [36] have reported increased α-2 antiplasmin and platelet endothelial cell adhesion molecule-1. These abnormalities may explain the finding by Zuin et al. of increased risk of deep vein thrombosis and pulmonary embolism after a mean follow-up of 8.5 months after COVID-19 [73].

There is also increased formation of microclots which are resistant to fibrinolysis after COVID-19 [74, 75]. The thrombophilic state as well as the decrease in red cell deformability [76], probably both contribute to increased risk of thrombosis in small vessels. Microclots, in turn, impair microvascular circulation and result in tissue hypoxia.

5. Haematological parameters

Mean platelet volume (MPV) and red cell distribution width (RDW), two routinely available parameters, have been shown to be higher after medium-term follow-up (around 5 months) in subjects who required hospitalisation when compared to those who did not [8]. This has been confirmed by other authors [76]. MPV is an indicator of platelet activation [77] and is associated with an increased thrombotic risk [78]. It is associated with cardiovascular disease [79, 80] and mortality [81].

RDW, which is a measure of heterogeneity in erythrocyte size, is a strong marker of cardiovascular disease including myocardial scar burden [82], fatal cardiovascular events [83] and all-cause mortality [84]. High RDW may be a marker of inflammation and oxidative stress [85], but it is also possible that it is causally related to increased cardiovascular risk. The heterogeneity in red cell size leads to heterogeneity in their deformability [76]. This may impair microvascular circulation. There is also evidence of a persistent decrease in neutrophil deformability. Both these factors might predispose to risk of microclots and tissue hypoxia as a result of impaired microcirculation [76].

Another haematological parameter linked to poor functional recovery and long-term mortality after COVID-19 is the neutrophil-lymphocyte ratio (NLR) [86–88]. Increased NLR is a known adverse cardiovascular marker, as shown by increased all-cause mortality and cardiovascular events in subjects undergoing invasive angiography or cardiac revascularization [89], as well as increased risk of in-hospital mortality in subjects admitted with acute coronary syndrome [90]. This is possibly related to the increased incidence of non-calcified coronary plaque burden noted with increased NLR [91].

6. Microbiome

The gut microbiome is also altered during acute COVID-19 infection and these changes persist after recovery from COVID-19 [92]. This is probably secondary to direct infection of the gastrointestinal tract by the SARS-CoV2 since ACE2 is highly expressed in the gut [93]. Changes include a decrease in biodiversity and an enrichment of opportunistic bacteria, fungi, and eukaryotic viruses [92]; this has been found to be correlated with the development of the long COVID-19 syndrome [94]. Another important change is a decrease in butyrate-producing bacteria such as *Faecalibacterium prausnitzii* [60, 94]. Butyrate-producing bacteria have been shown to reduce inflammation, increase insulin sensitivity and improve glycaemia [95–97], with potentially cardioprotective effects. These COVID-induced changes in the gut microbiome may have occurred in the background of similar changes as a result of hygiene measures taken during and beyond the pandemic [98, 99]. The gut microbiome may gradually recover, but more slowly that the oral microbiome [100].

7. Myocardial injury

Troponin I, a marker of myocardial injury, remains elevated in some patients after recovery from COVID-19 [3, 8, 101]. Interestingly, this rise in troponin months after COVID-19 infection was found to be an independent predictor of the presence of shortness of breath in a cohort of patients, most of whom had not been hospitalised [3]. This suggests that there is ongoing cardiac injury in a subset of post-COVID-19 patients.

Myocardial abnormalities have also been detected up to 1 year after COVID-19 on cardiac magnetic resonance (CMR), including reduced left ventricular ejection fraction, myocardial oedema, increased left ventricular global longitudinal strain, higher left ventricle volumes and myocardial late gadolinium enhancement [102–104] Endomyocardial biopsy in patients with severe findings has revealed active lymphocytic inflammation [103]. A small study in soldiers of a median age of 27 years found decreased right ventricular function, myocarditis and Takotsubo cardiomyopathy after a median follow-up of 139 days from COVID-19 [105]. A meta-analysis of 35 studies in 2021 [106] found that common abnormalities at <3 months post-COVID-19 included increased T1 (30%), T2 (16%), pericardial effusion (15%) and late gadolinium enhancement (11%) on CMR, with symptoms such as chest pain (25%) and dyspnoea (36%). In the medium-term (3–6 months), common changes included reduced left ventricular global longitudinal strain (30%) and late gadolinium enhancement (10%) on CMR, diastolic dysfunction (40%) on echocardiography and elevated N-terminal proB-type natriuretic peptide (18%). In addition, COVID-19

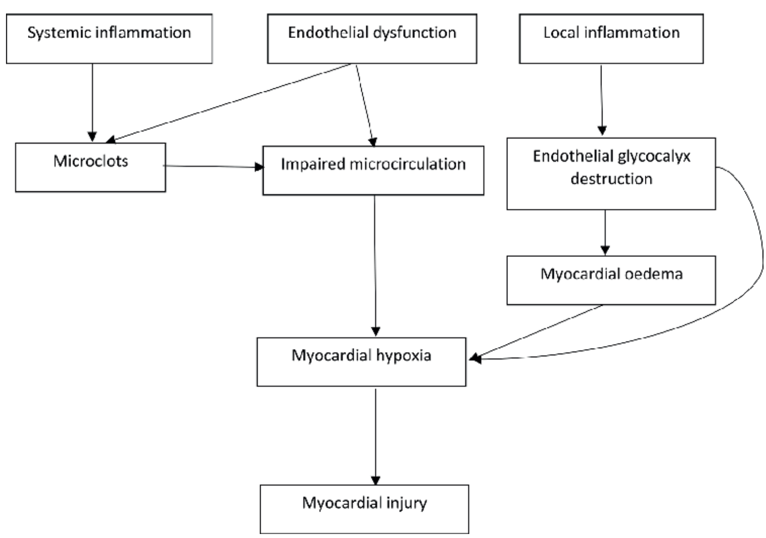

Figure 2.
Simplified scheme of the mechanisms of myocardial injury in long COVID-19 syndrome.

survivors had an almost 4-four increased higher risk (risk ratio 3; 95% CI 2.7–3.2) of heart failure, arrythmias and myocardial infarction.

Multiple mechanisms can explain these myocardial changes (**Figure 2**). These include systemic inflammation, coronary endothelial dysfunction and coronary microclots (see above). Furthermore, SARS-CoV2 may be persistent in cardiac tissue, resulting in local release of inflammatory cytokines [107]. Endothelial dysfunction can result in impaired coronary microvascular circulation and the promotion of the formation of microclots. Inflammation also leads to endothelial glycocalyx destruction, which in turn results in increased permeability and myocardial oedema [108, 109]. Myocardial oedema increases diffusion distances and can therefore lead to hypoxia. Impaired microvascular function and microclots also contribute to tissue hypoxia. Hypoxia can itself lead to glycocalyx destruction [110], resulting in a self-perpetuating cycle even in the absence of the initial insult. Myocardial oedema also directly impairs myocardial function [111].

8. Management

The knowledge with regards to the long COVID-19 syndrome is still relatively limited and so is our knowledge with regards to management of the disease. Till now, only one trial has followed up subjects with COVID-19 for >12 weeks [112]. In this randomised controlled trial, enoxaparin was administered daily for 14 days and study participants were followed up at 3, 7, 14, 30, and 90 days for both cardiovascular events and major bleeding events. However, the authors only presented results up to 30 days of follow-up and therefore it is not possible to derive conclusions on chronic cardiovascular complications. A Cochrane review found no evidence to recommend plasmapheresis with a view to removing amyloid fibrin(ogen) particles in patients with the long COVID-19 syndrome [113]. The potential role of sulodexide is discussed above.

To this extent, current guidelines suggest that the approach to long COVID-19 syndrome needs to be directed towards specific cardiovascular complications. These comprise mainly myocardial injury, arrhythmias as well as coronary syndromes (vide **Figure 3**). Consequently, patients generally present with shortness of breath,

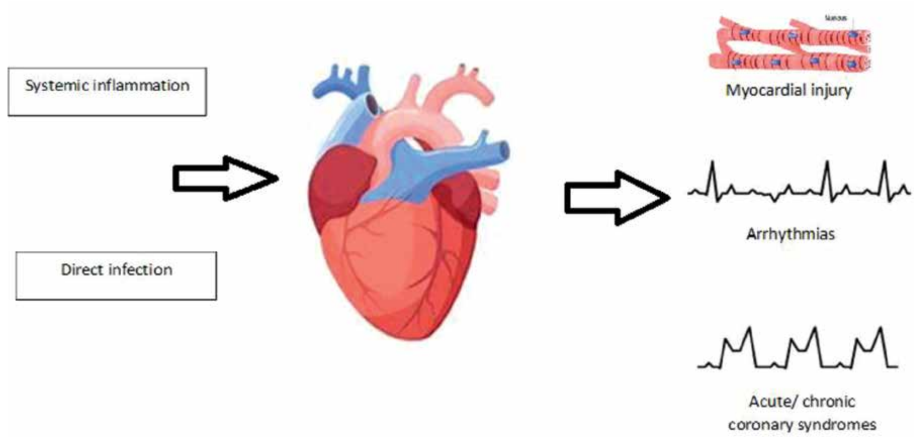

Figure 3.
Management of cardiovascular complications following COVID-19.

Symptomatology	Investigations
Chest pain	• Blood investigations including cardiac markers • Echocardiogram • CT coronary angiogram; to consider invasive coronary angiography in high-risk patients • Cardiac magnetic resonance
Shortness of breath	• Blood investigations including cardiac markers • CXR as preliminary investigation; to consider CT thorax if abnormal CXR • Pulmonary function test • Echocardiogram • Exercise stress testing/cardiopulmonary exercise testing • Cardiac magnetic resonance
Palpitations	• Blood investigations including cardiac markers & thyroid function tests • 24 hr. ECG monitoring • Echocardiogram • Autonomic testing

CXR = chest X-ray; CT =computerised tomography.

Table 2.
Suggested investigations in relation to cardiovascular symptomatology in long COVID-19 syndrome.

palpiations and chest pain. The suggested investigations are outlined in **Table 2**. The treatment given should follow international guidelines. This applies to the treatment of heart failure, myocarditis, arrhythmias, postural orthostatic tachycardia syndrome as well as acute and chronic coronary syndromes. β blockers are recommended for various cardiac complaints, including arrhythmias, angina as well as heart failure and therefore they might be a useful adjunct to the treatment of subjects with long COVID-19 syndrome.

In view of the various symptomatologies associated with long COVID, a multidisciplinary approach is suggested with the objective of improving the quality of life and possibly the life expectancy of subjects with persistent symptomatology following the disease. Undoubtedly, rehabilitation comprising individualised exercise training programmes could play an important role in regaining premorbid cardiovascular fitness. Interestingly, an amelioration in pulmonary function tests, quality of life as well as 6-minute walking distance following 6 weeks of physical and respiratory rehabilitation programmes has been reported [114].

The limited evidence with regard to the treatment of long COVID-19 highlights the importance of further research in this debilitating condition such that proper guidelines can be issued to guide specific treatment that can lead to improved outcomes in these COVID-19 survivors.

Conflicts of interest

The authors declare no conflict of interest.

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Chapter 6

Perspective Chapter: Respiratory Disorders and Brain Damage in Long COVID

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Abstract

In the last few years, we have realized that COVID-19 is a risk factor for new chronic diseases such as heart disease, diabetes, kidney disease, hematologic disorders, neurologic conditions, and cognitive disorders. Long COVID-19 symptoms continue or develop after initial SARS-CoV-2 infection and last 4 weeks or more. Some of our patients who have recovered from COVID-19 may experience varying degrees of functional impairment, radiological sequelae, and persistent symptoms requiring prolonged follow-up. Respiratory disorders are manifested by cough and breathing difficulties along with prolonged brain disorders expressed as cognitive dysfunction. The "brain fog symptom" is a collective term used to describe deficiencies in attention, executive functioning, language performance, processing speed, and memory among SARS-CoV-2 patients. A significant proportion of the morbidity associated with Long COVID is due to the syndrome of cognitive impairment as well as increased anxiety, depression, sleep disorders, fatigue, and sleep deprivation. Our findings indicate that Long COVID is associated with brain abnormalities and emphasize the value of neurological follow-up in recovered individuals.

Keywords: long COVID, respiratory disorders, cognitive dysfunction, brain fog, anxiety, dyspnoe

1. Introduction

Patients who have recovered from COVID-19 had reported physical, psychological, and social abnormalities. Patients suffering from anxiety and depression before contracting COVID-19 are prone to a longer course of symptoms. After the acute phase of a SARS-CoV-2 infection, a proportion of those infected show persistent somatic symptoms over weeks, months, and even years, including general tiredness, muscle pain, breathing difficulties, tingling extremities, and chest pain. As a result, clinical practice guidelines include recommending an interdisciplinary approach, taking into account the whole person and continuity of care, based on the clinical picture, usually lacking specific laboratory values.

2. Respiratory disorders in long COVID

Respiratory disorders associated with acute COVID can occur *de novo* or present as worsened problems in individuals with preexisting pulmonary conditions. People with chronic lung diseases were thought to be at high risk of having worse outcomes from COVID-19 early in the pandemic [1]. It is also possible that people with preexisting lung disease are more likely to develop Long COVID symptoms.

The most common symptoms in individuals with Long COVID, with one-third or more experiencing more than one symptom, are *fatigue* (13–87%), *dyspnea* (10–71%), *chest pain or tightness* (12–44%), and *cough* (17–34%) [2]. Persistent symptoms may vary depending on the COVID-19 variant.

Symptom resolution depends on a variety of factors, including premorbid risk factors, severity of the acute illness, and the spectrum of symptoms. Long COVID-19 is associated with factors such as female gender, comorbid conditions, and number of symptoms during the acute phase of the infection [3]. Individuals with shorter versus longer symptom intervals and individuals who are hospitalized versus those who are not can develop symptoms of Long COVID, although, in general, those with longer duration of symptoms and who were hospitalized are more prone to develop longer-lasting symptoms.

The need for chest imaging is determined by previous abnormal findings on chest imaging studies as well as the current symptoms. The majority of individuals who have not had chest imaging studies performed during their acute illness and have no current respiratory symptoms should not have any further imaging studies or radiological monitoring [4].

Further imaging studies are recommended for patients who had pulmonary infiltrates, new or worsening pulmonary symptoms, or abnormal findings on cardiopulmonary physical examination [5].

As mentioned before, among the most common symptoms in individuals with Long COVID are *shortness of breath*, *fatigue*, *exercise intolerance*, and *cough*. In addition to varying duration, these symptoms may be multifactorial in origin. For example, shortness of breath, fatigue, and exercise intolerance may be caused by pulmonary, cardiac, hematological, or deconditioning issues.

On the other hand, it would be disingenuous to state that some individuals who have Long COVID and persistent respiratory symptoms have no physiological or radiographic abnormalities (i.e., objective evidence) that could explain their current condition. Furthermore, the estimated date of maximum medical improvement (MMI) may still be unknown for patients with Long COVID.

For example, we looked at persistent symptoms and pulmonary function abnormalities at 3–6 months and at 1 year. We noted that one-third of patients had respiratory changes that persisted. We stated that these individuals will need prolonged follow-up [3, 4]. It appears that dyspnea persists regardless of the severity of the disease or the level of residual lung impairment in patients with COVID-19 pneumonia or milder forms. Even with minimal impairment of total lung capacity (TLC), there is often a mild/moderate reduction in lung diffusion capacity for carbon monoxide (DLCO) [6].

Pulmonary function studies are recommended for individuals with persistent, progressive, or new respiratory symptoms. Pulmonary function studies are also recommended for individuals with severe pulmonary problems, a history of COVID-19-related acute respiratory distress syndrome (ARDS), or neuromuscular weakness.

When pulmonary function studies are performed, an extended pulmonary function test (PFT) is recommended (spirometry with diffusion capacity) [7]. In general, it is recommended that the PFT be performed between 6 and 12 weeks after discharge. If abnormalities are found either radiographically or on physiological studies, repeat testing at 6 months is recommended. Thereafter, it is recommended that testing be performed for an additional 5 years. For individuals with unexplained respiratory symptoms after the initial cardiopulmonary evaluation (which includes an evaluation to eliminate the possibility of venous thromboembolic disease and/or heart disease), a 6-minute walk test is recommended [8].

For most individuals, a plain chest X-ray is sufficient. In cases after severe COVID-19 with more pronounced residual symptoms and functional loss, a CT scan is recommended. In general, the expectation of lung damage, as defined radiographically, resolves within 2 to 4 weeks, but full resolution may require 12 weeks or longer. There are studies suggesting that changes may occur within the first year, especially in patients who had severe disease. CT angiography is recommended in individuals who have unexplained cardiopulmonary symptoms and/or low oxygen saturations, despite normal chest radiography findings, to eliminate the possibility of thromboembolism.

There has been an association between persistent dyspnea and dysfunctional small airways 3 months after discharge, regardless of the extent of the disease and the radiological or parenchymal sequelae [9]. The purpose of our research is to describe the temporal dynamics of SARS-CoV-2 infections, characterize persistent symptoms, and identify factors associated with their resolution after infection. We followed patients with acute COVID-19 for 1, 3, 6, and 12 months after symptom onset and found interesting symptoms in the different periods.

2.1 Respiratory symptoms 1 to 3 months after acute SARS-CoV-2 infection

This is the earliest period in which residual symptoms after acute COVID-19 are recorded. Among the most common symptoms are shortness of breath with exertion (50%), cough (10%) and chest pain (16%). About 29% of patients were asymptomatic. Most of our patients reported that their breathing was worse after the initial illness. People with asthma reported increased inhaler usage and worse asthma control [10]. There were no significant differences with respect to gender, ethnicity, or household income.

High-resolution CT scans of the lungs showed persistent ground-glass opacities and/or consolidations. We found pleural abnormalities in 60% of the cases, abnormal diaphragmatic thickness and excursion, which correlated with abnormalities on CT examination [11].

Pulmonary fibrosis is a key component of the post-acute COVID-19 syndrome. Available data suggest that more than one-third of hospitalized COVID-19 patients develop lung fibrotic abnormalities after their discharge from hospital [12].

2.2 Respiratory symptoms 3 to 6 months after acute SARS-CoV-2 infection

The first 6 months following acute SARS-CoV-2 infection showed a rapid decline of symptoms. The most prevalent symptoms were *fatigue* (60%), *shortness of breath* (55%), and *impaired concentration* (34%). Overall, patients reported at least one symptom [6]. Fatigue or weakness (47%) were the most prevalent physical effects of post-acute COVID-19 syndrome, while psychosocial (28%) symptoms were the most common manifestations among several systems. We discovered abnormalities in lung function of recovering patients. The FEV1, FVC, DLCO, and TLC were all significantly lower in patients admitted to the intensive care unit compared to those who do not require oxygen therapy. However, only DLCO is decreased below the lower limit of normal and persisted for long periods [7].

Long-term progression to pulmonary fibrosis has previously been identified following infection with other species of the coronavirus family, for instance, severe acute respiratory syndrome. Factors related to increased incidence were extended length of stay, obesity, increased serum lactate dehydrogenase, and smoking status. Highly symptomatic long COVID patients show impaired DLCO and 6-MWT despite average or mildly affected mechanical lung parameters.

Another common symptom is a cough that may persist in some individuals for 3–6 months after recovery from acute phase. No clear risk factor associated with long-term post-COVID-19 cough was identified.

2.3 Respiratory symptoms 6 to 12 months after acute SARS-CoV-2 infection

COVID-19 patients with pathological pulmonary limitations and impaired pulmonary gas exchange during exercise were more likely to be obese than those without pathological pulmonary limitations.

In these individuals, shortness of breath and fatigue were the most frequent symptoms after the 6th month. We found CT abnormalities on lung scanning—ground-glass opacities and fibrosis. Our findings point towards respiratory muscle dysfunction as a novel aspect of COVID-19 sequelae. Our recommendations strongly advocate functional lung testing for persistently symptomatic, convalescent patients with COVID-19. While shortness of breath with exertion is one of the more frequent symptoms of Long COVID, as is fatigue, many individuals with these symptoms may have no objective abnormalities on formal physiological testing [8].

2.4 Respiratory symptoms 12 months after acute SARS-CoV-2 infection

Approximately 10% of people with symptoms still presented with at least one symptom at 1 year after infection. Older age, male gender, and higher BMI were associated with prolonged symptoms of COVID-19. Also, pulmonary restriction and reduced DLCO were associated with the accompanying diseases. DLCO was significantly improved at the 1-year visit in our patients [9]. The prevalence of exertional dyspnea, cough, and fatigue also decreased at the 1-year visit. It appears that in most patients, DLCO and respiratory symptoms normalize or improve 1 year after a COVID-19 infection. However, there is about one-third of patients in whom respiratory changes persist and will need prolonged follow-up. In conclusion, we found that the consequences of COVID-19 are diminishing over time.

The fact that Long COVID symptoms are common after infection, along with ongoing transmission, calls for careful attention in defining the syndrome and determining possible interventions. The data suggest that vaccination reduces the risk of Long COVID, so focusing on improving vaccination rates must remain the cornerstone of COVID-19 prevention and mitigation, not just locally but globally as well [13].

The number of people with persistent symptoms after 1 year in a pandemic context with a high cumulative incidence remains a major public health concern [14].

3. Brain disorders in long COVID

During the COVID-19 pandemic, millions of people around the world had been affected. After the initial interest in acute complications, it later became clear that the long-term consequences of the disease deserve just as much attention. Observations during the pandemic have shown that viral infection can affect *both the central (CNS) and peripheral nervous system (PNS) and skeletal muscle.*

A large number of our patients suffering from severe infection, as well as many of those after mild and moderate severity and treated outside hospitals, develop serious neurological disorders. Symptoms such as *insomnia, depression, anxiety,* and *cognitive impairment* were reported as the most common long-term neurological suffering, especially in older and vulnerable comorbid patients and in those after treatment in intensive care units with mechanical ventilation. Acute thrombotic complications, including *cerebrovascular events*, occur both during and after acute infection.

There are still many unknowns about long-term brain sequelae, most commonly cognitive and psychiatric disorders, especially in severe cases with high levels of proinflammatory cytokines and acute respiratory dysfunction with mechanical ventilation. It is assumed that all these factors cause cognitive decline, insomnia, depression, and anxiety. From a pathogenic perspective, these outcomes may result from the direct harmful impact of the immune response, the worsening or acceleration of existing cognitive deficits, or the onset of a neurodegenerative disease.

Several retrospective studies in the US have shown that 24% of patients with COVID-19 and neurological complications have short-term disturbances in memory and attention, and even more exhibit neurocognitive disorder [15]. According to other studies, one-third of patients treated for the infection in the intensive care unit demonstrate cognitive impairment, especially in the form of dysexecutive syndrome, characterized by inattention, disorientation, and poor organizational skills [16]. It should be noted that most reports indicate the need for a thorough neuropsychological examination, as in many of the patients the most frequently applied tests such as MMSE (Mini Mental State Examination) and MoCA (Montreal Cognitive Assessment) did not capture the cognitive impairments [17]. Cognitive symptoms can also appear in nonhospitalized patients with a mild or moderate infection and last weeks and even months after the acute phase, and in cases of previous brain damage, they remain irreversible [16].

The implementation of complete neuropsychological studies and satisfactory follow-up is hampered by the impact of the epidemiological situation and pandemic waves on the efficiency of the health system. There are at least four possible pathogenetic mechanisms that could explain central nervous system (CNS) involvement in COVID-19:

- Direct involvement due to neurotropism
- Systemic inflammation
- Dysfunction of internal organs—liver, kidneys, and lungs
- Cerebrovascular changes [16].

Many of the scientific reports indicate cognitive impairment as a common consequence of the COVID-19 infection. The underlying mechanisms of neurological impairment are still under investigation as well as the required recovery time if the damage is reversible. The hippocampus is believed to be a part of the brain susceptible to the coronavirus damage resulting in postinfectious memory impairment as well as progression of neurodegenerative diseases such as Alzheimer's or Parkinson's disease [17]. Sometimes months after the recovery from the acute infection there can be significant mood changes, confusion, memory and cognitive impairment, and physical discomfort [18]. Even with a mild course of the disease (no shortness of breath and no hospitalization treatment), cognitive impairments of varying severity may be detected, which probably means that COVID-19 infection has a systemic effect on cognitive functions [19].

Nonspecific factors such as a long stay in an intensive care unit, the application of mechanical ventilation, drug sedation, hypoxemia, side effects of secondary drugs, and others can be added to them [20]. In most cases, however, CNS damage occurs through a combination of several of the above mechanisms. Each of these, as well as their combination, puts survivors of COVID-19 infection at risk of developing long-term neurological sequelae either by exacerbating preexisting neurological damage or by generating it [21]. About one-third of patients have evidence of cognitive impairment and motor deficits at discharge [22]. This is extremely important, since the most severe COVID-19 infection occurs in elderly patients, who usually have already developed cerebrovascular or neurodegenerative disease, which creates a compelling need for future neurological monitoring and care [16].

The elderly population, especially those with comorbidities such as cerebrovascular disease or some form of dementia, is a vulnerable group at risk of infection and re-morbidity in a more severe form with higher mortality and less favorable long-term health outcomes. Therefore, it is important to perform a long-term follow-up of survivors of COVID-19 infection using *comprehensive cognitive and neuropsychological instruments, combined with neuroimaging methods and clinical assessment*, especially in patients who were in intensive care and with established neurological manifestations during the acute phase of the disease.

Our experience strongly suggests that survivors of COVID-19 infection are at high risk of subsequent long-term development of neurological complications, including cognitive impairment. General practitioners, neurologists in outpatient practice, physiotherapists, and other specialists caring for these patients must be prepared for this possibility in order to provide adequate health care for the patients and support for their families. Patients with established long-term sequelae should be referred for appropriate psychological care and cognitive rehabilitation to minimize potential negative effects on survivors' psychosocial functioning and quality of life.

4. Long COVID neurologic aspects

Long COVID syndrome is a multifaceted condition characterized by the persistence of symptoms and health complications beyond the acute phase of COVID-19. Affecting a significant portion of those who have recovered from the initial infection, estimates suggest that approximately 10–30% of individuals with COVID-19 experience Long COVID symptoms. This syndrome can impact various organ systems, including the respiratory, cardiovascular, musculoskeletal, and gastrointestinal systems, leading to a broad spectrum of health issues. Among these, neurological manifestations are particularly notable, encompassing cognitive impairment, headaches, dizziness, and neuropathic pain. This chapter delves into the neurological aspects of Long COVID, exploring the underlying mechanisms, clinical presentations, and potential therapeutic strategies to manage these persistent and often debilitating symptoms [23].

COVID-19 exerts a profound impact on the vascular system, primarily through mechanisms such as inflammation and endothelial dysfunction. The virus induces a robust inflammatory response, leading to the release of cytokines and other inflammatory mediators that damage the endothelium, the delicate lining of blood vessels [24]. This endothelial damage disrupts normal vascular function, promoting the formation of blood clots, or thrombosis. Additionally, the inflammatory response can cause microvascular injury, where small blood vessels are particularly affected, leading to impaired blood flow and oxygen delivery to various tissues. This can result in complications such as microthrombosis, which obstruct capillaries and further exacerbate tissue damage. In the brain, these vascular disturbances can lead to significant consequences, including chronic hypoperfusion, contributing to cognitive impairments and other neurological symptoms observed in Long COVID patients, as well as several acute neurological emergencies such as stroke and cerebral venous thrombosis [25]. Understanding these vascular effects is crucial for developing strategies to prevent and treat the long-term cardiovascular and cerebrovascular complications associated with COVID-19.

Ischemic stroke, which occurs when a blood clot obstructs a cerebral artery, depriving brain tissue of oxygen and nutrients, is a critical concern in Long COVID. The endothelial dysfunction and heightened inflammatory state induced by COVID-19 promote a prothrombotic environment, increasing the likelihood of clot formation within the cerebral arteries [26]. The incidence of ischemic stroke is the highest in the acute phase of the SARS-CoV2 infection, but the risk of having an ischemic event in the following weeks remains relatively high. Most of our patients have preexisting comorbidities such as hypertension, dyslipidemia, diabetes, and obesity. However, it was observed that the median age of the patients was younger at 64-years of age. We also observed that in some patients, the sole predisposition for the event was a recent COVID-19 infection [27]. In the acute setting of ischemic stroke, revascularization therapy remained the best treatment option, that is, intravenous tissue plasminogen activator or endovascular thromboaspiration and mechanical thrombectomy.

Hemorrhagic stroke, characterized by the rupture of weakened blood vessels and subsequent bleeding into brain tissue, is also more likely in Long COVID patients. The vascular fragility caused by the persistent inflammatory response and endothelial damage associated with the virus can lead to increased blood vessel permeability and rupture [28]. When these weakened vessels burst, blood spills into or around the brain, causing increased intracranial pressure and damage to brain cells. Another reason an increased incidence of hemorrhagic stroke during the pandemic may be due to the widespread use of antithrombotic medications for the prevention of ischemic events. Hemorrhagic stroke can result in severe neurological impairments, including loss of consciousness, severe headaches, and sudden neurological decline [29]. The combination of inflammation, endothelial dysfunction, and a hypercoagulable state creates a precarious situation, where the risk of both clot formation and vessel rupture is elevated. This set of patients has the least favorable outcome prognosis and needs close monitoring and requires treatment in the intensive care unit.

Cerebral venous thrombosis (CVT) is another severe complication observed in Long COVID. This condition involves the formation of clots in the brain's venous sinuses, impeding normal blood drainage and resulting in increased intracranial pressure and potential hemorrhagic conversion [30]. The prothrombotic state induced by

COVID-19, along with direct viral effects on the vascular endothelium, underlies this heightened risk for CVT. These vascular disturbances contribute to a range of neurological symptoms, from headaches and seizures to focal neurological deficits and encephalopathy. As such, addressing the vascular dysfunction in Long COVID is essential for mitigating these significant and potentially life-threatening neurological outcomes [31]. The SARS-CoV2 infection was proven to be an independent risk factor for this particular kind of cerebrovascular event [32].

One of the most common and therefore troubling aspects of Long COVID is its impact on cognitive functions. Key symptoms include dysautonomia (also known as postural orthostatic tachycardia syndrome), post-exertional malaise, fatigue, and cognitive challenges commonly referred to as “brain fog.” *Brain fog* is a nonmedical term used to describe a constellation of cognitive symptoms that include persistent memory problems, difficulty concentrating, and a general sense of mental sluggishness [33]. These cognitive issues can vary in severity from mild forgetfulness and distraction to more profound impairments that significantly hinder daily functioning. Individuals with Long COVID may find themselves struggling to perform routine tasks, retain new information, or focus on their work, leading to a decrease in productivity and quality of life. The cognitive impairments associated with Long COVID can affect professional responsibilities, personal relationships, and overall well-being, causing considerable distress and frustration for those affected [34].

The cognitive issues seen in Long COVID patients likely result from a combination of multiple factors. Endothelial cells, pericytes, and astrocytes all have high levels of angiotensin-converting enzyme 2 (ACE2), suggesting that SARS-CoV-2 can disrupt the blood–brain barrier. This disruption can affect the proteins that form tight and adherens junctions, leading to increased permeability of the blood–brain barrier, leakage of blood components, and infiltration of immune cells into the brain tissue. Additionally, SARS-CoV-2 may enter the brain by passing through microvascular endothelial cells *via* an ACE2 receptor-related pathway. Inflammation plays a central role, as the body’s prolonged immune response to SARS-CoV-2 can lead to chronic neuroinflammation [35]. This ongoing inflammation can damage brain cells and disrupt neural networks, contributing to cognitive deficits. Hypoxia, or oxygen deprivation, is another significant factor. COVID-19 can impair respiratory function, reducing oxygen supply to the brain, which can result in cellular damage and cognitive impairments. Patients experiencing brain fog commonly report issues such as trouble concentrating, slowed thinking, forgetfulness, and difficulty finding the right words when speaking. These subjective symptoms are confirmed by cognitive tests, which show a notably reduced capacity to remember words and images.

Patients with cognitive complaints scored a median of 26 on the MoCA Test, which set the baseline, but after a year’s follow-up and nootropic treatment with medications such as piracetam and citicoline, the cognitive effects seem to resolve and the patients scored an average of 28 on the MoCA Test. So, the damage seems to be reversible although it may take a long time to recover.

There is also concern that these cognitive symptoms may not be entirely reversible in all patients. In some cases, the persistent inflammation and hypoxia could potentially lead to long-term neurodegeneration, where progressive damage to neurons and brain structures results in chronic cognitive decline. This is the case in patients who are already at high risk of developing dementia, and the SARS-CoV2 infection seems to precipitate that process. This potential for lasting brain injury underscores the importance of early recognition and management of cognitive symptoms in Long COVID patients. Understanding these underlying mechanisms is crucial for developing effective therapeutic strategies aimed at mitigating cognitive impairments and improving the quality of life for those suffering from Long COVID [36].

Long COVID can significantly affect the *peripheral nervous system (PNS),* leading to a variety of debilitating symptoms. One of the most common manifestations is *neuropathy,* which includes symptoms such as tingling, numbness, and pain in the extremities. These sensations, often described as pins and needles, can range from mild discomfort to severe pain, impacting daily activities and overall quality of life. *Autonomic dysfunction* is another prominent feature, manifesting as dizziness, fatigue, and orthostatic intolerance (difficulty maintaining blood pressure upon standing). These symptoms reflect disruptions in the autonomic nervous system, which controls involuntary bodily functions like heart rate, blood pressure, and digestion. Additionally, many Long COVID patients experience *smell and taste disorders*, which may persist long after the acute infection has resolved. This anosmia (loss of smell) and ageusia (loss of taste) significantly affect appetite and quality of life.

The mechanisms by which COVID-19 damages the peripheral nervous system are multifaceted. The virus may directly invade peripheral nerves, utilizing the same receptors it uses to enter respiratory cells. This direct viral invasion can cause acute nerve damage and subsequent neuropathy. Moreover, the body's immune response to the virus can trigger inflammatory processes that damage peripheral nerves. This immune-mediated damage is seen in conditions like Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP). GBS, a rare but serious condition, involves the body's immune system attacking the peripheral nerves, leading to weakness, tingling, and, in severe cases, paralysis. CIDP is a related condition that involves prolonged inflammation and demyelination of peripheral nerves, causing progressive weakness and sensory loss [26].

These inflammatory processes are thought to be driven by the body's attempt to combat the virus, which can inadvertently target the nervous system. Cytokines and other inflammatory mediators released during the immune response can damage nerve fibers and disrupt their function. The resultant nerve damage from both direct viral invasion and immune-mediated mechanisms underpins the diverse and often severe peripheral nervous system manifestations observed in Long COVID. Understanding these mechanisms is crucial for developing targeted treatments to alleviate the PNS symptoms and improve the quality of life for those affected by Long COVID.

To address peripheral nervous system damage in Long COVID, a multifaceted approach to treatment is essential. Pharmacological interventions, such as anti-inflammatory medications and neuropathic pain medications like gabapentin and pregabalin, can alleviate pain and reduce inflammation. Immune-modulating therapies, including intravenous immunoglobulin (IVIG) and plasmapheresis, are beneficial in immune-mediated conditions like Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP). Rehabilitation through physical and occupational therapy helps maintain muscle strength, improve motor function, and enhance daily living skills. Nutritional support, emphasizing adequate intake of B vitamins and omega-3 fatty acids, aids nerve health and repair [24]. Lifestyle modifications, such as regular gentle exercise and a balanced diet rich in antioxidants and anti-inflammatory foods, further promote nerve function and overall health. Emerging therapies, including stem cell therapy and treatments involving nerve growth factors, hold potential for stimulating nerve regeneration and repair. By integrating these strategies, healthcare providers can develop comprehensive treatment plans tailored to the individual needs of Long COVID patients, promoting nerve regeneration and improving overall nerve function.

5. Conclusions

Post COVID-19 lung damage results in significant impairment of lung function, quality of life, and effort tolerance. Long COVID presents a complex array of respiratory and neurological manifestations that significantly impact the lives of those affected. Key issues include cough, dyspnea, chest pain or tightness, stroke, cognitive impairments such as brain fog, memory problems, and difficulty concentrating, as well as peripheral nervous system damage manifesting as neuropathy, autonomic dysfunction, and smell/taste disorders. The underlying mechanisms involve inflammation, hypoxia, neurotransmitter imbalances, and direct viral invasion of nerves, contributing to both acute and potentially long-term neurodegenerative changes. Current treatment strategies focus on pharmacological interventions, rehabilitation, nutritional support, lifestyle modifications, and emerging therapies like stem cell treatments and nerve growth factors. Ongoing research is crucial for unraveling the precise mechanisms of Long COVID and developing more effective treatments. Additionally, managing the mental health aspects of Long COVID, including anxiety, depression, and cognitive fatigue, is vital for comprehensive patient care, underscoring the need for a holistic approach to this multifaceted condition.

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Chapter 7

Perspective Chapter: Diabetes as a Post-COVID Syndrome – Possible Mechanisms Involved

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Abstract

There is a well-established association between hyperglycemia and severe coronavirus 2019 (COVID-19) infection. During the SARS-CoV-2 pandemic, mortality was higher in patients with type II diabetes mellitus (DM) than in those without DM. In addition, readmission and COVID-19 reinfection rates were similar in both groups. Evidence shows that individuals who have had COVID-19 are at a significantly increased risk of developing new-onset diabetes mellitus in the post-infection phase. The current literature suggests that direct cytotoxic effects of the virus and inflammation are possible pathophysiological mechanisms. In this chapter, we review the association between COVID-19 infection and new-onset diabetes mellitus after acute infection and discuss the available evidence on the mechanisms of action involved. These findings may have significant implications for understanding and managing COVID-19 and diabetes.

Keywords: diabetes, post-COVID syndrome, mechanisms, SARS-CoV-2, acute infection

1. Introduction

As has been widely documented, coronavirus disease 2019 (COVID-19), which originated in Wuhan City, Hubei Province, central China, is a disease caused by a new coronavirus (SARS-CoV-2) and has been named severe acute respiratory syndrome coronavirus (COVID) and 19 because the new virus emerged during 2019 (COVID-19) [1–3]. The precise origin of SARS-CoV-2 is still under investigation, although the initial cases were connected to the Huanan seafood market in Wuhan City. In addition to seafood, some wild animals, such as birds, snakes, marmots, and bats, were sold at the Huanan seafood market. Environmental samples collected from the market have shown positive results for the new coronavirus; however, the specific animal source has yet to be identified [3]. Recent studies have indicated that bats might play a role as natural hosts for SARS-CoV-2. Additionally, the virus has been isolated from pangolins, whose isolated coronaviruses exhibit approximately 85.5 to 92.4% genetic similarity to SARS-CoV-2. This finding suggests that pangolins could potentially serve as an intermediate host for the virus, highlighting the complexities of zoonotic transmission (**Figure 1**). However, further confirmation is required to determine whether SARS-CoV-2 is transmitted directly from bats or *via* an intermediate host [3]. What is certain is that SARS-CoV-2 can be transmitted between humans *via* respiratory droplets and is currently an epidemic infection, like others, such as influenza and respiratory syncytial virus.

It is essential to understand that the respiratory tract is not the only route of transmission for SARS-CoV-2 infection. Intimate contact is also a source of SARS-CoV-2 transmission. For example, SARS-CoV-2 has been reported to be transmitted by direct or indirect contact with the mucous membranes of the eyes, mouth, or nose. In addition, aerosol transmission in relatively closed environments with continuous exposure to high aerosol concentrations is also conducive to virus spread [3]. Moreover, COVID-19 patients frequently exhibit gastrointestinal symptoms, including diarrhea, nausea, and vomiting. Angiotensin-converting enzyme (ACE) and its counterpart, ACE2, play critical roles in hypertension, the renin-angiotensin-aldosterone system, and other cardiovascular disorders. The COVID-19 pandemic has undeniably highlighted the significance of ACE2 receptors, which SARS-CoV-2 effectively uses to penetrate human cells [4]. ACE2 receptors are highly abundant in various tissues throughout the body. They are significantly overexpressed in the intestinal epithelial cells of the gut and in the endothelial and smooth muscle cells of blood vessels. In the heart, ACE2 receptors are prominently present in the epicardium, adipocytes, fibroblasts, myocytes, and coronary arteries. The lungs show a strong expression of these receptors,

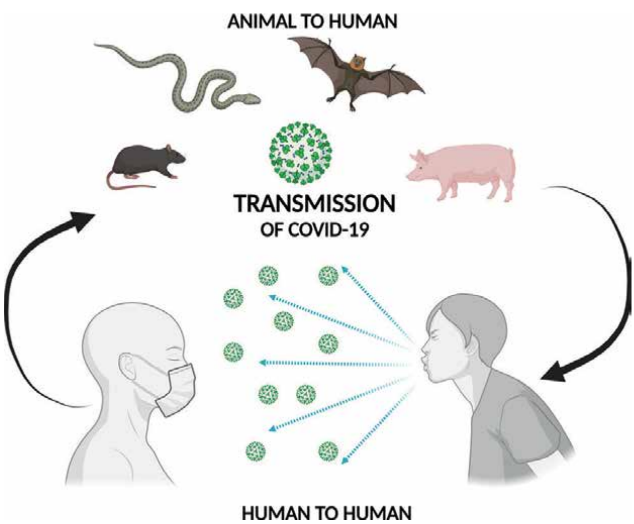

Figure 1.
Transmission of COVID-19. SARS-Cov-2 is most transmitted through the air in small droplets of fluid between people in close contact. After 48 hours, a person can develop COVID-19. The origin of COVID-19 remains unknown.

particularly in macrophages, bronchial and tracheal epithelial cells, and type 2 pneumocytes. Furthermore, ACE2 receptors are also critical in the brain, testis, and tubular epithelial cells of the kidneys [2, 4]. Recent studies clearly demonstrate that gastrointestinal symptoms of COVID-19 pneumonia are directly associated with the invasion of enterocytes that express angiotensin-converting enzyme 2 (ACE2). This establishes the gastrointestinal tract as a significant potential route for SARS-CoV-2 infection; in addition to the respiratory tract (**Figure 2**), additional research is required to confirm this possibility [2]. The possibility of transmitting SARS-CoV-2 through breast milk or from mother to infant vertically remains undetermined.

During the pandemic, several reports from around the world demonstrated that people with diabetes mellitus (DM) before COVID-19 infection were more likely to have a fatal or worse outcome than people without DM. People with diabetes who are hospitalized for COVID-19 are significantly more likely to require oxygen or ventilatory support need intensive care unit (ICU) admission, or face the risk of premature death due to the infection. Furthermore, individuals with additional comorbidities, such as heart disease, high blood pressure, or obesity, are at an even higher risk of experiencing severe complications from COVID-19 [5].

Continuing with this idea, new-onset diabetes (NOD) has been established for many years and has re-emerged in recent years due to COVID-19 [6]. The term "new onset" clearly indicates that symptoms first arise in individuals who have no prior history of diabetes. It is crucial to address these symptoms promptly, as untreated cases can escalate into severe, life-threatening complications such as ketoacidosis and hyperosmolar hyperglycemic state [7–9]. Certain factors definitively trigger the disease, such as organ transplantation, the use of antihypertensive medications, thiazide diuretics, beta-blockers, and severe infections. However, according to several reports, there are cases of NOD in children and adults with no previous diagnosis of T1D or T2D before SARS-CoV-2 infection [10–12]. Initially, this was related to the theory that these individuals had undiagnosed DM, but over time, more cases of DM

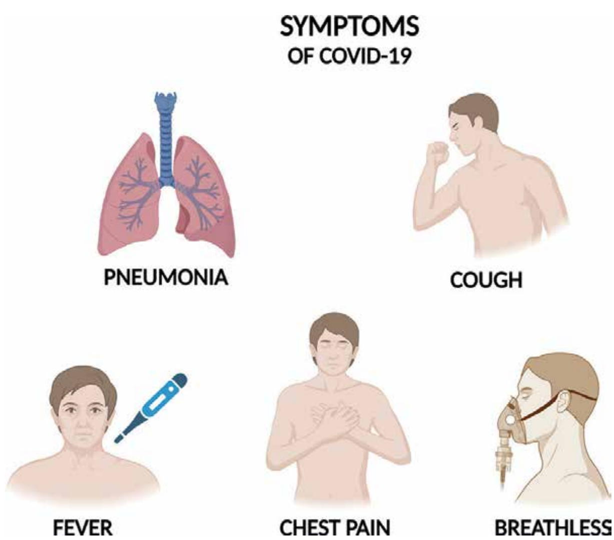

Figure 2.
Symptoms of COVID-19. Once the virus infects humans, the main symptoms are cough, fever, chest pain, dyspnea, and pneumonia.

emerged after patients with COVID-19 [10, 13]. On the other hand, some patients with transient DM were cured, and patients recovered after 6 months of COVID-19 presentation [14].

Diabetes mellitus (DM) is a serious and complex chronic disease characterized by significant dysregulation of glucose levels due to either absolute or relative insulin deficiency. The most prevalent types are type 1 diabetes (T1D) and type 2 diabetes (T2D). T1D is defined by the autoimmune destruction of insulin-producing pancreatic β-cells, while T2D arises from a combination of β-cell secretory defects and insulin resistance. The global burden of diabetes is substantial and cannot be ignored, with a prevalence rate of 9.3% and approximately 463 million individuals affected worldwide. This disease is strongly associated with numerous comorbidities and long-term complications, including obesity, hypertension, vasculopathy, pro-inflammatory and hypercoagulable states, and cardiovascular disease (CVD). Addressing diabetes is a critical public health priority that requires immediate attention and action [15].

It is essential to recognize that a significant bidirectional relationship exists between diabetes and SARS-CoV-2 infection following the rise of COVID-19. Diabetes often serves as a pre-existing comorbidity that heightens the risk of severe COVID-19 outcomes. However, it can also emerge acutely for the first time due to the infection. In these cases, immediate and aggressive treatment is imperative, as the progression of the disease is heavily influenced by the patient's clinical status [16].

2. Diabetes type 1 and diabetes type 2

2.1 Diabetes

Diabetes is a chronic metabolic disease characterized primarily by elevated blood glucose levels due to inadequate insulin secretion. Chronic high blood glucose levels can cause various organ damage, including damage to the heart, blood vessels, eyes, and nerves [15]. Diabetes is diagnosed in individuals whose fasting plasma glucose is ≥126 mg/dL, or whose 2-hour plasma glucose is ≥200 mg/dL, or whose glycohemoglobin is ≥6.5% [17, 18]. Diabetes encompasses a range of types, including type 1 and type 2 diabetes mellitus, gestational diabetes, and other specific types that result from genetic factors, syndromes, exocrine pancreatic disorders, or medications. Understanding these variations is crucial for effective management and treatment [19]. The most important of which are type 1 diabetes and type 2 diabetes, which will be discussed below [20].

2.1.1 Type 1 diabetes

All types of diabetes are characterized by elevated blood glucose levels, but the difference is in the cause. Type 1 diabetes (T1D) is a multifactorial autoimmune disease characterized by T-cell destruction of pancreatic β-cells, impairing insulin synthesis and secretion [21]. Previously, T1D was thought to be more common in children than adults; however, T1D can occur at any age, and more than 50% of cases are diagnosed in adulthood [22]. In terms of symptoms, children with T1D present with polyuria, polydipsia, and weight loss; in addition, approximately one-third present with diabetic ketoacidosis, whereas adults may not have the classic symptoms seen in children [23]. To differentiate the diagnosis of this diabetes from others, the identification of biomarkers such as antibodies against specific β-cell proteins such as insulin, glutamate decarboxylase, islet antigen 2, zinc transporter 8, and tetraspanin-7 is necessary [24].

Regarding the epidemiology of this disease, T1D is a disease that affects a large portion of the world's population; in general, about 8.8% of the population suffers from diabetes mellitus, of which 10–15% have T1D. More than 500,000 children are living with T1D, and an estimated 90,000 children are diagnosed with the disease each year. The highest prevalence of T1D is found in the northern European countries, where 30–60 per 100,000 have T1D, followed by southern European countries and North America, where 10–30 per 100,000 have T1D, and China and other Asian and South American countries, where 1–3 per 100,000 have T1D [25–27]. The incidence of T1D has been increasing by about 3–4% per year over the years; however, this incidence could increase due to genetic, environmental, and epigenetic factors.

On the other hand, genetics plays an important role in T1D; T1D is an inherited polygenic disease with a risk of 30–70% in twins, 6–7% in siblings, and 1–9% from parents with T1D in children [28]. There are different HLA haplotypes associated with T1D; HLA is a gene located on chromosome 6p21.3, spans about 4000 kb, and has more than 200 genes. The function of this gene is related to environmental pathogens and autoimmune diseases and has been widely associated with T1D. There are two haplotypes of the HLA gene: HLA DRB1*0301-DQA1*0501-DQ*B10201 (DR3) and HLA DRB1*0401-DQA1*0301- DQB1*0301 (DR4-DQ8), and these factors are linked to 50% of the cases. Are other HLAs related to different racial groups but poorly characterized [29, 30]. Sixty other non-HLA variants have been implicated as risk factors for T1D, including INS, PTPN22, CTLA4, IFIH1, CLEC161, and PTPN2; these variants have been associated with insulin gene expression, T-cell activation, or viral responses [30, 31]. Combining these HLA and non-HLA alleles may help predict T1D, allowing earlier diagnosis and treatment [32, 33].

Within the mechanism of T1D autoimmunity, molecular mimicry plays a central role as in other autoimmune diseases; a potential cross-reactivity between the non-structural protein P2-C of coxsackievirus and the autoantigen GAD65 has been found in T1D, another example is the VP1 protein of enteroviruses and the beta cell autoantigen tyrosine phosphatase IA-2. Furthermore, it has been reported that infection with other viruses can accelerate the autoimmune process, such as rotavirus, mumps virus, and CMV; molecular mimicry can only potentiate or initiate the autoimmune process in T1D [34]. Molecular mimicry has led to the identification of autoantigens that trigger the autoimmune process in type 1 Diabetes (T1D). These autoantigens include proinsulin, GAD65, IA-2, imogene 38, ZnT8, non-specific islet cell autoantigens (ICA), pancreatic-duodenal homeobox factor 1 (PDX1), islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP), chromogranin A (CHGA), heat shock protein 60 (hsp60), and islet cell antigen 69 (ICA69) [35, 36]. In the autoimmune mechanism of T1D, B lymphocytes recognizing some autoantigens (among those mentioned above) will interact with CD4+ and CD8+ T lymphocytes and dendritic cells, and the presentation of autoantigens will activate T lymphocytes to attack pancreatic β-cells; furthermore, the activated B lymphocytes will produce the autoantibodies against the islets of Langerhans, which will cause dysfunctions in the pancreas, especially in insulin production [37, 38]. Undoubtedly, T1D is a public health problem worldwide, affecting not only children but also adults, and if not adequately treated in time, this disease can cause serious side effects, including death, just like type 2 diabetes (T2D).

2.1.2 Type 2 diabetes

This type of diabetes is unrelated to autoimmunity; T2DM is characterized by relative insulin deficiency caused by pancreatic β-cell dysfunction and target organ insulin resistance. There are several risk factors associated with T2DM, such as advanced age, non-white race, family history of type 2 diabetes mellitus, genetic factors, components of metabolic syndrome (elevated waist circumference, blood pressure, plasma triglycerides, LDL cholesterol, low HDL cholesterol), overweight or obesity, abdominal or central obesity, unhealthy dietary factors (diet high in sugar, red meat and low liver intake, smoking, sedentary lifestyle, physical or mental stress) and use of some medications (statins, thiazides and beta-blockers) [39]. Previously, T2DM was considered to be a disease of adults and the elderly; however, due to the lifestyle of new generations, children and adolescents with T2DM are becoming more common [40]. Several complications due to T2D have been described, the most important being cardiovascular disease (coronary heart disease, peripheral vascular disease, and cerebrovascular disease), renal disease (chronic kidney disease), diabetic retinopathy, non-traumatic lower limb amputation, liver, and digestive disorders, among others [41].

Regarding the epidemiology of T2D, it is estimated that 1 in 11 adults aged 20–79 years, about 537 million adults worldwide will suffer from T2D in 2021; by 2030 and 2040, it is speculated that 643 million and 783 million people will suffer from T2D, respectively. In terms of mortality, 4.2 million people died from T2D in 2019. T2D is an underdiagnosed disease, and it is speculated that 1 in 3 people with T2D do not know they have it, which is about 232 million people [42, 43].

Insulin resistance and elevated blood glucose in T2D could be related to different phenomena; for example, dysfunction of β-cells in insulin production and elevated blood glucose levels contribute to increased oxidative stress resulting in ROS generation that inhibits Ca2 mobilization activating proapoptotic signals affecting insulin production in these cells [44]. The second phenomenon that plays a central role in T2D is insulin resistance, which can be stimulated by decreased insulin secretion by β-cells and plasma insulin antagonists. These molecules compete with insulin for receptors, which can be hormonal, for example, glucagon, or non-hormonal, and finally, by altered insulin responsiveness in target tissues, such as skeletal muscle, adipose tissue, and liver. In skeletal muscle, the change in the structure of proteins such as the insulin receptor or GLUT4 will increase insulin resistance. In adipose tissue, increasing the number of adipose tissue size will increase the inflammatory process, increasing the production of proinflammatory cytokines. As a result of chronic inflammation, insulin loses its activity in this tissue, raising blood glucose levels. As for the liver, insulin resistance increases lipolysis and free fatty acids, which accumulates in the liver and generates fatty liver [45–47]. Dysfunctional β-cells and insulin resistance are mainly responsible for elevated blood glucose levels in patients.

T2D is considered a multifactorial disease. There are different factors associated with this disease, and one of them is genetic. There are several single-nucleotide polymorphisms associated with T2D. For example, TCF7L2, FTO, PPARG, HHEX, and IGF2BP2 have been associated with changes in glucose levels, BMI, or insulin levels; the association of these genes was individually or together [48]. Gut microbiota also plays an important role in T2D. Intestinal bacterial species have important functions in organisms, such as immune system modulation, inflammatory response, and metabolite synthesis. However, diet, sedentary lifestyle, or antibiotic use can cause dysbiosis and change the proportion or type of bacteria residing in the gut, and these changes can decrease the production of some amino acids, such as branched amino acids and trimethylamine, a fact that by altering glucose homeostasis contributes to the development of T2D [49–51]. Mitochondrial dysfunction is another important fact associated with T2D; this phenomenon causes mitochondria not to efficiently use O2 in the oxidation process to produce energy, which will increase ROS in mitochondria, promoting inflammation and insulin resistance [52], and T2D is a complex disease. The more it is studied, the more etiological factors are found. There is no doubt that the best way to combat T2D is prevention since so many people suffer from this disease.

3. Diabetes mellitus following SARS-CoV-2 infection

Hayden et al. (2020) suggested several mechanisms that were likely involved in NOD at the onset of COVID-19: undiagnosed diabetes, damage to the pancreas by SARS-CoV-2, and hyperglycemia due to the stress of acute COVID-19 infection, leading to decreased insulin production [53].

Various factors commonly associated with diabetes mellitus may increase the risk of severe COVID-19. These include advanced age, a pro-inflammatory and hypercoagulable state, hyperglycemia, and various underlying comorbidities such as hypertension, cardiovascular disease, chronic kidney disease, and obesity [5, 16]. Severe COVID-19 infection and the administration of steroids can adversely affect individuals with diabetes. These factors may lead to increased blood sugar levels, known as hyperglycemia. This occurs primarily for two reasons: First, the body becomes more resistant to insulin, resulting in diminished cellular response. Second, the pancreas produces less insulin due to the reduced function of the β-cells that are responsible for insulin production [54, 55]. Exacerbation of hyperglycemia may, in turn, negatively affect the progression of COVID-19. In addition, several studies illustrate a possible association between new-onset hyperglycemia and severe coronavirus 2019 (COVID-19) disease [54, 56]. Other reports have documented autoimmune DM following COVID-19 vaccination in adults [57–59].

Interestingly, this newly identified occurrence of hyperglycemia is not correlated with other recognized risk factors, including obesity, prediabetes, diabetes mellitus, or corticosteroid administration [16, 60–62]. Several reports suggest that individuals with COVID-19 may experience the onset of new diabetes. There is a notable prevalence of diabetic ketoacidosis and hyperosmolarity observed in patients after a COVID-19 infection. Additionally, case reports indicate that COVID-19 may exacerbate diabetic ketoacidosis (DKA) in patients with newly developed hyperglycemia (diabetes) or those with pre-existing diabetes mellitus [63–65]. The timely recognition of symptoms associated with DKA is essential for enhancing the prognosis of DKA related to COVID-19.

3.1 SARS-CoV-2 pathophysiology

The SARS-CoV-2 virion possesses structural proteins facilitating its entry into cells and subsequent respiratory and metabolic disease pathogenesis. Among these proteins, the so-called spike or S protein is responsible for recognizing the cellular receptors for which the virus has tropism; once inside, the virus initiates the replication process, such as human aminopeptidase N, angiotensin-converting enzyme 2

(ACE2), dipeptidyl peptidase 4 (DPP4), among others. This virion is also covered by an envelope (E), a membrane (M), and a nucleocapsid, which contains the genetic material of the virus [66].

SARS-CoV-2 entry into the pancreatic β-cell (located in the pancreatic islets of Langerhans) is mainly triggered after viremia in virus-infected patients, and then, SARS-CoV-2 enters pancreatic β-cells that express cellular receptors for which SARS-CoV-2 has tropism, that is, the ACE2 receptor, which is the main mechanism by which the virus enters the cell. According to numerous experimental data, angiotensin-converting enzyme 2 (ACE2) has long been identified as a key receptor for the SARS virus. Since ACE receptors are more abundantly expressed in the pancreas than in the lung, they are also overexpressed in diabetic/hyperglycemic patients [67]. In addition, they have several proteins that help the virion enters the cell, such as the transmembrane glycoprotein CD147, which facilitates virion entry into the pancreatic cell in the absence of ACE2 receptor expression, and neuropilin 1 (NRP1), which binds directly to the S1 subunit of the S protein. This binding accelerates cleavage of the S1 and S2 subunits and exposure of the S2 cleavage site to transmembrane serine protease type 2 (TMPRSS2), facilitating viral internalization into cells. However, NRP1 has been shown to function more as a cofactor for viral entry, as it cannot infect the host cell on its own and requires the co-expression of ACE2 and TMPRSS2 for proper infection. Other receptors, such as dipeptidyl peptidase 4 (DPP4), which is more highly expressed in the lung than in the pancreas, asialoglycoprotein receptor 1 (ASGR1), ring-containing transmembrane protein (KREMEN1), and transferrin receptor (TFRC), are another class of receptors thought to facilitate virus entry into the pancreatic cell. However, insufficient studies show that these receptors are involved in the pathogenesis of diabetes mellitus in SARS-CoV-2-infected patients [6, 68].

Once the virus is internalized and replicates in the pancreatic β-cell, it is released following pyroptosis, a type of programmed cell death characterized by necrotic and inflammatory features. This type of cell death is activated by a signaling pathway involving systems such as the caspase pathway, mainly caspase 1, which is activated by an inflammasome. The peculiarity of this virus that causes this type of cell death is the activation of proinflammatory interleukins such as IL-1β and IL-18. IL-1β is responsible for the recruitment of immune cells such as neutrophils and macrophages and increases the survival of T cells. This series of effects is carried out after coactivation of the nuclear factor kappa β (NFK-β) pathway, which also plays a key role in the pathogenesis of DM as it is the executor of biological effects commanded by inflammatory effector proteins such as IL-6 and TNF-α. IL-18, on the other hand, is a proinflammatory cytokine constitutively expressed in macrophages that regulate the innate and adaptive immune response by regulating the activity of T-helper cells (TH1 and TH2). TH1 activation would lead to the production of IL-2 and IFN-γ involved in the activation of cell-mediated immunity, and TH2 activation would be responsible for the synthesis of IL-4, IL-5, and IL-10 characteristic of humoral immunity [69].

It has been suggested that activation of multiple proinflammatory cytokines could lead to the pathogenesis of DM, which could be mediated by different mechanisms: cell-mediated autoimmunity exerted by SARS-CoV-2, molecular mimicry, and generated cytokine storm [16, 63, 69–71].

3.1.1 Cellular autoimmunity and molecular mimicry

Cellular autoimmunity begins with virus presentation by macrophages to T lymphocytes, which initiates their differentiation. Within the role of cell destruction, CD8 lymphocytes will exert their action on the pancreatic β-cell, inducing it to apoptosis, which generally takes place after the binding of the Fas receptor with its Fas-L (toxic enzymes produced by CD8 LsTs), which is known as a type of extrinsic apoptosis, combined with the involvement of other cellular mechanisms due to destruction mediated by other cells of the immune system such as neutrophils, dendritic cells, macrophages, and natural killer (NK) cells, which are also capable of inducing cytotoxicity [71, 72].

On the other hand, molecular mimicry occurs when some structures of the pancreatic β-cell are recognized as part of a foreign agent due to the similarity between the SARS-CoV-2 spike protein and the structural components of the β-cell. Various studies have shown that SARS-CoV-2 contains mimotopes in the spike proteins that are capable of generating autoantibodies due to cross-reactivity with mainly zinc transporter 8 (ZnT8), glutamic acid decarboxylase (GAD), and insulinoma antigen2 (IA-2), among other proteins highly expressed in the pancreas [73, 74].

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3.1.2 Cytokine storm

Another mechanism discussed for Neurogenic Orthostatic Hypotension (NOD) is the cytokine storm, which can cause inflammation and immune system dysfunction, thereby contributing to pancreatic beta-cell destruction. In cases of severe NOD, there is a notable increase in the release of counterregulatory hormones and pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha). This phenomenon is referred to as a cytokine storm. It is characterized by an overwhelming surge of cytokines that can lead to insulin resistance, resulting in elevated blood glucose levels, also known as hyperglycemia. In diabetic animal models, viral infections provoke natural killer cells and T cells to release inflammatory cytokines that can damage beta cells. In patients with COVID-19, a dual immune response is observed: T helper (Th) 1 cells are activated by interferon-gamma (IFN-gamma) and monocyte chemoattractant protein-1, while Th2 cells secrete IL-4 and IL-10 to help suppress inflammation. Furthermore, the macrophage activation syndrome associated with COVID-19 is marked by increased levels of IL-6, IL-1 beta, TNF-alpha, IFN-gamma, and ferritin [66]. Moreover, Th17 cells are activated during a cytokine storm, leading to the secretion of IL-17 and granulocyte colony-stimulating factor. These Th17 cells are prevalent in the pancreas of patients with

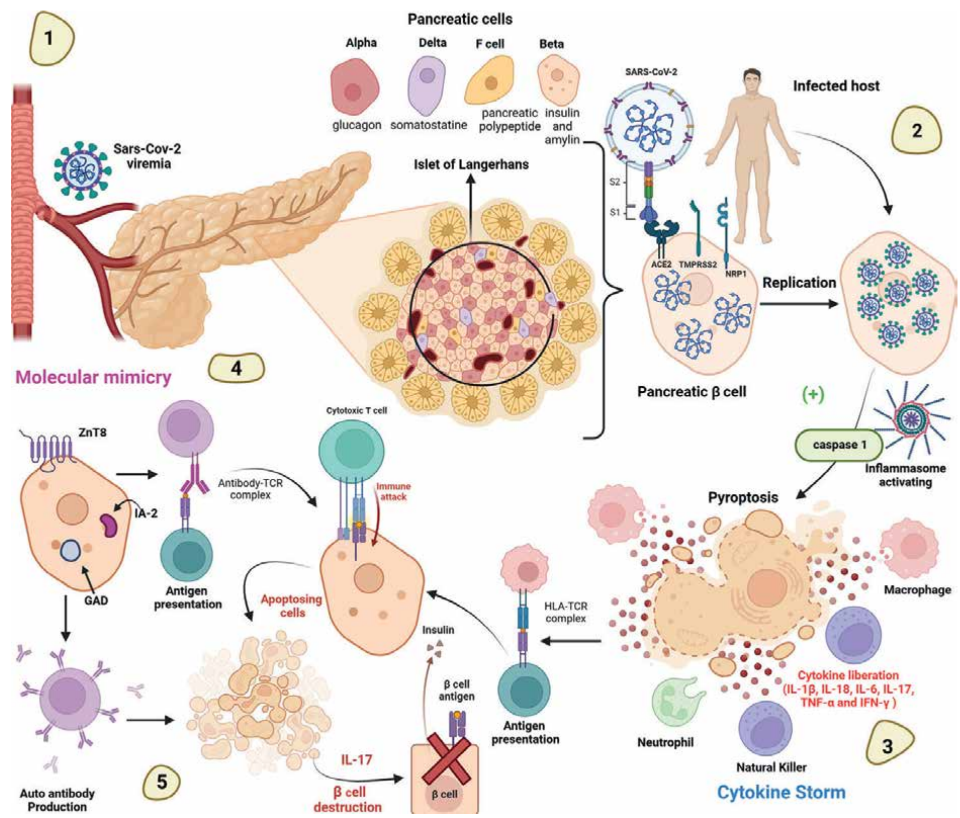

Figure 3.
Mechanism of development of new-onset diabetes associated with COVID-19. (1) SARS-CoV-2 infects the host and can enter the pancreatic cells due to its being recognized by AC2 receptors. In this pathway, the virus is helped by the proteins NRP1, TMPRSS2, DPP4, ASGR1, KREMEN1, and TFR. Once the virus infects the cells, (2) this is replicated, inducing then programmed cell death (perhaps pyroptosis), and via *the caspase 1, then cells such as neutrophils, macrophages, and NKs are recruited, and (3) the cytokine storm can occur. In addition, (4) molecular mimicry and (5) the production of antibodies results in the destruction of pancreatic cells, which are essential for the function of β-cells. These β-cells play a vital role in maintaining glucose homeostasis by secreting insulin, the sole hormone capable of lowering blood glucose levels. When insulin secretion is impaired, it leads to chronic hyperglycemia.*

T1DMD. In type 2 diabetes mellitus (T2DM), elevated levels of IL-17 are associated with inflammation in adipose tissue, which subsequently upregulate pro-inflammatory cytokines and contribute to insulin resistance [66, 67]. SARS-CoV-2-induced cytokine storm in diabetic patients aggravates the systemic immune imbalance, which may worsen their clinical status [6, 69].

4. Clinical cases of new-onset diabetes after COVID-19

As the specific metabolic complications of COVID-19 are not yet well defined, an international group of leading diabetes researchers has established a global registry of COVID-19-related diabetes, the CoviDIAB project, to conduct worldwide registries of patients with COVID-19-related diabetes (https://covidiab.e-dendrite.com/). The purpose of the registry is to delineate the phenotype of new-onset diabetes in patients diagnosed with COVID-19. This characterization will be based on confirmed COVID-19 status,

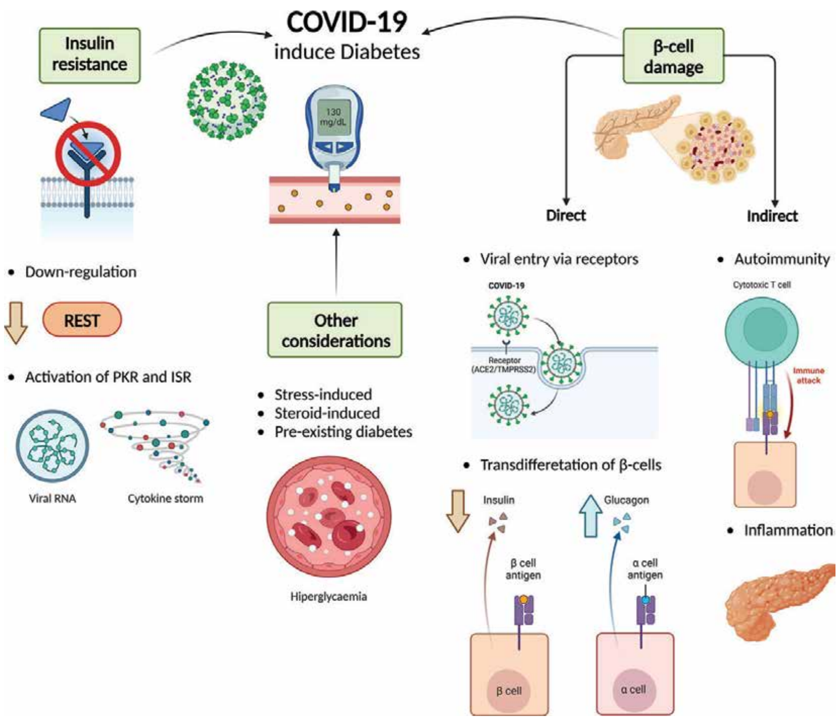

Figure 4.
Summary of all proposed mechanisms for T1D and T2D new-onset diabetes after SARS-CoV-2 infection. In the new-onset diabetes, people develop diabetes due to insulin resistance or beta-cell damage. In addition, during the begin of the COVID-19, others considerations caused hyperglycemia due to stress, treatments of the illness with steroids, and pre-existing diabetes undiagnosed. For insulin resistant, this was caused by the cytokine storm induced by the virus. In this state, there is a down-regulation of the RE1 transcription factor linked to the alteration of genes involved in the metabolism of glucose. For beta-cell damage, there are two pathways, the virus enters in the cells and the results are the destruction or damage of pancreatic cells, resulting in a lower insulin production and higher glucagon production and hyperglycemia.

a negative diabetes history, the presence of hyperglycemia, and a history of normal HbA1c levels. Furthermore, the registry will be expanded to include patients with pre-existing diabetes who subsequently experience severe acute metabolic disturbances. Thus, these data are expected to elucidate the epidemiology and pathogenesis of COVID-19-associated diabetes and guide the selection of appropriate treatment for patients, as well as increase the knowledge of this metabolic disease and prevent new-onset diabetes after COVID-19 episodes in the future. Further studies are needed to prevent and avoid NOD because of the metabolic complications and challenges this disease poses to the quality of life of the human population. In addition, more cases of NOD in children and adults should be reported and investigated, especially where DM has a high prevalence [14, 54, 71]. **Figure 4** shows the hypothetical mechanism of NOD after COVID-19 in children and adults during the establishment of SAS-CoV-2.

5. Conclusion

New-onset diabetes mellitus (NODM) is a significant and long-term complication that can arise from acute COVID-19 infection. The enzyme ACE2 plays a crucial role in the development of new-onset diabetes, as there is a clear connection between diabetes and COVID-19 in their molecular pathogenesis. The management of acute hyperglycemic states is often contentious, with many studies showing inconsistent results. It is imperative to make informed decisions based on the patient's clinical status and any existing comorbidities in order to select the most effective treatment that ensures optimal outcomes. Nonetheless, prevention should always be the primary focus.

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Conflict of interest

The authors declare no conflict of interest.

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Section 3

Pediatric Implications

Chapter 8

Perspective Chapter: Sequelae and Consequences of COVID-19 in the Paediatric Population

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Abstract

During the pandemic and in subsequent years, we observed that COVID-19 caused by the SARS-CoV-2 virus affected the paediatric population in different ways. In certain groups of children and adolescents, social isolation, changes in family dynamics, increased exposure to technological screens and changes in diet, among others, have affected their development, education, emotional, physical and social aspects, including access to immunizations, medical surveillance and medical control. COVID-19 is considered a generally benign pathology in children; however, some patients develop well-defined post-COVID-19 entities: multisystem inflammatory syndrome in children (MIS-C) and long COVID. In this chapter, we review, in relation to the paediatric population, the effects of the pandemic and confinement during its development and its subsequent consequences, the forms of clinical presentation of COVID-19 and post-COVID-19 entities and MIS-C and long COVID, including prevalence, pathophysiology, presentation, evolution, detection and management recommendations.

Keywords: COVID-19, coronavirus disease 2019 (COVID-19), MIS-C, long COVID, persistent COVID, COVID sequelae, multisystem inflammatory syndrome, post-acute sequelae of COVID-19, paediatric population, post-COVID-19 condition

1. Introduction

The COVID-19 SARS-CoV-2 pandemic changed the lives of families around the world. The changes it caused in people can be divided into two types: those related to

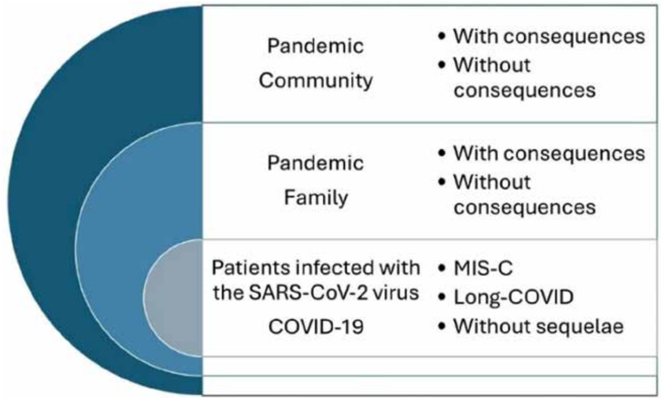

Figure 1.
SARS-CoV-2 can affect paediatric patients in various ways, directly causing an acute infection with the development of COVID-19, and in some of these patients, the post-infection development of multisystem inflammatory syndrome in children (MIS-C) or persistent COVID. On the other hand, paediatric patients who did not suffer infection by the SARS-CoV-2 virus presented various alterations due to confinement and the pandemic, both in their family and community role.

the pandemic and those related to infection by the SARS-CoV-2 virus, both during the acute stage and others as consequences or sequelae. The confinement and the pandemic itself affected the paediatric population, both in their family and community environment, in aspects of their development, psychology, mental and physical health and due to situations related to health systems and their consequences, such as reductions in immunisation coverage and limitations in access to health services, among others, which occurred during confinement and the pandemic. Since the first cases of COVID-19 due to the SARS-CoV-2 virus were reported, it was observed that paediatric patients presented milder manifestations of the disease compared to the adult population, in addition to the fact that very few patients developed severe symptoms, which is why COVID-19 was considered a low-risk disease in the paediatric population; however, during the pandemic, in some patients who suffered infection by the SARS-CoV-2 virus, two entities arose that occur after the infection: multisystem inflammatory syndrome in children (MIS-C) or long COVID (**Figure 1**) [1–4].

2. Epidemiology of COVID-19 in the general population and in the paediatric population

According to the World Health Organization (WHO), 776,007,137 cases of COVID-19 had been accumulated in the general population worldwide, including 7,059,612 deaths (global fatality rate of 0.9%), since the beginning of the pandemic until 18 August 2024. **Table 1** lists the cases and deaths from COVID-19 that have occurred in the different regions of the world [5].

At the beginning of the COVID-19 pandemic, the incidence in the paediatric population was around 2% of the total reported cases. As the pandemic progressed, the incidence increased; in the first 4 months of 2023 in the United States and Italy, accumulated cases of SARS-CoV-2 represented between 18% and 18.5% of the total reported cases. In Mexico, from 2020 to epidemiological week (EW) 13 of 2024, six epidemic waves occurred, with a national cumulative incidence rate of 58.3 cases per 1000 inhabitants. During this period, 20,440,060 cumulative cases were reported

Main regions	Cases	Deaths	Fatality rate
Africa	9,582,654	175,528	0.02%
Americas	193,293,860	3,027,535	1.57%
Eastern Mediterranean	23,417,911	351,975	0.12%
Europe	279,839,772	2,274,365	0.81%
South-East Asia	61,315,364	808,814	1.32%
Western Pacific	208,556,812	421,392	0.20%
World	776,007,137	7,059,612	0.90%

Table 1.
COVID-19: cumulative number of cases and deaths in the global general population in major regions of the world, reported to WHO since the start of the pandemic as of 18 August 2024. Prepared with data from World Health Organization 2023 data.who.int, WHO Coronavirus (COVID-19) dashboard > Cases [Dashboard]. https://data.who.int/dashboards/covid19/cases.

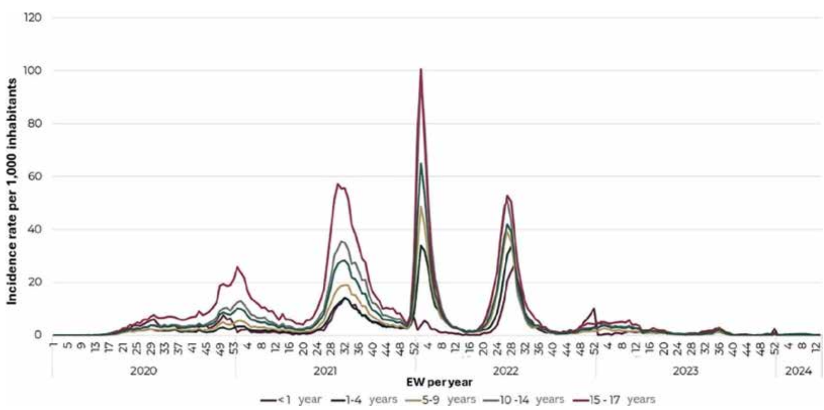

Figure 2.
Cumulative incidence rate for COVID-19 by age group in children under 18 years of age in Mexico from 2020 to EW 13, 2024. Taken from: Government of Mexico. Ministry of Health. General Directorate of Epidemiology. Comprehensive report on COVID-19 in Mexico. 2024 published July 2024 [6].

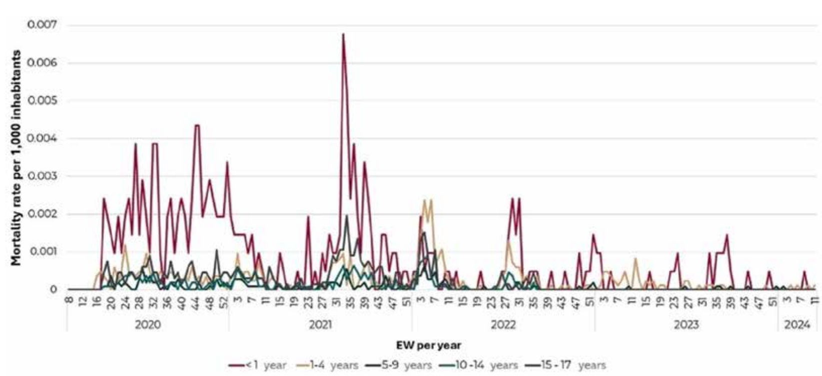

Figure 3.
Mortality from COVID-19 by age groups in children under 18 years of age in Mexico from 2020 to EW 13, 2024. Taken from: Government of Mexico. Ministry of Health. General Directorate of Epidemiology. Comprehensive report on COVID-19 in Mexico. 2024 published July 2024 [6].

in the general population (including confirmed, negative and suspected cases) and 503,258 confirmed cases in children under 18 years of age. In children under 18 years of age, the mortality rate was 3.9 per 100,000 inhabitants and the highest incidence and mortality rates occurred in the 15–17 age group, as shown in **Figures 2** and **3** [6–8].

3. Clinical presentation of COVID-19 in the paediatric population

The clinical presentation of COVID-19 in children is generally less severe that in adults. The most common signs are cough (41–51%), fever (35–40%), headache

Clinical syndromes of COVID-19	Characteristics
Infection asymptomatic	Positive test for SARS-CoV-2. No symptoms or clinical signs. No radiological alteration.
Mild illness	Symptomatic patient who meets the case definition for COVID-19. Nonspecific symptoms: fever, fatigue, cough, sore throat, anorexia, general malaise, muscle pain, dyspnoea, nasal congestion, headache, myalgia, diarrhoea, nausea and vomiting. No evidence of viral pneumonia, hypoxia or sepsis. Most recover in 1 or 2 weeks.
Moderate illness—pneumonia	With or without fever. Clinical data of non-severe pneumonia: • Children: cough, respiratory distress, tachypnoea, intercostal indrawing. • Adolescents: cough, tachypnoea. No evidence of severe pneumonia. Imaging studies confirm the diagnosis and allow complications to be detected.
Serious illness—severe pneumonia	Children: • Clinical data of pneumonia: cough or respiratory distress, plus any of the following data: central cyanosis. Oxygen saturation less than 90%. Respiratory difficulty (groaning, use of accessory muscles, tachypnoea). Intermittent apnoea. Warming data: oral intolerance, signs of dehydration, altered state of consciousness (drowsiness, lethargy, coma), seizures. Tachypnoea. • Imaging studies confirm the diagnosis of pneumonia and allow complications to be detected.
	Adolescents: • Clinical signs of pneumonia: fever, cough, dyspnoea, increased respiratory rate, plus one of the following: respiratory rate greater than 30 breaths per minute. Severe respiratory failure. Oxygen saturation less than 90% breathing room air. • Imaging studies confirm the diagnosis of pneumonia and allow complications to be detected.
Critical illness	Acute respiratory distress syndrome in paediatric patients. • Sudden manifestation of days after the infectious process or as part of poor evolution of respiratory symptoms. Alteration in oxygenation (hypoxemic respiratory failure). It's not due to heart failure or volume overload. Image: bilateral heterogeneous opacities (not explained by volume overload), lobar or pulmonary collapse.
Sepsis	• Suspected or proven infection plus two criteria for systemic inflammatory response (one of them to be temperature or the number of leukocytes).
Septic shock	• Arterial hypotension plus two or more of the following: alteration of mental status, tachycardia, prolonged capillary refill, increase in respiratory rate, cold or mottled skin, petechial or purpuric rash, elevation of lactate, decrease in urinary output, hyperthermia or hypothermia. • Any of the above plus organic dysfunctions: pulmonary thromboembolism, acute coronary syndrome, cerebral vascular accident.

Table 2.
Clinical syndromes of COVID-19 in paediatric patients. Adapted from Márquez-Aguirre et al. [1].

(15–41%), diarrhoea (13%), sore throat (12–28%), myalgia (10–30%), nausea/vomiting (9–10%), rhinorrhoea (6.8–8.1%), abdominal pain (6.7–7.7%) and loss of smell or of taste (1.3–9.9%). During the predominance of circulation of the Delta and Omicron variants, nasal congestion, headache, sneezing and pharyngeal pain predominated. The Omicron variant can cause severe inflammation of the upper airway with symptoms like croup. The clinical syndromes associated with COVID-19 are classified as asymptomatic infection, mild disease, moderate disease—pneumonia, severe disease—severe pneumonia and critical illness; see **Table 2**. Young children develop fewer symptoms or are more likely to be asymptomatic than older children and adolescents. The infants, toddlers, adolescents and children with diabetes, lung disease, cardiovascular diseases, neurological disorders, chronic diseases and prematurity, among others, are at greater risk of suffering from severe COVID-19 [1, 8–11].

As we have already mentioned, the sequelae and consequences that COVID-19 produced in the paediatric population can be divided into two large groups (**Figure 1**): (a) those directly related to the COVID-19 pandemic and manifested in children and adolescents in general and who were not necessarily infected by the SARS-CoV-2 virus and (b) the development of some post-infectious entity, observed in some patients who had suffered acute infection by the SARS-CoV-2 virus, even if they were asymptomatic: either MIS-C or persistent COVID. Both have different natural history and treatment strategies [12, 13].

4. Effects of the COVID-19 pandemic on the general paediatric population

The effects that an epidemic or pandemic can have on the general population, without considering those caused by the infection or disease itself, are multiple and varied. In previous pandemics and epidemics such as AIDS, H1N1 flu or Ebola, various mental and emotional consequences have been reported: severe anxiety or depression, acute stress disorder, post-traumatic stress, anxiety disorder and depression in children [14].

During the COVID-19 pandemic, the child population was exposed to various events and circumstances such as school closures, confinement, social distancing, restrictions on family life, death of a family member due to COVID-19 (mother, father, siblings, grandparents, etc.), parents working from home, excessive exposure to device screens and restrictions on health care services, among others, which generated various side effects in the short, medium and probably long term.

One in seven children lived confined to their homes for much of 2020, suffering from anxiety, depression and isolation as a result. At least one in three school-aged children was unable to access remote learning while schools remained closed. In November 2020, it was estimated that 6–7 million children under 5 years of age could have suffered from acute malnutrition during that year [15].

4.1 Confinement

During the COVID-19 pandemic, the governments of many countries ordered confinement as a pandemic control measure, and it affected more than half of the world's population. It was ordered on different dates in each country and its duration varied greatly between them and even between regions of the same country. In some places, the confinement lasted a few days or weeks; in many, between 1 and 2 months; in the United Kingdom, around 4 months and in regions of Mexico (Mexico City and

State of Mexico), more than a year. The confinement forced the closure of schools, businesses, health care centres, recreational centres, sports activities, shows and offices, among others, developing work from home, online education and coexistence of like-minded groups, friends and family online, among others. The repercussions it had on the paediatric population occurred during the confinement itself; some of which were reversed at the end of the confinement and others have remained.

Confinement, school closures and working from home forced families to change their usual dynamics and implement new activities, even using technology.

Additionally, many households suffered from the illness or death of family members or friends or acquaintances. The impact on children and adolescents was diverse and with different magnitudes between countries and regions. Among the reported effects, we find the following [2, 15–19]:

- Negative psychological effects: post-traumatic stress symptoms, fear of going outside, anger, confusion, decreased life satisfaction, depressive symptoms, worsening mental health, emotional hypersensitivity, sleep disorders, nightmares, night terrors, insomnia, behavioural changes, apathy, negative reactions, lack of attention, suicidal ideation.

- Physical health effects: decreased physical activity, increased sedentary behaviours, increased use of screens or electronic equipment, increased consumption of unhealthy foods, increased number of children with physical injuries from child abuse, delays in language and motor development.

- Effects on access to health services: decrease in the number of visits to health services, decrease in child protection and control assessments, decrease in the application of immunizations, increase in child mortality in some countries.

- Social effects: increase in pre-existing inequalities, exacerbation of vulnerabilities, limitations in access to usual and emerging social support.

The role played by parents during the pandemic was very important in minimising the impact of the pandemic on their children by organising their schedules, encouraging physical activity and promoting communication. Among the recommendations to maintain mental well-being in adolescents and children, the intervention of a multidisciplinary network of health professionals was one of the most important, with better results when involving parents and teachers. And although many of these effects were more prevalent at the beginning of the pandemic and were transitory, several persist and may persist in the long term [19, 20].

4.2 Mental health

During the COVID-19 pandemic in the general population in China, Spain, Italy, Iran, the United States, Turkey, Nepal and Denmark, there was an increase in the rates of anxiety (from 6.33% to 50.9%), depression (from 14.6% to 48.3%), post-traumatic stress disorder (from 7% to 53.8%), psychological distress (from 34.43% to 38%) and stress (from 8.1% to 81.9%). Before the pandemic, problems such as poverty, malnutrition and climate change were already causing a drastic increase in the number of children in need of both medical and psychological assistance, and the COVID-19 pandemic aggravated the situation. In many countries, mental health and well-being in children and adolescents worsened, with risk figures for psychological difficulties between 18% and 60%. Poor quality of life increased from 15% before the pandemic to 40% during the pandemic, thus persisting after months or even more than a year after the start of the pandemic and even when restrictions were no longer in place. The situations observed were an increase in symptoms of depression and anxiety, post-traumatic stress and an increase in the demand for psychiatric care 1 year after the pandemic began. A correlation was also observed between a greater presence of symptoms (such as anxiety) and times with a higher rate of infection and/or pandemic restrictions. According to UNICEF, 3 out of 10 children between the ages of 6 and 17 developed a mental problem associated with the COVID-19 pandemic and even more children whose parents also presented some type of mental disorder [15, 16, 18, 20, 21].

Children with previous psychological disorders showed greater attachment to their caregivers and those with introverted traits and tendencies to worry excessively showed anxious reactions, apprehensive anticipations of threats, fear of contagion, obsessive-compulsive symptoms, depressive manifestations and avoidance behaviours. In children under 7 years of age, an increase in attachment, anxiety, insecurity, boredom, lack of cooperation and attention seeking was found. In children from 7 to 13 years of age, greater anxiety and depression, school problems, restlessness, lack of attention, social isolation and inappropriate behaviour were observed. Mental disorders also intensified after the pandemic, the most common being attention deficit disorder, hyperactivity, anxiety, bipolarity, conduct disorders, depression, eating disorders and schizophrenia [15, 21].

Clinical manifestations generated by chronic stress were observed in many children, regardless of whether they had SARS-CoV-2 infection. Chronic stress is associated with alterations in learning, cognition and memory and in the activity of various systems and organs of the body, due to modifications in the structure and function of the central nervous system. Among the most common symptoms derived from chronic stress are memory loss, hyperhidrosis, exercise intolerance, confusion, mood changes and even dysautonomia due to dysfunction of the autonomic nervous system [22].

During the COVID-19 pandemic, suicide rates increased by 31%. In the United States, suicide is the second leading cause of death in subjects aged 5–24 years. In Mexico, prior to the pandemic, suicide was the second leading cause of death in young people. In 2020, a record number of suicides were recorded in girls, boys and adolescents, with an increase in the rate of 12% between 2019 and 2020. Cases of girls between 10 and 14 years old increased by 37% and 12% for adolescents between 15 and 19 years old [15, 21].

Patients with autism spectrum disorder (ASD) were affected by the loss of their routines, therapies and support at school, although for some, confinement was more comfortable, and it was difficult for them to return to their daily routines as they had to get used to certain stimuli that caused them stress. Likewise, many children with a condition stopped receiving their regular treatments. In anxious children, it was seen that their fears and need for control worsened; in hyperactive children, online teaching did not work, and some tutors stopped giving them their medications [15, 20].

4.3 Child development

Due to isolation, decreased social interaction and stimulation by others, poverty, loss of education, food insecurity, loss of parents and caregivers, loss of routine health checks in childhood, decreased vaccination coverage, increased stress and deterioration of mental and nutritional health, which occurred during the pandemic, the development of many children was affected. Impacts on the evolution of language, social communication, empathy, expression and understanding of emotions have been reported [12, 13].

Significant reductions in verbal, non-verbal and cognitive performance were also reported in babies born during the pandemic compared to children born before the pandemic. Delays were also reported in the following areas: decreased in average cognitive performance in babies born since mid-2020, delay in language development at the level of productive vocabulary and development of morpho-syntactic complexity in children who experienced the pandemic in the initial period of language development and delay in the Oedipus phase, in cases where the mother stayed close to the child for longer, the child unconsciously refused to give up on her. After the pandemic, many children suffered delays in their development due to their poor ability to relate to others, leading some children to self-stimulating behaviours, to be more withdrawn and disinterested, to cry for no reason, to become excited or to fall into isolation [15, 23, 24].

4.4 Obesity

During the first year of the pandemic, overweight and obesity increased in children and adolescents, with a 20% increase in the prevalence of obesity compared to the previous period, due to decreased physical activity, increased consumption of ultra-processed and unhealthy foods, increased exposure to electronic screens, decreased use of preventive services and chronic stress related to the pandemic. Social inequalities disproportionately widened overweight and obesity in some ethnic and socioeconomic groups, differentially affecting food-insecure children [18, 25].

4.5 Vaccination

The COVID-19 pandemic has had a major impact on childhood immunisation. UNICEF revealed that the world has lost more than a decade of progress in just 3 years. Between 2019 and 2021, 67 million children did not receive the full or partial systematic vaccination they needed, of which 48 million did not receive any vaccine, leading to figures not seen since 2008 globally. The fact that one in five children has never been vaccinated or has not received all the vaccines they need leaves them unprotected against various preventable diseases. Of every four unvaccinated children worldwide, more than three are in just 20 countries, children living in the most remote rural areas, in urban slums, in crisis regions or in migrant and refugee communities. Some diseases are resurfacing in countries where they had been brought under control, while at the same time, there are increases in cases in countries that had not yet managed to eradicate them, for example, outbreaks of cholera, measles and polio. In 2022, cholera cases and deaths increased worldwide, affecting regions of East Africa, the Middle East and South Asia that had not seen a large-scale outbreak in more than 10 years, while in Haiti, a severe cholera epidemic affected thousands of children [26, 27].

In 2021, nearly 40 million children did not receive the measles vaccine, and the following year dozens of massive and devastating outbreaks occurred around the world. Afghanistan, Ethiopia, Nigeria, Somalia and Yemen were among the most affected countries. In 2023, more than 600,000 children did not receive the measles vaccine, leading to multiple outbreaks and a 30-fold increase in cases in Europe. Globally, the number of cases in 2023 increased by 64% compared to 2022, prompting WHO to issue a measles alert in January 2024 [26–28].

Extraordinary progress has been made on the road to polio eradication, but in 2021 and 2022, these efforts were threatened by an increase in outbreaks, especially among children in Chad, Nigeria, the Democratic Republic of the Congo and Yemen. In 2022, polio cases emerged in Malawi and Mozambique, two countries that had been free of the virus for decades [26, 27].

UNICEF emphasises that efforts must be made to vaccinate all children by catching up with lagging children, strengthening vaccine demand and confidence, spending more and better on immunizations and health and establishing resilient and shock-proof systems [27].

4.6 Education

The Latin American and Caribbean region has been one of the hardest hits by the suspension of in-person classes during the pandemic. Countries in this region had schools closed or partially open for 62 weeks, on average, equivalent to more than a year and a half of classes. During the pandemic, there was a drop in attendance rates at all educational levels, mainly in 2020, with pre-primary education being the most affected. The real magnitude of the setback caused by this crisis remains unknown, and it is possible to anticipate that its consequences will last for several years. Some indicators have recovered, such as attendance, which by 2022 reached magnitudes like the pre-pandemic scenario in primary and secondary education and slightly lower in pre-primary education. It is estimated that in 2022 the number of children not attending school was 9.6 million, of whom 4.3 million were children of primary or lower secondary school age [29].

Learning achievements in the region were low even before the pandemic. Post-pandemic assessments show very disparate results depending on the year and area of learning. In almost all countries, there is a significant drop in learning and an increase in inequalities, with greater intensity in primary education. The results of PISA 2022 show a scenario like 2018 on average for countries in the region, with a drop concentrated in mathematics. In addition, there has been an increase in inequalities: the poorest population, children in rural areas and indigenous students have been the most affected by the increase in exclusion during the pandemic, with wider gaps in pre-primary and higher secondary education [29].

Educational expenditure as a percentage of total public expenditure has been declining in the last 5 years. In 2019, countries allocated 14.1% of total expenditure to education; 3 years later, this proportion was reduced to 12.5%. In relation to the gross domestic product (GDP), between these years, educational expenditure has remained around 4% on average. UNESCO proposes that a framework for the recovery and acceleration of learning in Latin America and the Caribbean after the pandemic, which considers the axes of educational inclusion, improvement of learning, strengthening of teaching and the governance and financing capacities of the region's educational systems. The recovery of learning is the main challenge facing the region today [29].

4.7 Economy

Four years into the COVID-19 pandemic, the world's economies have yet to rediscover a reliable path to prosperity. In the decade before the COVID-19 pandemic, global growth averaged 3.1% per year but is now stabilising at an average of 2.7%

per year through 2026. This pace of growth will not advance key development goals. By the end of 2024, one in four developing economies will be poorer than it was before the pandemic. Average growth will be slower in 2026 in countries where more than 80% of the world's population is concentrated, compared to the decade before COVID-19, and global interest rates through 2026 are expected to be on average twice as high as in the previous two decades. High inflation and rising public debt levels could be a major obstacle to countries' ability to support vulnerable groups and facilitate recovery and sustainable growth [30].

5. Multisystem inflammatory syndrome in children (MIS-C)

The pathogenesis of SARS-CoV-2 infection has two distinct phases. The first phase is triggered by the entry of the virus into the host cells. It is responsible for the first respiratory symptoms and ends with the elimination of the virus or the progression of lung disease. Sometimes and because of the host's immune response, a second phase characterised by a "cytokine storm" may occur. While in adult patients with COVID-19 hyperinflammation is associated with respiratory failure, in the paediatric population, the predominant manifestation is MIS-C, with relative lung preservation that develops 2–4 weeks after acute SARS-CoV-2 infection. It occurs in less than 0.01% of infected children and approximately 70–80% of cases are admitted in an intensive care unit [1, 3, 10].

In addition to the hypothesis that the pathophysiology of MIS-C is related to a cytokine-mediated inflammatory response triggered by SARS-CoV-2 infection and autoimmune phenomena such as molecular mimicry between viral and self-antigens, HLA alleles have been found that suggest a certain genetic predisposition. On the other hand, the presence of SARS-CoV-2 in the digestive tract can lead to inflammation of the local mucosa, increasing the release of zonulin and in turn increasing permeability, which allows SARS-CoV-2 antigens to cross mucosal barriers, enter the bloodstream and cause hyperinflammatory immune activation [1, 11, 31, 32].

MIS-C case definitions were developed by the Royal College of Paediatrics and Child Health (RCPCH) in the United Kingdom, the Centers for Disease Control and Prevention (CDC) in the United States of America and the World Health Organization (WHO) and basically include the following criteria: patient with severe illness that required hospitalisation, age under 21 years, fever or report of subjective fever of at least 24 hours duration, evidence of inflammation in laboratory test reports, multisystem involvement of organs and laboratory-confirmed SARS-CoV-2 infection and an epidemiological link to a person with COVID-19 [3, 33–35]. The epidemiological, pathological, pathophysiological and clinical aspects have been presented in another publication [36].

The clinical picture may include persistent fever, mucocutaneous alterations, low blood pressure, myocarditis, alterations in coagulation and gastric and intestinal digestive manifestation and in severe patients the development of shock, multiple organ failure and effusions (pleural, pericardial and ascites). Children with MIS-C have few respiratory symptoms, and when they require mechanical ventilation, it is due to cardiovascular reasons [3, 33–35].

The most frequent cardiovascular alterations in MIS-C are elevation of biomarkers such as BNP and troponin, electrocardiographic changes and arrhythmias, myocardial dysfunction with decreased ventricular ejection fraction, dilation of the coronary arteries, pericardial effusion, valvular insufficiency and alteration in segmental contractility [31, 37].

When faced with a patient with MIS-C, the primary objectives are to make an early diagnosis and initiate treatment immediately. The management of MIS-C is aimed at treating systemic inflammation using immunoglobulin, corticosteroids and acetylsalicylic acid. Stabilisation in the acute phase prevents the development of long-term complications, such as cardiac fibrosis, cardiac conduction abnormalities and coronary aneurysms. In refractory disease, treatment with anakinra and other options such as infliximab and tocilizumab have been suggested [1, 8, 12, 32].

The prognosis of MIS-C is usually favourable, the mortality rate is 1–2% and most patients recover completely, without long-term sequelae. However, in children with underlying chronic disease present prior to hospitalisation for MIS-C, there is often a longer persistence of symptoms related to the affected organs, up to 2–4 months after the initial hospitalisation. Studies that followed up from 6 weeks to 6 months after discharge of patients who suffered from MIS-C have reported worse performance in working memory and worse quality of life, worse performance in visual memory, attention and planning, as well as lower quality of life scores, grater fatigue, severe emotional difficulties and a greater risk of post-traumatic stress. Other neurological conditions and symptoms reported are stupor, confusion, mood and behavioural disorders, meningismus, dysgeusia and speech problems, as well as family and anxiety problems at 6 months. In these patients, imaging studies have shown various findings such as acute disseminated encephalomyelitis, acute necrotizing encephalopathy, ischemic stroke, splenial lesions of the corpus callosum, myelitis, cerebellar ataxia, peripheral nervous system involvement, miosis and posterior reversible encephalopathy [8, 10, 32, 38].

For patients presenting with MIS-C and cardiac complications, follow-up is recommended at 7–10 days, 4–6 weeks, 4–6 months and 9–12 months after initial presentation with measurement of inflammatory markers and serial echocardiograms. The American College of Rheumatology recommends that all patients with MIS-C be followed with serial echocardiograms at 7–14 days and 4–6 weeks after initial diagnosis, and for patients in whom cardiac involvement occurred during the acute phase of the disease, the recommendation is to perform an echocardiogram 12 months after the diagnosis of MIS-C [31, 37, 39].

The prevalence of neurological symptoms varies between 22% and 88%. Neurological and psychiatric symptoms can persist for more than 6 months, in 66% of patients who presented with COVID-19 and MIS-C, and in 31% of patients who only had SARS-CoV-2 infection. In imaging studies performed in patients with MIS-C who were hospitalised, a greater proportion of grey matter reduction has been reported than in patients who were not hospitalised. It has also been considered that in patients with MIS-C, both the experience generated by hospitalisation and the severity of the condition itself can cause neurological and psychiatric disorders, among which we find excessive daytime sleepiness, difficulty falling asleep, nocturnal awakenings, mood swings, neurological deterioration, severe emotional difficulties, hyperactive delirium and acute-onset psychosis [38].

The incidence and severity of MIS-C have been decreasing, probably due to viral mutations, increased population immunity and mRNA vaccination [10, 13, 40].

In **Table 3**, we find the differences between MIS-C and long COVID.

	Multisystem inflammatory syndrome in children MIS-C	Long COVID
Age at presentation	More common between 5 and 14 years old	Pre-teen and teenage patients
Onset of the clinical picture	Acute Appears between 2 and 6 weeks after acute SARS-CoV-2 infection.	Subacute to chronic
Signs/ symptoms	Persistent fever, greater than 38.5°C; mucocutaneous alterations (skin rash, oedema of hands and feet, strawberry tongue, conjunctivitis, mucositis); hypotension; coagulation disorders; gastrointestinal manifestations (abdominal pain, vomit, diarrhoea); neurocognitive symptoms (headache, lethargy, irritability, confusion). In serious patients: myocarditis, left ventricular systolic dysfunction, shock, multiple organ failure, effusion (pleural, pericardial, ascites).	Mood symptoms (sadness, tension, anger, depression, anxiety), fatigue, sleep disorders (insomnia, hypersomnia, poor sleep quality), headache, respiratory symptoms, sputum production or nasal congestion, cognitive symptoms (lower concentration, learning difficulties, confusion, memory leak, loss of appetite, exercise intolerance, smell disorders [hyposmia, anosmia, hypersomnia, parosmia, ghost smell]).
Laboratory findings	Lymphopenia, elevation of inflammatory markers (C-reactive protein, erythrocyte sedimentation rate (ESR), D-dimer, fibrinogen, ferritin, procalcitonin), increased markers of cardiac damage (troponin).	There are no specific markers.

Table 3.
Differences between MIS-C and long COVID in the paediatric population [8, 32, 40, 41].

6. Long-COVID (post-COVID-19 condition)

Since the first months of the COVID-19 pandemic, cases of adult patients who persisted with symptoms weeks or months after infection with SARS-CoV-2 virus were observed. The first cases in children and adolescents began to be reported at the end of 2020. Due to the great variety of signs and symptoms (more than 200 have been reported), forms of presentation and duration of the condition, the names are very varied; however, in this chapter, we will use the terms long COVID and post-COVID-19 condition interchangeably. The prevalence is estimated at around 15%, although reports vary from 1.6% to 70% in different parts of the world. The prevalence of long COVID in the paediatric population is 26% between 3 and 6 months of evolution, 20% between 6 and 12 months of evolution and 15% for more than 12 months of evolution. Diagnosis has been a real challenge due to the great variety of signs and symptoms that can be considered part of the condition, the lack of specific laboratory markers and the ruling out that it is not a consequence of confinement. The impact on the daily life of patients is very variable and, in some cases, can lead to physical, psychological and socio-emotional consequences [12, 19, 32, 41, 42].

In 2021, WHO published a case definition of post-COVID-19 condition that included only adult patients. The most relevant definitions for children and adolescents were presented in the United Kingdom in March 2022 by a Delphi Consensus and in February 2023 by WHO (**Table 4**) [43–46].

According to WHO, in the paediatric population, post-COVID-19 condition is defined as “a condition after COVID-19 in children and adolescents that occurs in

Long COVID (post-COVID-19 condition) in children and adolescents	
Delphi consensus **United Kingdom, March 2022**	**WHO** **February 2023**
Children or adolescents with symptoms (at least one symptom is physical) that: • Have continued or developed after the diagnosis of COVID-19. • COVID-19 confirmed with at least one positive test. • Impact their physical, mental or social well-being. • Interfere with some aspect of daily life. • Persist for a minimum duration of 12 weeks after initial testing for COVID-19 (even if symptoms waxed and waned over that period).	Children or adolescent with: • History of SARS-CoV-2 infection. • SARS-CoV-2 laboratory confirmation. • Minimum time from onset of symptoms (or from date of positive test for asymptomatic) 3 months. • Minimum duration of symptoms at least 2 months. • Symptoms and/or impairments. • Time-course nature of symptoms (fluctuating, increasing, new onset, persistent, relapsing). • Impact on everyday functioning.

Table 4.
Clinical definition of long COVID (post-COVID-19 condition) in children and adolescents proposed by the Delphi Consensus in the United Kingdom, March 2022 [43] and the World Health Organization (WHO) in February 2023 [44].

individual with a history of confirmed or probable SARS-CoV-2 infections, when they experience symptoms lasting at least two months and that the initially occurred within three months of acute COVID-19," stating that "symptoms generally have an impact on daily functioning, such as changes in eating habits, physical activity, behaviour, academic performance, social performance, and developmental milestones," in addition "they may be new after initial recovery from acute episode of COVID-19 or persist from initial illness" and "may fluctuate or relapse over time" [12, 40, 44, 47].

In **Table 5**, we can see the domains of WHO case definition for post-COVID-19 condition, for both adults and children [44].

6.1 Pathogeny

The pathogenesis of long COVID is still unclear, although it is considered that it may be similar in children, adolescents and adults. The following are among the multiple probable pathogeneses that have been considered: (a) persistence of the virus in different tissue forming viral reservoirs; (b) in some patients with long COVID, viral RNA and proteins have been detected 2 months after the initial infection; (c) autoimmune/post-infectious inflammatory changes; (d) alterations in metabolic pathways, with a specific focus on the central nervous system; (e) specific mechanism of induction by the Epstein-Barr virus (EBV); (f) persistent disorder of the inflammatory response after recovery; (g) molecular mimicry; (h) disturbances in the intestinal microbiome; (i) autonomic dysfunction; (j) chronic vasculitis with circulating micro-clots that affect microcirculation and oxygenation of the tissues; (k) inflammation of the vagus nerve with consequent dysautonomia; (l) reduction of serotonin levels [11, 32, 41].

The risk of patients developing long COVID doubles if they have an underlying pathology or condition, triples in cases where the severity of acute COVID-19

Domains	Clinical case definition for post-COVID-19 condition	
	Adult	Children and adolescents
History of SARS-CoV-2 infection	X	X
SARS-CoV-2 laboratory confirmation	X	X
Minimum period from onset of symptoms: 3 months	X	X
Minimum duration of symptoms at least 2 months	X	X
Symptoms and/or impairments	X	X
Minimum number of symptoms	X	
Clustering of symptoms	X	
Time-course nature of symptoms	X	X
Sequelae of well-described complications of COVID-19	X	
Symptoms cannot be explained by an alternative diagnosis	X	
Application of definition to different population	X	
Impact on everyday functioning	X	X

Table 5.
WHO clinical case definition domains in adults, children and adolescents [44].

condition requires hospitalisation of the patients and quadruples in patients over 10 years of age. Protective factors have also been reported that lead to a shorter and less severe COVID-19 condition, and it is very likely that these same factors are protective for long COVID cases in children. These protective factors include the following: (a) fewer underlying comorbidities; (b) strong innate immune responses; (c) reduced expression of angiotensin-converting enzyme 2 (ACE2) receptors; (d) active thymic function leading to increased, present and decreased T cell deficit; (e) environmental or non-heritable variants (vaccines, previous infections, nutrition, gut microbiome) [10, 13, 22, 32, 48].

6.2 Clinical manifestations and diagnosis

The acute presentation of long COVID is not as severe as that of MIS-C; however, its long impact may be intense and the severity of clinical manifestations may be conditioned by multiple risk factors. Signs and symptoms may be multiple and diverse and usually affect several body systems. 90% of patients with long COVID may experience difficulties in daily life [32, 41].

The most common manifestations are neurological and psychiatric symptoms, cardiorespiratory symptoms and mood-related symptoms (sadness, tension, anger, depression, anxiety), fatigue, sleep disorders, taste and smell disturbances, headache, dyspnoea, nasal congestion, chest pain and palpitations. Some patients present with postural tachycardia syndrome (PoTS) and a few meet clinical criteria for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [41, 47, 49].

Signs and symptoms may affect various body systems: motor, circulatory, digestive, immune, nervous and respiratory. Signs and symptoms in different systems may be due to various causes: those of the motor system due to an autoimmune reaction or chronic dysfunction or persistence of the virus; those of the haematological system due to immune dysregulation, coagulation dysfunction or damage to the vascular endothelium; those of the nervous system and mental health due to the impact of the pandemic, brain infection, neuroinflammation or autoimmune reaction and those of the respiratory system due to vagus nerve disorder or persistence of the virus [13, 47, 49].

The diagnosis of long COVID is aimed at ruling out other pathologies, both somatic and psychiatric, for which it is necessary to perform a complete clinical history, psychosocial study, complete physical examination and psychological evaluation, and, although to date there is no diagnostic marker, laboratory and/or imaging tests must be performed to rule out other pathologies [13, 47, 49].

The actual prevalence of signs/symptoms following the development of COVID-19 in children and adolescents remains unknown due to heterogeneity, terminology used and methodology applied; however, a recent systematic review estimated that the prevalence of residual symptoms 1 month after COVID-19 may be as high as 25%. A large multinational study estimates that around 3% of individuals under 20 years of age with symptomatic COVID-19 disease have persistent fatigue, cognitive and residual respiratory symptoms from the acute infection, while data from a recent UK Office for National Statistics study suggests that the incidence of post-COVID-19 symptoms is currently less than 1%. Other studies estimate a cumulative incidence of persistent symptoms after COVID-19 infection between 24% and 58% of children and adolescents. Appropriate instruments must be established to measure fatigue, gastrointestinal, neurocognitive and physical function disorders, as manifested by patients, to establish a consensus applicable to the entire population [50].

6.3 Treatment

Currently, there is no specific treatment for long COVID. It has been considered that the body's inflammatory response could be inhibited with the use of drugs as levocetirizine and montelukast. In most cases, treatment is oriented to the symptoms and individual characteristics of each patient, which may involve the intervention of a multidisciplinary team from the medical field (paediatrician, rehabilitation physician, psychiatrist), psychological and paramedical (nurse, physiotherapist) as well as the teaching field, among others. Exercise therapy has been showed to be very useful in improving cardiopulmonary dysfunction and fatigue, cognitive-behavioural therapy accelerating recovery, and playful, artistic therapies and psychological and communication counselling to improve psychological aspects of the patient [32, 41].

Paediatric rehabilitation in the management of long COVID includes behavioural intervention and an exercise programme. The multidisciplinary rehabilitation programme encompasses paced aerobic exercise, resistance training, relaxing exercise, pulmonary exercise, treatment of postural orthostatic tachycardia syndrome, cognitive brain training and linkage to school and community resources [39].

Microglial cells are crucial for the regulation of brain development and neuronal health. Neuroinflammation can lead to microglial dysfunction, affecting both neuronal plasticity and synaptic pruning in patients with COVID-19. The resulting dysfunction in neuronal activity and synaptic plasticity can have long-lasting consequences on the central nervous system. COVID-19-induced neuroinflammation may have particularly adverse effects during critical periods of brain development in children. It is important to establish the presence of long COVID in paediatric patients to assess the risks associated with delays in neurocognitive development, academic performance and potential long-term medical and neuropsychiatric sequelae and to consider microglia-dependent mechanisms that may be useful for developing rehabilitation strategies for long COVID symptoms, including approaches aimed at modulating microglial activity and promoting neuroplasticity and neuronal regeneration [51].

6.4 Prognosis and prevention

The prognosis for most children and adolescents with prolonged COVID is favourable, since most signs and symptoms revert within 6 months. However, in other patients whose symptoms are more intensive or require greater restrictions, the prognosis will depend on access to multidisciplinary teams, the intensity of their symptoms and the support they receive at home, school and society. Some will not be able to attend school or will do so partially and will have to limit extracurricular activities and/or sports [47, 49].

There are no specific measures for the prevention of long COVID; however, the following are considered useful: (a) vaccination, preferably multi-dose vaccination: reducing the rate of severe COVID-19 disease and therefore long-term COVID; (b) reduction of risk factors such as obesity; (c) breastfeeding in infants and (d) providing accurate and sufficient information to the patient about COVID-19 to reduce the likelihood of psychological symptoms [13, 25, 41].

7. Conclusions

As we have seen, the SARS-CoV-2 virus caused various manifestations in the paediatric population, usually mild and with a satisfactory evolution. However, both MIS-C and long-term COVID can be serious and cause complications and sequelae in the medium and long term. On the other hand, the pandemic and confinement impacted children and adolescents in various ways, some directly and others indirectly.

As doctors, we must continue working with patients who still have sequelae to achieve their full recovery and keep in mind the ways in which COVID-19 can manifest and develop in the paediatric population. Research must also continue to be carried out to better understand them. As a society, we must continue to carry out multidisciplinary interventions to prevent children and adolescents from developing any problem derived from the economic situations and poor health conditions generated by the pandemic in various countries, and governments must strengthen their health systems and invest and work to close the gaps that have opened in health systems at the preventive and care levels, in education, food security and general well-being.

The COVID-19 pandemic has shown us how a new germ can impact society in general and individuals in particular, including the paediatric population. We are all aware that it is only a matter of time before a new pandemic occurs and we must work on generating protection and care strategies, making the most of the lessons learned.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 9

Perspective Chapter: Uganda's COVID-19 Response and the Unintended Consequences for Children and Adolescents – Lessons for the Next Pandemic

David Lagoro Kitara and Emmanuel Olal

Abstract

Pandemics are not contemporary spectacles, as many outbreaks have occurred all over human history. Globally, pandemics caused deaths, destruction of political administrations, loss of livelihoods, financial and psychosocial burdens. However, on some occasions, pandemics resulted in scientific discoveries that helped the human race adapt. Understanding the mechanism of the emergence and spread of pandemics is critical for designing and planning for control, management, and preparation for the next potential new one. The range of pandemic outbreaks dates from the Antonine plague in 165 to the most recent COVID-19 in 2019. Recently, Africa faced unique challenges during the COVID-19 pandemic, and there were many unintended consequences for the African population, especially children and adolescents. Drawing lessons from experiences of the Ebola virus, human immune virus (HIV), Lassa fever, and COVID-19 pandemics, the unintended consequences of the pandemics have been enormous on children and adolescents.

Keywords: COVID-19 pandemic and response, unintended consequences, children and adolescents, lessons for the next pandemic, Uganda

1. Introduction

Pandemics and Epidemics are not contemporary phenomena as lethal pandemic outbreaks have happened throughout recorded human history [1]. Pandemics for example, the great plague, the Spanish Flu, the HIV, and Ebola caused deaths, annihilation of political administrations, loss of lives and livelihoods, and financial and psychosocial burdens globally [1, 2]. However, on some occasions, pandemics resulted in scientific discoveries that have helped the human race adapt [1, 2]. Understanding the mechanism of the emergence and spread of any pandemic is critical for designing and planning control, management, and preparation for the next potential new one [1–3]. The range of pandemic outbreaks dates back to the Antonine plague in the year

165 to the most recent COVID-19 in 2019 [4]. The most common method of pandemic spread has been mainly human-to-human contacts and interactions [5, 6]. In the recent past, several regulations and policies were designed to combat disease transmission; most of which were devised to reduce and prevent human-to-human contact [5, 6]. Border closures, social gathering restrictions, patients' isolation, testing, and mandatory facemask use among others were some of the policies implemented during the recent pandemic outbreak.

Despite all these policies enacted to avoid loss of lives and livelihoods in pandemics, some policies made life difficult for people, especially in Africa [5, 6]. This is likely because most African households require physical interactions for their daily livelihoods [5, 6]. Thus, well-intended health policies such as movement restrictions and lockdowns to combat pandemic spread can put households at risk of poverty, loss of livelihoods, death, starvation, hunger, mental health, and psychological problems [5–8].

Recently, Africa faced unique challenges during the COVID-19 pandemic, and there were many unintended consequences for the African population, especially children and adolescents. Drawing lessons from experiences of the Ebola virus, HIV, Lassa fever, and COVID-19 pandemics, the unintended consequences of the pandemics have been enormous on children and adolescents. The law of unintended consequences is often cited but hardly ever defined as actions of people and governments that always have effects that are unanticipated or unintended [9]. In a publication by Robert Merton in the 1930s, he discussed five causes of the unintended consequences: errors, basic values, short-term and long-term interests, ignorance, and self-defeating prophecy [9]. The most interesting question to ask in Uganda's scenario was, what were the causes of the unintended consequences of the COVID-19 response on children and adolescents? Were all the five causes of unintended consequences as described by Merton observed in Uganda?

2. Background

From the time severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2) and coronavirus disease-19 (COVID-19) emerged in Wuhan in mid-December 2019, its spread has been dramatic internationally [10]. From the onset, the pathogenic patterns of the virus in the pediatric population have been less clear, particularly in sub-Saharan Africa, where authorities' initial projections estimated a higher number of cases and deaths [11]. At the end of the COVID-19 pandemic, it was clear that the number of pediatric COVID-19 patients had been much lower than in adults [12]. The clinical presentations and progression of the disease have varied and were characterized by morbidity and mortality among children and adolescents [12], even though COVID-19 has been one of the major worldwide health challenges in this millennium [13, 14]. It was reported in 2020 that more than 38 million people had been infected by SARS-CoV-2, and more than 1 million people had died due to the illness [13, 14]. In most studies, children roughly comprised just about 10% of all infected persons with COVID-19 [15].

Thus, the vast majority of COVID-19 cases were in adult populations, who had severe manifestations and higher mortality occurred among (those 60 years and above) chiefly among those with underlying systemic conditions, specifically cardiovascular diseases, diabetes, obesity, and chronic pulmonary disorders [15].

SARS-CoV-2 reached Africa much later than other continents and this gave time for better response preparations compared to other continents [16–18]. Also, sub-Saharan Africa (SSA) had a higher proportion of youth under 20 years (52.7%) than Asia (31.2%), North America (24.5%), and Europe (21.2%) [19] and this may in part explain the relatively lower COVID-19 case burdens and case fatality rates. Some scholars suggested that there was an underestimation of cases in Africa during the pandemic as a result of undercounting due to low population coverage and testing capacity for COVID-19 in most African countries than others [20].

Available data on COVID-19 among children at the time were from China, the United States of America (USA), and Europe [21–24]. These reports indicate that COVID-19 patients aged 0–19 years accounted for 1–5% of all confirmed cases [21–24]. Furthermore, most cases among children were milder, had better treatment outcomes, and significantly lower mortality rates than the adult population [21–24]. However, the clinical presentation of COVID-19 among pregnant women and neonates was more severe compared to non-pregnant women [25–29].

To date, there are limited formal reports on the direct and indirect impacts of COVID-19 among children and adolescents in sub-Saharan Africa (SSA).

Beyond that, there had been bantam available information on COVID-19 case counts and spectrum of clinical presentations among children and adolescents, except the African Centers for Disease Control (ACDC) report that children <15 years constituted 2.1% of all cases in Africa [30].

Important factors such as underequipped health/research infrastructures, political denials, misinformation, disinformation, conspiracy theories, ongoing civil conflicts, and humanitarian emergencies could have contributed to the suboptimal disease surveillance on the African continent [31–33]. These factors masked the true impact of COVID-19 on children and adolescents in sub-Saharan Africa [31–33]. This was of particular concern since children in the SSA region bear a significant burden of global infectious disease morbidity and mortality. In addition, social and economic lockdowns further intensified their vulnerabilities [34], including loss of household incomes and livelihoods, poor access to healthcare services, and other multidimensional impacts [35].

For some African countries, movement restrictions, workplace/school closures, and travel bans were imposed on the population as early as March 2020 [36]. As the COVID-19 pandemic continued to ravage healthcare systems, economies, livelihoods, cultures, and responses across countries varied from one to another, there were many adverse consequences for children and adolescents [4, 5, 37, 38].

Uganda was one of the few countries in the SSA that adopted its own model to manage the pandemic by taking into consideration its cultures, values, environment, socio-economic activities, beliefs, and previous successful epidemic experiences [4, 5, 37]. This response model was based on its long experience in successfully controlling many previous epidemics that afflicted it and neighboring countries, for example, HIV and acquired immunodeficiency syndromes (AIDS) in the 1980s, Measles in the 1990s, Hepatitis B in the 2000s, Ebola in 2000, 2017 and 2018 and Marburg in 2018 [4, 5, 37].

3. Incremental statistics of SARS-CoV-2 among children and adolescents

As of 1 January 2023, more than 664 million cases and 6.7 million deaths associated with SARS-CoV-2 were reported worldwide, with 57 million cases and 43,000 deaths estimated among children and adolescents aged 0–19 years [1]. Africa contributed 1.4% of all reported confirmed cases, which was the lowest of all World Health Organization (WHO) regions globally [3, 4, 37].

There were many guesses on the reasons why Africa had been relatively spared from the COVID-19 pandemic including underreporting and limited testing capacity. However, children younger than 18 years constitute almost 50% of the people in Africa today [3–5]. Despite the higher proportion of children and adolescents in Africa and the unprecedented volume of COVID-19 globally, research conducted over the past 3 years (200–2003), epidemiological data, clinical features, and outcomes in children and adolescents in Africa remained scanty [5–8].

As in all countries affected by the SARS-CoV-2, the need to define the symptomatology of the disease in children, develop and implement school health policies, and determine what constituted a clinical case definition was lacking [3]. This approach was expected to ease counting, contact tracing, and management of all cases of COVID-19 among children and adolescents in communities with limited resources.

Even though research suggests that children had a lower susceptibility to SARS-CoV-2 infection than adults [5, 7, 38], children became infected and transmitted the virus to others [39, 40]. Research suggests that children are less likely to develop symptomatic infections and develop severe COVID-19 disease compared to the adult population [7, 41].

However, children in many countries were indirectly affected by COVID-19 in circumstances such as prolonged school closures, loss of lives and livelihoods, and no schooling for long periods [42–44]. The controversy surrounding return-to-school policies after or during the pandemic remained unresolved, though there was increasing evidence that transmission dynamics in children differed from that of the adult population [45, 46].

In most children and adolescents, symptoms and signs of the illness were like other acute respiratory viral infections, with the upper airways being affected more than the lower airways [47]. In the United Kingdom, for example, most children were asymptomatic, and only a few were severely ill unlike their adult counterparts, and the incidence of death from COVID-19 was rare and occurred mainly in children with underlying comorbidities such as cardiovascular diseases (CVDs), diabetes, asthma, obesity, and cancers [47].

4. Challenges of COVID-19 pandemic response to children and adolescents in Uganda

The total lockdown of the country through closing down air, road, water, and congregate settings, and restrictions on people's movement through stay-home policy played a significant role in this pandemic containment and control in Uganda [4, 37–39, 48]. Most notable were the unshakable and clear leadership structure, employment of experienced health workforce, good political will, enabling environment, good epidemic response by the population, and the Ugandan Ministry of Health [4, 5, 37, 38]. Even though one can reasonably argue that the number of COVID-19 cases that were seen in Uganda was not near to the large numbers observed in the United States, Asia, and other European countries, Uganda's experience on how it managed the pandemic is worth talking about as it might provide useful lessons for future public health interventions to a pandemic of this magnitude, particularly in low-resource settings [4, 5, 37, 38, 48, 49].

On the one end, Uganda's authorities provided national leadership, guidance, and coordination to the COVID-19 National Task Force for the response [3–7, 37]. Uganda's national task force for the response to the COVID-19 pandemic was set up by Uganda's authorities. It was comprised of groups of multidisciplinary teams derived from all sectors of society (Government, United Nations (UN) agencies, non-governmental organizations, civil society, the Army, scientists, private sectors, Universities, multi-donor organizations, business communities, members of Parliament, and common members of the society) [3–7, 37]. Its function was to advise Uganda's leadership on new directions of management of the pandemic based on their expertise, specializations, and experiences [4, 5, 7, 37].

Uganda's authorities employed both electronic and social media such as radios, drama, gingles, music, televisions, Short Message Service (SMS) messages, Twitter, group emails, and WhatsApp messages to engage, mobilize, and sensitize the Ugandan population on COVID-19 preventive interventions through the provision of regular updates [3, 4, 6, 37]. These actions by authorities resulted in simultaneous and multiple public health interventions through structured leadership, which contributed to reasonable and timely control of COVID-19 in Uganda [3–7, 37].

5. Navigating new threats: A description of the Ugandan government's response strategy to COVID-19

Following the World Health Organization (WHO) declaration of COVID-19 as a pandemic in March 2020, mass influx of returnees to Uganda forced the Ministry of Health (MoH) to swiftly institute enhanced surveillance through mandatory screening for flu-like symptoms and measuring of temperatures for travelers at its airports and border points to prevent the importation of cases into the country [37].

The government also identified all persons who came from high-risk countries and subjected them to a mandatory 14-day quarantine and testing for COVID-19 [37]. Those who did not complete their mandatory 14-day quarantine but escaped from the quarantine centers were traced to their communities, returned for quarantine, and re-tested [3, 37]. Those who tested negative continued to be monitored by the MoH authorities using mobile phones and village health teams [3, 37]. In addition, community contacts of returnees from high-risk countries were registered and monitored by authorities.

Throughout 2020, country-wide contact tracing and testing for COVID-19 continued at a centralized laboratory located at the Uganda Virus Research Institute (UVRI) in Entebbe [37]. Other centers, especially the regional referral hospitals, national referral hospitals, and general hospitals (at the district level), set up COVID-19 treatment centers (CTUs) [37]. At the same time, congregate settings such as schools, recreation centers, sports, parks, places of worship, bars, markets, hotels, public transport, and other public gatherings that attract large numbers of people were closed, and the government imposed a curfew on the population [37].

Lower down the administrative ladder, COVID-19 committees at district and community levels were formed and supported by the National Task Force (NTF) to implement the response interventions within their communities [5, 37]. Although treatment of confirmed cases was initially provided only in two national-level health facilities, as time went on, it got decentralized to regional hospitals, district hospitals, and home-based care to enhance efficiency and equity [4, 5, 37]. The home-based care management approach for mild cases of COVID-19 helped to prevent congestion in hospitals and strengthened communities' management capability during the pandemic [4, 5].

Although Uganda registered the lowest statistics on the incidence, prevalence, number of hospitalizations, and COVID-19-related deaths in the East African region in early 2020 [5, 37], Uganda went through presidential, parliamentary, and local government elections from September 2020 to March 2021 reversed this gains. Massive rallies, and non-adherence to infection, prevention, and control (IPC) protocols were in part to blame for this occurrence [3, 5, 37]. Thus, by December 2020, Uganda experienced the first wave of COVID-19, which affected 40,000 people and registered 300 deaths [3, 5, 37].

Subsequently, Uganda experienced a second and more severe wave in May, June, and July 2021 [6, 7]. In that wave, Uganda registered more than three times the number of COVID-19 cases, with more than 2000 deaths registered than the first wave [6, 7].

COVID-19-related losses of lives, and livelihoods, poverty, economic losses, and psychosocial problems increased and were substantial challenges that affected communities in Uganda [3–8]. However, COVID-19-related opportunities in many communities in Uganda remained unexplored or unreported [5].

The pandemic enabled the government to strengthen its disease surveillance systems, increase the number of beds in health facilities, increase the number of intensive care units (ICUs), tap into resources from the private sector, establish oxygen plants in most regional referral hospitals, procure more ambulances, recruit more health workers into the healthcare systems, and increase supplies that helped save the lives of many people in Uganda [5, 8].

6. Beyond the headlines: Exploring the ripple effects of Uganda government's response measures on the health, education, and well-being of Ugandan children and adolescents

As the COVID-19 pandemic progressed, more evidence on the transmission of SARS-CoV-2 in children and adolescents became obtainable, and it became clearer that children acquired COVID-19 at a similar rate to adults and were sources for further transmission in households [38–46]. The severe COVID-19 disease was shown by extreme difficulty in breathing and low oxygen saturation at admission. From the many studies in Uganda, the severe form of the disease was not observed among children and adolescents 20 years and below in the Ugandan population. This explains, in part, the low complication rates and deaths observed among children and adolescents in Uganda. This finding among children and adolescents had inferences on how the Ugandan authorities could use this information to plan the national response (lockdown measures) while preserving lives, and livelihoods, and saving the economy [4, 5, 8].

7. Learning from experiences: An analysis and valuable lessons from Uganda's response for future pandemic preparedness strategies

Many scholars raised fears about the short and long-term effects of COVID-19 on prolonged school closures, students' performances, and learning of school-going children and adolescents in Uganda. They proposed a formal and comprehensive quantitative and qualitative study to determine its impact on children and adolescents [3, 4, 45, 46]. Scholars were concerned that most Ugandan population 20 years and below (approximately 15 million people) were school-going children who had missed the opportunity of schooling for more than 2 years; the longest duration in the world. Throughout the pandemic, community's experience affirmed the fears raised by scholars and academicians about the negative impact of the disease on children's education.

For this, some scholars questioned the rationale for the prolonged lockdown measures (stay-home policy) and school closures imposed on children and adolescents with a resulting loss in physical teaching and learning opportunities in schools. Eventhough the online teaching and learning opportunities were available in some elite schools in Uganda, the majority of children from urban and rural areas, hard-to-reach, and those that lacked ICT equipment and electricity could not benefit from this option.

For children and adolescents who were not in school anymore but were involved in productive socio-economic activities, the lockdown measures were restrictive and not helpful for the economic activities of the country. In its place, some scholars suggested the "*enhanced shielding approach*" where the most vulnerable people (the elderly and those with comorbidities) were to be quarantined as the most optimum approach for handling the COVID-19 situation in Uganda while the young continued their socio-economic activities uninterrupted [4, 5, 37, 38].

In addition, a collective regional approach to containment of the virus was recommended to enhance and promote closer collaboration with other regional countries by ensuring that the virus was not spread from one to another [3–5, 37]. Therefore, limiting the regional spread of the virus was ideal as most countries' borders were porous, and there were unofficial cross-border movements among communities in most East African countries. This collective and collaborative approach was considered important as countries in the East African region applied different methods for controlling and containing the pandemic. For example, the United Republic of Tanzania did not lock down its population, and there were no movement restrictions, no large gathering restrictions, and no routine testing of probable, suspected, contact cases of COVID-19 was strictly followed. This was in contrast to Uganda, where the whole population was locked down, with movement restrictions and banning of large gatherings, with regular surveillance and testing of suspected and contact cases [3–5, 37]. In addition, the implementation of the lockdown measures in Uganda was superintended by the security forces that ensured that the population did not default [3–5, 37].

Another important aspect of the needed collaborative approach was that the three East African countries shared tribes, communities, and families across borders. Because of these shared values, cultural activities, and cultures across porous borders, the implementation of movement restrictions for community members across artificial countries was affected. Many cultural activities among communities across the porous borders were major setbacks in movement restrictions of community members in East Africa during the pandemic.

8. Building a more resilient future

There are key considerations for policymakers and healthcare professionals to make based on lessons learned from past epidemic experiences as they develop a future pandemic response plan.

9. The COVID-19 pandemic introduced new sets of challenges in many communities

Through distinct global and national transmission channels, families and children have been adversely impacted by the COVID-19 pandemic and the measures taken to control it including the lockdown measures [4, 8, 38–46]. These household challenges included falling family incomes, rising prices, and disruptions of social services.

i. *Lower household incomes and assets:* Household incomes were directly affected by job losses by parents and guardians, lower earnings were experienced, and reduced employment benefits as well as fewer remittances from friends and relatives from abroad. Assets were diminished as families spent savings, sold livestock and other valuable items, and borrowed resources to meet essential consumption needs during the pandemic. These lower household incomes affected children and adolescents during the pandemic, causing increased socioeconomic vulnerabilities of households [47, 48].

ii. *Higher costs of living:* Higher costs of living in the population were driven by a combination of supply and demand factors where prices of basic needs such as food, water, soap and sanitizer, medicines, and transport increased during the pandemic and lockdown (**Table 1**). Since increased inflation required more money to purchase the same items over time, higher prices ultimately served as another type of income shock to families. This situation persisted during the pandemic, and when lockdown measures were implemented to curb the effects of the pandemic [5, 7]. Most families could not afford the cost of their social and economic needs including adequate food in quality and quantity and this resulted in poor nutrition in children and adolescents with the accompanying adverse consequences.

iii. *Reduced access to social goods and services:* These challenges were observed when the COVID-19 lockdown measures were implemented and closed or limited availability of quality early childhood development programs, childcare services, schooling, nutrition programs, immunization campaigns (**Table 1**), and many others [5, 7, 8, 38–46]. On the demand side, factors such as misinformation, disinformation, malinformation, fears, stigmatization, multiple conspiracy theories, and inability to afford healthcare services contributed to the lower utilization of social and health services during and after the pandemic [5–8, 49]. These had adverse consequences on children and adolescents in Uganda, where most essential preventive health services including modern family planning methods, immunization, and adolescent health were missed.

iv. *Increased incidence of teenage pregnancies due to the prolonged stay-home policy during the pandemic* (**Table 1**). Reports from Uganda showed an increased prevalence of teenage pregnancies across most communities during the lockdown as young people got more engaged in unrestricted and unprotected sexual activities [50]. The increased incidence and prevalence of unintended pregnancies, miscarriages, and abortions were associated with reduced utilization of modern family planning methods, higher school dropouts, and adverse psychological effects as some services were not readily available to the population due to the lockdown measures [50]. Thus, child marriages and teenage pregnancies were major social and public health issues in Uganda, with far-reaching consequences for the age group [50].

v. According to the United Nation Children Educational Fund (UNICEF) report of 2022/2023, 34% of women aged 20 to 24 years were either married or in a union before the age of 18 years, while 7% were married before 15 years [50].

S/no	COVID-19 and responses	Unintended consequences in children and adolescents

1	SARS-CoV-2 infection	• *Long COVID*
		  ○ *Presentations:* Rash, abdominal pain, conjunctivitis, tachycardia, hypotension, altered level of consciousness, shock, and death.
		  ○ Deranged CRP, ferritin, hemoglobin, neutrophil counts, cardiac markers, and coagulation markers.
		• *Multisystem inflammatory syndromes in children (MIS-C)*
		• *Presentations:* mental health, pulmonary and neurologic disorders, pulmonary fibrosis, myocardial dysfunction, post-viral chronic fatigue syndrome, acute pulmonary embolism, myocarditis, cardiomyopathy, venous thromboembolic events, renal failure, and type 1 diabetes.
		  ○ Cognitive deficit, insomnia, intracranial hemorrhage, ischemic stroke, nerves, nerve roots, plexus disorders, psychotic disorders, and seizures.

2	Lockdown measures and stay-home-policy	• *Lower household incomes and assets* (increased household food insecurity and malnutrition). • *Higher costs of living* (Lack of access to food and amenities). • *Reduced access to social goods and services* (education, health, nutrition programs, immunization campaigns, reproductive health services, and social security). • *Increased incidence of teenage pregnancies.* • *Increased incidence of mental health and psychological conditions* (depression, anxiety, suicidal ideations, suicide, violence, and lack of concentration increased among the group). Increased school dropout, disability, morbidity, poor school performance, and deaths were experienced. • *Increased incidence and prevalence of drug and alcohol abuse* (addiction, mental health problems, crimes, accidents, violence, malnutrition, dependency, and school dropout were observed). • *Increased incidence of school dropout* (decreased enrollment in schools, child marriages, and lack of access to reproductive health services).

Table 1.
The unintended consequences of COVID-19 and responses on children and adolescents in Uganda.

These numbers of teenage pregnancies were troubling, with approximately one-quarter of all Ugandan girls between 15 and 19 having begun childbearing already [50].

vi. In addition, The United Nations Population Funds (UNFPA) in 2021 reported that about a quarter (one in four or 25%) of Ugandan women had given birth by 18 years while Uganda's maternal Mortality Ratio (MMR) was 336 deaths per 100,000 live births and 17.2% of the deaths were among 15–19 years old [51].

vii. Regrettably, the COVID-19 pandemic and the lockdown measures worsened teenage pregnancy situation in Uganda. A study commissioned by the Forum for African Women Educationalists of Uganda (FAWE-U) in 2021 and citing the International Labor Organization (ILO) of 2020 found that during Uganda's first COVID-19 lockdown (between March and June 2020), teenage pregnancies among girls aged 15 to 19 years increased by 25.5% above their pre-COVID average, while pregnancies among girls between 10 and 14 years increased to an astounding 366% [47]. The data taken during and after the

COVID-19 lockdowns in Uganda suggest that the country was already in a teenage pregnancy crisis with longer-term social, cultural, and economic adverse consequences [50, 51].

viii. Data from UNFPA revealed that between March and November 2020, an estimated 354,736 teenage pregnancies were reported in Uganda in the 8 months of school closure [50, 51]. In addition, between January and September of 2021, 290,219 teenage pregnancies were reported in Uganda, and this number was five times higher than the cumulative number of COVID-19-positive cases that had been reported since 2020 [50, 51].

ix. *Increased incidence of mental health and psychological effects among children and adolescents* (**Table 1**). The strict adherence to the lockdown measures substantially affected the psychological and mental well-being of children and adolescents in Uganda, with some developing depression, suicidal ideations, suicide, psychotic, and anxiety disorders [5, 6, 8]. This led to increased incidence of school dropout, disability, morbidity, increased healthcare costs, poor school performance, and deaths [7, 8].

x. There has been little attention on the psychological effects of COVID-19 on children and adolescents' mental health [52], yet the pandemic created chaos that resulted in many infections and deaths and forced millions into isolation due to the lockdown measures [53]. As a result of social isolation and constant fears of getting infected, the adverse mental health consequences associated with the pandemic and the control measures implemented were substantial on the population [54, 55]. The pandemic enormously impacted adolescents' mental health with many stressful life events, addiction, depression, worries, anxiety, overuse of the internet, and social media that adversely affected their mental health during and after the period [54, 55]. Several children and adolescents in Uganda have not returned to school or normal lives because of the mental health problems experienced during the pandemic and lockdowns.

xi. *Increased incidence and prevalence of drug and alcohol abuse among children and adolescents* (**Table 1**). The incidence and prevalence of alcohol and drug use substantially increased among children and adolescents in Uganda during the lockdown periods [56]. Cheap alcohol was provided in sackets, and drugs such as marijuana were accessible to children and adolescents during the lockdown. More redundant time (out of school) was available to school-going children over the prolonged school closures that exposed children and adolescents to access and use of alcohol and drugs [56]. Several cases of addiction, mental health problems, crimes, accidents, violence, malnutrition, dependency, and school dropouts were observed [56]. The end result of these experiences was the increased incidences of alcohol and drug use, dependency, and the rise of violent gangs ("Aguu") in the region that have caused enormous insecurity to the population of northern Uganda, for example. Had the children and adolescents remained in schools, particularly boarding schools, most likely this situation would have been different.

xii. *Increased incidence of school dropout among children and adolescents.* Because of the 2-year lockdown, many school-going children and adolescents in Uganda dropped out of school indefinitely and have never returned to school to date [57–59]. Some became parents and focused their attention on raising their own families and children (**Table 1**). The most affected group was the girl child that experienced many reproductive health challenges including lack of vaccinations and modern family planning services that were crucial for their well-being. These had adverse consequences on the young generation and population of Uganda in the short and long term [57, 58].

10. Learning from experience: Analyzing valuable lessons from Uganda's response for future pandemic preparedness

10.1 How COVID-19 jeopardized children's well-being

There were many immediate risks to children and adolescents during the pandemic that were identified. Lessons from the experiences of the food, finance, and fuel (3Fs) crisis of 2007–2008 on families appeared to be similar [43–46, 53–55, 60–70]. Among the many unfavorable factors were deaths, sicknesses, poor nutrition, exposure to various forms of violence, mental health problems, accidents, and lower educational achievements observed among children and adolescents [60–64, 71]. Each household's coping capacity largely determined the prevalence, strength, and variety of negative outcomes on children and adolescents. In addition, the limited financial capacity of each household at the beginning of 2020 was exhausted by the end of the same year [61–64]. Thus, the most substantial reality was that in many communities in Uganda, children and adolescents in underprivileged households continued to suffer more from the pandemic's socioeconomic effects. This scenario is a lesson learned for future considerations in epidemic management.

11. Multisystem inflammatory syndrome in children (MIS-C)

As of April 2020, the first report of multisystem inflammatory syndrome in children (MIS-C) as a serious pediatric manifestation of COVID-19 emerged in the United Kingdom [67]. Since then, several reports on MIS-C appeared in other parts of the world [68–70, 72–74]. Although MIS-C was reportedly more common in black children, there was limited published data on MIS-C in Africa [68, 70, 72–74], and there was uncertainty on the accurate incidence of MIS-C. In addition, there was difficulty in precisely estimating the total number of children exposed to SARS-CoV-2 as different testing strategies were used worldwide [68–70, 72–74].

Even though MIS-C occurred in <1% of children with confirmed COVID-19, several reports suggested that the decreasing prevalence and severity of MIS-C with subsequent SARS-CoV-2 variants were likely explained by increasing seroprevalence and COVID-19 vaccination [66–70, 72–77]. However, a report from South Africa describing the largest group of African children with MIS-C revealed that SARS-CoV-2 variance did not affect the clinical presentation or outcomes of children with MIS-C [69].

Nevertheless, the description of MIS-C in African children was generally similar to those in high-resource settings, and nearly all children responded to intravenous treatment with Immunoglobulins (IVIg) and/or steroids [67–70, 72–78].

Five cohort studies in Africa describing 251 children with MIS-C from four countries (South Africa, Nigeria, Kenya, and Egypt) shed more light on the condition in African children [68, 70, 72–74].

In a report on 29 children from KwaZulu Natal, the mean age of the patients was only 55 months, and those with markedly elevated biomarkers and critical organ involvement were associated with severe disease [70]. Mortality was high (20.6%) and risk factors for poor outcomes included higher ferritin levels and the need for mechanical ventilation [70].

The median age of children with MIS-C across many studies in Africa was 4.0–7.5 years compared to 9 years in the United States [70, 72–74]. In the United States, only 24.5% of children were <5 years while two cohorts in Africa reported the number of children <5 years at 59% and 39.3% in South Africa and Nigeria, respectively. Studies over time showed that more younger children were being diagnosed with MIS-C with the youngest presenting during the Omicron wave. In addition, a male majority was noted in all four African studies [68, 70, 72–74].

Morbid conditions such as coronary artery dilatation and first-degree heart block were seen in 46.4% and 16.0% of the children, respectively.

Although all the children survived the complications, 7.1% of children still had coronary artery abnormalities 3 months later [73], and in 6 months, all the abnormalities had resolved.

Similar clinical presentations of MIS-C in African children were reported from other continents, with rash, abdominal pain, conjunctivitis, and tachycardia with hypotension as the commonest presentation [69].

In addition, 34% of children from South Africa and 44.4% from Egypt were reported with altered levels of consciousness and coma associated with shock, respectively [68, 70, 74]. Also, CRP, ferritin, hemoglobin concentration, neutrophil counts, cardiac markers, and coagulation markers were markedly deranged in children with MIS-C in Africa [68, 70, 72–74].

12. Long coronavirus disease-19 (long COVID-19) in children

During the early phases of the pandemic, public authorities and scientific committees focused their attention on the acute phase of the COVID-19 pandemic. After substantial COVID-19 vaccination coverage, there was an emergence of clinically milder coronavirus variants in the population. However, some patients who suffered from COVID-19 continued to report some sequelae of the disease in its aftermath. Thus, the evaluation and characterization of all enduring conditions related to COVID-19 infection such as long COVID-19 became essential [75–79].

Long COVID was defined as a heterogeneous multisystemic condition with signs and symptoms that developed, persisted, and fluctuated after SARS-CoV-2 infection [75–79].

In a systematic review of 57 studies with more than 250,000 survivors of COVID-19, the most encountered sequelae of long COVID were mental health, pulmonary, and neurologic disorders, which were prevalent 6 months after SARS-CoV-2 infection [78, 79].

To our knowledge, there has only been a handful of published reports of long COVID-19 in children and adolescents in Africa. Most articles on long COVID-19 were generated from adult literature with limited data on children and adolescent populations [78].

Furthermore, the definition of long COVID-19 encompassed a broad range of symptoms, including anatomical complications (pulmonary fibrosis and myocardial dysfunction), mental health disorders, and, more subjectively, non-specific symptoms such as post-viral chronic fatigue syndrome [67, 77–79]. The broad definition may have in many ways, contributed to the considerable disparity of the prevalence estimates of long COVID-19 in different communities worldwide [67, 77–79].

In addition, when assessing nine potential post-COVID-19 signs and symptoms and 15 potential post-COVID conditions among children and adolescents <18 years and comparing them with children without the infection in the USA by the CDC, symptoms and conditions reported as likely in the COVID-19 group were rare or uncommon [79].

Also, it was reported that clinical conditions such as acute pulmonary embolism, myocarditis and cardiomyopathy, venous thromboembolic events, acute and unspecified renal failure, and type 1 diabetes were rare or uncommon conditions in children and adolescents [79]. Similarly, symptoms and conditions that were less likely in children with COVID-19 were respiratory signs and symptoms, mental health symptoms, neurological conditions, muscle disorders, and sleeping disorders [79].

However, 6 months after the SARS-CoV-2 infection, children with long COVID had increased risks of cognitive deficit, insomnia, intracranial hemorrhage, ischemic stroke, nerve, nerve root, and nerve plexus disorders, psychotic disorders, and seizures than children with other respiratory infections [79].

Furthermore, in a 2-year retrospective cohort study, a cohort of COVID-19 patients (of any age) identified and propensity score matched (1:1) to a concurrent cohort of patients with any respiratory infection [79], the data suggested that long COVID and long non-COVID illnesses in children were similar but with different clinical features than adults. Eventhough long COVID were rare, its adverse consequences profoundly impacted children's quality of life. For that reason, there were many unintended consequences of COVID-19 and control measures that adversely affected children and adolescents' lives and livelihoods in Uganda, with impacts that in the short term could not easily be reversed but could be learning points for considerations in future epidemic management.

13. Conclusions

There were good policies and practices for the management and control of the COVID-19 pandemic in Uganda. There were also many unintended adverse consequences observed among children and adolescents which should draw lessons for the next pandemic management. The most severe effects of the pandemic were high school dropout, teenage pregnancies, mental and psychological problems, alcohol and drug abuse, and many others that were detrimental to the lives of many children and adolescents in Uganda. This paper draws information on the unintended consequences of policies and frameworks for the management and control of the COVID-19 pandemic. Whether these unintended consequences among children and adolescents in Uganda were due to errors, basic values, short-term and long-term interests, ignorance, and self-defeating prophecy needs a comprehensive analysis which should be accomplished shortly.

14. Recommendations

Governments in low-resource settings should:

1. Invest in building and training leaders in epidemic management.

2. Invest in disease surveillance by establishing special units for early disease detection and identification.

3. Invest in training of human resources for health in disease surveillance, management, and control.

4. Establish and equip more ICUs and Treatment centers that are equitably distributed across its borders to assure accessibility and equity.

5. Establish algorithms for early detection and management of diseases with epidemic potential.

6. Establish collaborative research and partnerships with institutions and countries in the early detection and management of diseases with epidemic potential.

7. Establish and maintain internal funding mechanisms to promote impactful research and fund the management of diseases with epidemic potential.

8. Establish centers of excellence with advanced technology to identify and manage diseases with epidemic potentials.

9. Take holistic care and welfare of the population by addressing its livelihoods, psychological, and mental health care in a post-epidemic/pandemic era.

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Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

AIDS	acquired immunodeficiency syndromes
ACDC	African Centers for Disease Control
COVID-19	coronavirus disease-19
CTUs	coronavirus treatment units
HIV	human immune virus
CVDs	cardiovascular diseases
ICU	intensive care unit
MIS-C	multisystem inflammatory syndrome in children
SARS-CoV-2	severe-acute-respiratory-syndrome-coronavirus-2
SMS	Short Message Service
SSA	sub-Saharan Africa
UBOS	Uganda Bureau of Statistics
UDHS	Uganda Demographic and Health Surveys
UN	United Nations
WHO	World Health Organization

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Following the global impact of the COVID-19 pandemic, the medical and scientific community is now confronting a new and complex challenge: the long-term consequences of SARS-CoV-2 infection. Known collectively as post-COVID syndromes or Long COVID, these conditions affect millions worldwide, with a hefty burden in low- and middle-income countries. These syndromes are characterized by a wide range of persistent symptoms, including fatigue, dyspnea, neurocognitive dysfunction, and cardiovascular complications, and demand sustained attention, research, and clinical innovation. *Current Topics in Post-COVID Syndromes* offers a comprehensive and timely examination of this emerging public health concern. Drawing on recent advances in pathophysiology, diagnostics, therapeutics, and rehabilitation, this book highlights the multifactorial nature of post-COVID syndromes and the importance of interdisciplinary approaches to their management. It also explores the intersection of these conditions with socioeconomic disparities and the resilience of health systems. As the world transitions into a post-pandemic phase, understanding and addressing the long-term effects of COVID-19 is essential to achieving full recovery and preparing for future pandemics. This volume is a vital resource for clinicians, researchers, public health professionals, and policymakers.

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