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Current Evidence on the Pathophysiology, Multidisciplinary Treatment Approaches, and Long-Term Outcomes of Post-Acute Sequelae of SARS-CoV-2: A Comprehensive Review

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Abstract

Post-Acute Sequelae of SARS-CoV-2 (PASC), also referred to as long COVID, afflicts millions worldwide and shows as chronic, multisystem symptoms following acute COVID-19 infection. The most current data on the complex pathophysiology of PASC, new multidisciplinary therapies, and prolonged clinical results are combined in this methodical review. It investigates important processes, including immune dysregulation with cytokine storms, viral persistence in tissue reservoirs, microvascular damage leading to thrombosis, and organ-specific injury involving pulmonary, cardiac, and neurological systems. Models of integrated care that combine diverse experts, including pulmonologists, cardiologists, and neurologists, to handle PASC's variable presentation are evaluated in the review. Assessed results over as far as three years from the original infection include a higher chance of death, a higher likelihood of hospitalization, and the onset of chronic medical illnesses, particularly among those who were seriously impacted. There are, in fact, major problems that need to be solved, including the existence of variable diagnostic criteria, a lack of thorough data on the efficacy of several treatment modalities, and severe disparities in healthcare access, especially in underprivileged areas that have other barriers. The urgent need to establish standardized diagnostic algorithms to guarantee diagnosis uniformity, to conduct thorough randomized clinical trials to fully assess therapeutic interventions, and to develop equitable models of care able to efficiently counter the current differences in the healthcare system is highlighted in this review. This project aims to lessen PASC's

enormous worldwide burden using policy and research, therefore improving the quality of life for those impacted and reinforcing world health systems.

Keywords: Long COVID, PASC, pathophysiology, multidisciplinary care, health equity

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1. Introduction

The COVID-19 pandemic has sickened more than 775 million people worldwide due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While most of those infected recover within weeks, there is a significant population that undergoes persistent disease symptoms or long COVID symptoms. PASC is defined as a pathological syndrome lasting at least two months or more, usually appearing three months after infection, with debilitating, adverse effects on multiple organ systems (World Health Organization, 2024). PASC prevalence ranges from 5% to 80%, depending on study design, group, and severity of acute illness (Woodrow et al., 2023). The complexity of PASC comprises neurological, cardiovascular, pulmonary, and psychological pathological symptoms. This review presents challenges to the diagnosis and treatment of PASC; elucidates PASC's pathophysiology, including immune, viral, and organ-specific mechanisms; evaluates multidisciplinary treatment approaches, from pharmacological to rehabilitative strategies; analyzes long-term outcomes, including mortality, hospitalization, and organ-specific sequelae; outline research gaps and develop future agendas in clinical practice and policy. It should therefore be a high priority to understand the mechanisms underlying and optimize the care provided to PASC patients.

2. Pathophysiology of PASC

2.1. Immune Dysregulation and Inflammation

The pathophysiology of PASC is complex, and immune dysregulation is a major causation. SARS-CoV-2 infection causes a robust immune response, with release of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), frequently resulting in a "cytokine storm" (Castanares-Zapatero et al., 2022). Recurrent inflammation is reflected by increased IL-6, C-reactive protein (CRP), and tryptase in PASC, with correlation with fatigue, myalgia, and neurocognitive impairment (Tsilioni & Theoharides, 2023). Mast cell activation syndrome (MCAS) is also being recognized with increasing frequency, with elevation of tryptase and histamine implicating a pathogenetic role for symptoms such as brain fog and gastrointestinal discomfort (Davis et al., 2023). SARS-CoV-2 interaction with mast cells precipitating MCAS has been theorized, facilitating systemic inflammation (Theoharides et al., 2022).

Autoimmune processes are also implicated. Abnormal antinuclear antibody titres are reported in 43.6% of cases of PASC at 12 months, with association with neurological and musculoskeletal syndromes (Seeßle et al., 2022). Molecular mimicry, with viral antigens having a resemblance to self-antigens, is a process by which autoantibodies against neural or muscular membranes are initiated (Son et al., 2023). Discordant findings do, however, exist with, for instance, a population from Germany finding no association with autoantibodies, and herein implicating population variability (Woodruff et al., 2021). Such variability is taken to suggest that autoimmune responses are context-dependent, with genetic determination or viral strain influencing responses.

2.2. Viral Persistence and Latent Reactivation

One of the top theories for the chronicity of PASC is viral persistence. SARS-CoV-2 RNA and viral antigens were recognized within reservoir locations, including the gastrointestinal tract, lymphoid tissue, and central nervous system, more than a few months post-infection (Xiao et al., 2021). Immune activation and flares of fatigue and dyspnea occur with such persistence (Lopez-Leon et al., 2022; Bonilla et al., 2023). A viral antigen within gut mucosa, for instance, is linked with the continuation of gastrointestinal complaints, including diarrhea and abdominal pain (Jeong et al., 2025).

Reactivation of latent viruses, including Epstein-Barr virus (EBV) and human herpesvirus-6 (HHV-6), is a further mechanism. EBV reactivation, which presents in 66.7% of PASC individuals, is linked with myalgia, cognitive impairment, and fatigue (Gold et al., 2021). SARS-CoV-2 has been shown to impair immune surveillance, resulting in latent virus reactivation, triggering an inflammatory response by way of molecular mimicry (Peluso et al., 2022). SARS-CoV-2 interaction with latent pathogens is a testament to PASC complexity, for which targeted diagnosis for detection of viral reservoirs is needed.

2.3. Organ-Specific Damage and Microvascular Damage

Binding of SARS-CoV-2 with ACE2 receptors causes extensive organ damage. Pulmonary sequelae with reduced diffusing capacity and interstitial lung disease are frequent, with a hazard ratio (HR) of 1.61 for chronic pulmonary disease (Lam et al., 2023). They are a result of injury and fibrosis of alveoli, mediated by sustained inflammation (Babar et al., 2024). Cardiovascular features of myocarditis, heart failure (HR 1.82), and arrhythmias are a result of endothelial damage and microthrombosis (Xie et al., 2022). Endothelial damage, reflected by elevated von Willebrand factor and D-dimer, promotes hypercoagulation, with cardiovascular events (Pretorius et al., 2022).

Neurological symptomatologies, including memory loss and brain fog, are linked with cerebral hypoperfusion, loss of integrity of blood-brain barriers, and hypometabolism on positron emission tomography (PET) scans (Guedj et al., 2021). Microglial activation and neuroinflammation may play a role in cognitive impairment, replicating patterns encountered with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (Komaroff & Bateman, 2021). Renal and gastrointestinal pathways are targeted, with

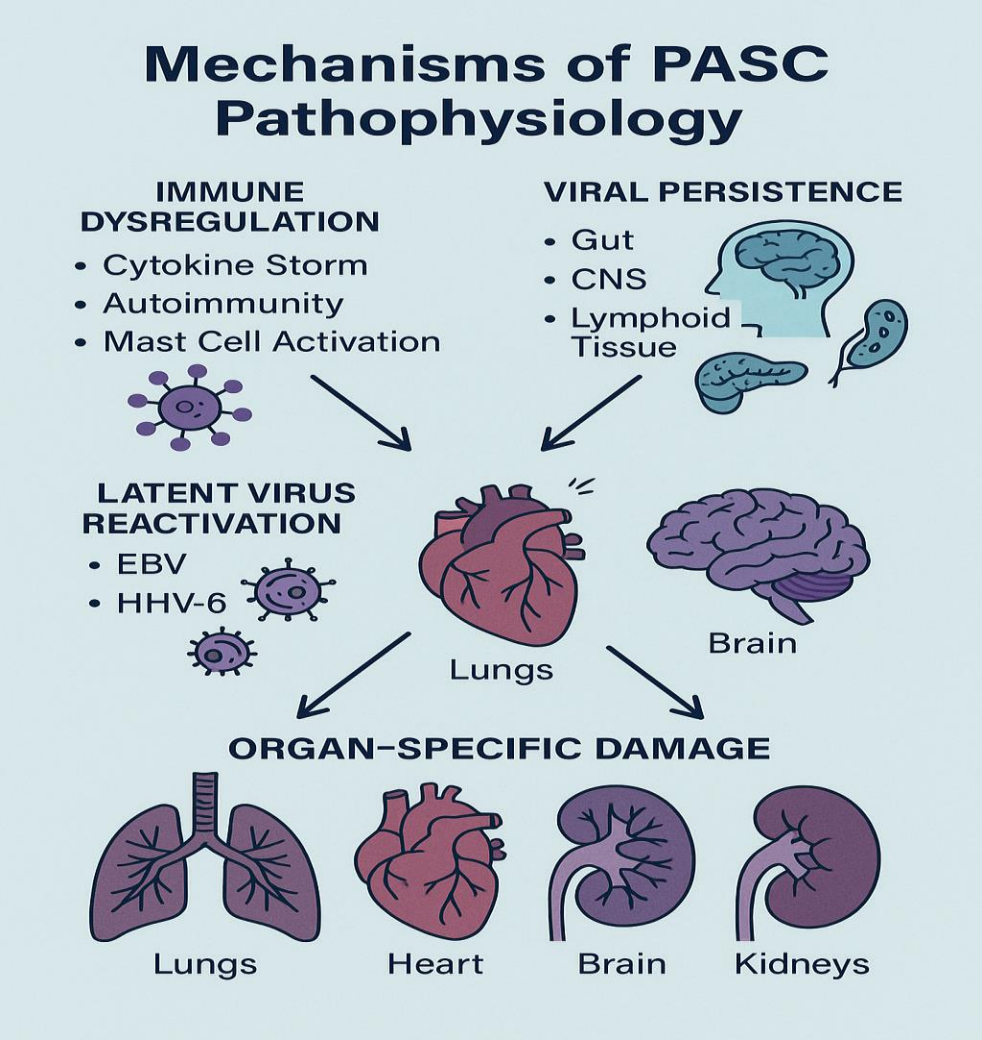

Figure 1. The interconnected mechanisms of PASC Pathophysiology.

acute kidney injury (HR 2.14) and chronic dysmotility reported, suggesting ACE2-mediated damage and autonomic dysfunction (Lam et al., 2023; Brooks & Bhatt, 2021). These findings point toward a systemic nature of PASC, which requires integrated diagnostic and therapeutic approaches. Figure 1 represents the interconnected mechanisms of PASC Pathophysiology.

3. Multidisciplinary treatment approaches

3.1. Integrated Care Models

Multisystem presentation of PASC involves multidisciplinary care. Yale New Haven Long COVID Multidisciplinary Care Center involves cardiologists, neurologists, pulmonologists, gastroenterologists, and mental health experts for caring for multiple varied symptoms (Fogerty et al., 2022). Effective models are based on five principles, including a core lead team, multidisciplinary skills, comprehensive diagnosis, patient-centered care, and scalability with demand (Chou et al., 2024). Practice-based models, typically primary care-led, are for targeted populations, while system-based models harness teleservices for maximizing accessibility, particularly for underserved groups (Parker et al., 2021).

It requires cross-specialty collaboration, standardised pathways, and patient navigation mechanisms for coordinating care. UK National Health Service (NHS) long COVID clinics, for example, employ integrated care pathways, integrating specialist referral and community care (van der Feltz-Cornelis et al., 2024). These models improve symptom control but are challenged by scalability issues to manage global demand, particularly for low-resource environments.

3.2. Pharmacologic interventions

Pharmacological treatments target PASC-specific pathways. NSAIDs reduce cardiovascular syndrome-related myocardial inflammation within PASC, and at six months, improvement of myocardial abnormalities is shown by cardiac MRI (Gyöngyösi et al., 2023). Antihistamines, such as famotidine, are being evaluated for MCAS-related symptoms, with reduced anecdotal fatigue and cognitive fog, and a randomized controlled trial is needed (Davis et al., 2023). Antiviral treatments, such as nirmatrelvir/ritonavir (Paxlovid), target viral reservoir depletion, and trials for prevention and treatment of PASC are ongoing (Fogerty et al., 2022).

Immunomodulatory drugs, including low-dose corticosteroids, are also under investigation for persistent inflammation, but with contentious use due to immunosuppression risks (Fernández-de-Las-Peñas et al., 2022). Early NSAID administration is also recognized to hinder antiviral responses, and timing should thus be used with caution (Gyöngyösi et al., 2023). These therapies point to the requirement for precision medicine strategies, with patient-specific targeting of treatments.

3.3. R**ehabilitation and Supportive Therapy**

Rehabilitation is a mainstay of PASC care. Pulmonary rehabilitation, including aerobic and strength exercises, enhances dyspnea and exercise capacity among those with pulmonary sequelae, with an average increase of 50 meters of six-minute walk distance (Parker et al., 2021). Cognitive rehabilitation, including cognitive behavioral therapy (CBT) and mindfulness-based stress reduction, is applied for neurocognitive and psychiatric symptom management, with heterogeneous evidence based on adherence and symptom severity (Sisó-Almirall et al., 2021).

Exercise programs must be tailored so that post-exertional malaise, a hallmark of PASC and of ME/CFS, is avoided. Graded exercise, with a start at low intensities, can facilitate musculoskeletal healing but must be carefully supervised lest it actually worsens symptoms (Retornaz et al., 2022). Nutritional advice and gut microbiota modulation, such as with probiotics, are emerging therapies for gastrointestinal symptom control, based upon evidence of dysbiosis in PASC (Brooks & Bhatt, 2021). Treatments point towards customized, multi-professional rehabilitation (Figure 2).

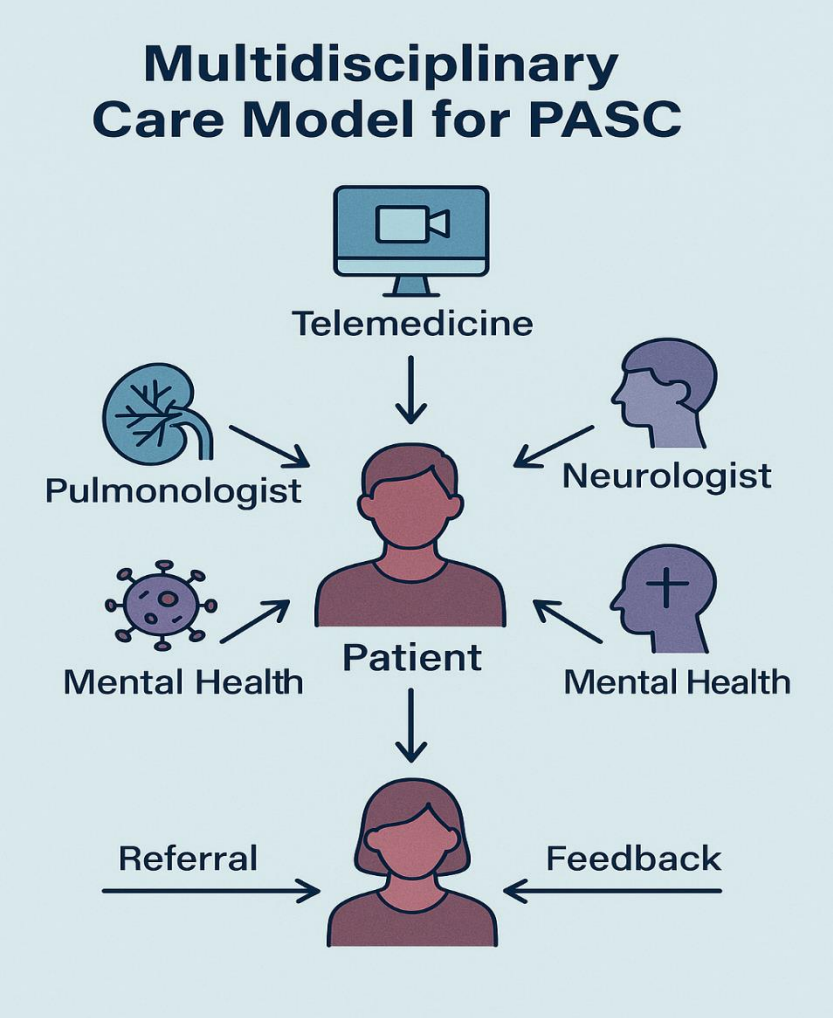

Figure 2. The multidisciplinary care model for PASC.

4. Challenges of Implementation

The implementation of the PASC model is facing huge challenges. Rural regions do not have multidisciplinary staff, and only 20% of U.S. counties have necessary access to specialist clinics for extended COVID (Chou et al., 2024). High patient volumes overburden health systems, with waiting times of over three months for some regions (van der Feltz-Cornelis et al., 2024). Inadequate insurance coverage disproportionately affects those who are underinsured, increasing health inequities (Chou et al., 2024). Primary care integration is necessary but is threatened by staff shortages, with 30% of primary care American clinicians experiencing burnout (Sisó-Almirall et al., 2021). Teleservices are a solution but require robust digital infrastructure for engagement with vulnerable groups, mirrored by the call for transformation of the system.

5. Long-term effects

The prevalence of PASC is reported to range from 10% to 80% because of population heterogeneity and the range of diagnostic criteria (Woodrow et al., 2023). 36% prevalence has been reported among a university population, with increased prevalence among women, unvaccinated individuals, and those with severe COVID-19 (Landry et al., 2023). Symptoms are fatigue (51%), dyspnea (40%), cognitive impairment (35%), and chest pain (30%), which persist for months to years (Nalbandian et al., 2021). Symptoms are categorized based on factor analysis into cardiopulmonary, neurological, and musculoskeletal categories,

with reduced quality of life and work capacity (Peter et al., 2022). The symptom patterns reflect differing phenotypes of PASC, which must be targeted separately.

Long-term consequences vary with severe illness acutely. Non-hospitalized individuals face a greater risk of death within 1 year (incidence rate ratio: 1.15) that later declines, though the risk of hospitalization is increased up to 19 months (Xie et al., 2023). Hospitalized individuals experience a greater risk of death (incidence rate ratio: 1.29) with a severe load of PASC, contributing 90 disability-adjusted life years (DALYs) per 1,000 people by year 3 (Cai et al., 2024). Risks are increased by reinfection, with an HR for death of 2.17, for hospitalization of 3.32, and for sequelae of PASC of 1.74 (Bowe et al., 2022). This points toward the overall impact of PASC on health care systems.

PASC's systemic consequences persist throughout organ systems. Cardiovascular consequences include increased risk of heart failure (HR 1.72), atrial fibrillation (HR 1.66), and ischemic stroke (HR 1.53), particularly among hospitalised individuals (Lam et al., 2023). Pulmonary complications, including interstitial lung disease and reduced diffusing capacity, are present in 20–30% of survivors, with resulting chronic respiratory dysfunction (Babar et al., 2024). Neuropsychiatric illness, including anxiety (HR 1.65), depression (HR 1.55), and post-traumatic stress disorder (HR 1.52), is prevalent, with reduced quality of life (Lam et al., 2023). Renal complications, including acute kidney injury (HR 2.14), and gastrointestinal issues, including dysmotility and irritable bowel syndrome, further demonstrate PASC's multisystem impact (Lam et al., 2023; Brooks & Bhatt, 2021).

Vaccination lowers the risk for PASC considerably, with a boosted immune status being 30–50% lower prevalence compared with unvaccinated individuals (Landry et al., 2023). Prevaccination studies, however, tend to overestimate risk for vaccine individuals (Xie et al., 2023). New variants, such as Omicron, present a lower incidence of PASC, which could be a function of lower pathogenicity, although evidence is preliminary (Spiliopoulos et al., 2023). These patterns hint at a changing epidemiology, with a need for variant-specific studies for prevention.

6. Socioeconomic and psychological implications

PASC's long-term effects extend into psychological and socioeconomic health. 20% of all PASC patients are expected to experience reduced work capacity, with economic losses totaling $3.7 trillion globally (Cutler, 2022). Mental illness, including depression and anxiety, worsens feelings of loneliness, with 40% of patients reporting stigma for continuing to experience ongoing symptoms (Sisó-Almirall et al., 2021). Women, minority groups, and lower-income individuals disproportionately experience its impact, suggesting the need for integrated care models with psychosocial consideration (Chou et al., 2024).

7. Policy and Practice Implications

The infrastructure for PASC must become a priority within the health system. Workforce training and an increase in telemedicine are required to develop multidisciplinary clinics, such as Yale and the NHS have created (Fogerty et al., 2022; van der Feltz-Cornelis et al., 2024). Policy must reduce burnout among providers, incentivize clinician engagement for payment, and require insurance for reimbursement for care for PASC, with a focus on underinsured individuals (Chou et al., 2024). Global consensus, abetted by groups like the WHO, must standardize definitions, exchange data, and generate evidence-based practice (World Health Organization, 2021). Public education must also reduce stigmatization, with increased knowledge of PASC as an accepted, chronic disease.

8. Conclusion

PASC is a systemic, multifaceted illness with an overwhelming global health impact. Its pathophysiology, driven by immune dysregulation, viral persistence, microvasculature damage, and organ-specific damage, supports a wide range of chronic symptom patterns. Care models are needed that are multidisciplinary, including pharmacologic, rehabilitative, and support therapies, yet are limited by scalability and accessibility. Outcomes over the longer term show elevated mortality, hospitalization, and risk by organ, heightened vulnerability in hospitalized cases, yet potentially abrogated by vaccine and less virulent strains.

Socio-economic and psychiatric consequences further compound PASC's impact, disproportionately so among vulnerable groups. Research deficits—standardized definitions, mechanistic understanding, longitudinal follow-up, impact on treatments, and on health equity—take priority. Through disciplined research, innovative care models, and targeted policy, health care systems are able to protect against the impact of PASC, improving outcomes for millions globally.

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الدليل الحالي على الفيسيولوجيا المرضية، النهج العلاجي متعدد التخصصات، والنتائج طويلة الأمد لمضاعفات ما بعد حاد لفيروس كورونا (كوفيد-19): مراجعة شاملة

الملخص

تؤثر متلازمة ما بعد الإصابة الحادة بفيروس كورونا (PASC)، والمعروفة أيضًا باسم كوفيد الطويل، على ملايين الأشخاص حول العالم، وتظهر على شكل أعراض مزمنة متعددة الأنظمة بعد الإصابة الحادة بفيروس كوفيد-19. يجمع هذا الاستعراض المنهجي أحدث البيانات حول الفيزيولوجيا المرضية المعقدة لـ PASC، والعلاجات متعددة التخصصات الجديدة، والنتائج السريرية طويلة الأمد. يستكشف العمليات الرئيسية، بما في ذلك اضطراب المناعة المتميز بعواصف السيتوكين، استمرار الفيروس في خزانات الأنسجة، الإصابة الدقيقة للأوعية الدموية التي تؤدي إلى التخثر، والإصابات الخاصة بالأعضاء التي تشمل الجهاز التنفسي، والقلب، والجهاز العصبي. يقيّم الاستعراض نماذج الرعاية المتكاملة التي تجمع بين خبراء متنوعين، بما في ذلك أطباء الرئة، وأطباء القلب، وأطباء الأعصاب، للتعامل مع الظهور المتغير لـ PASC. تشمل النتائج المقيّمة على مدى ثلاث سنوات من الإصابة الأولية زيادة في مخاطر الوفاة، وارتفاع احتمالية الدخول إلى المستشفى، وظهور أمراض طبية مزمنة، خاصة بين أولئك الذين تأثروا بشدة. هناك، في الواقع، تحديات كبيرة يجب معالجتها، بما في ذلك وجود معايير تشخيصية متغيرة، ونقص البيانات الشاملة حول فعالية وسائط العلاج المختلفة، وتفاوتات شديدة في الوصول إلى الرعاية الصحية، خاصة في المناطق المحرومة التي تواجه حواجز أخرى. يسلط هذا الاستعراض الضوء على الحاجة الملحة لإنشاء خوارزميات تشخيصية موحدة لضمان توحيد التشخيص، وإجراء تجارب سريرية عشوائية شاملة لتقييم التدخلات العلاجية بشكل كامل، وتطوير نماذج رعاية عادلة قادرة على مواجهة الفوارق الحالية في النظام الصحي بكفاءة. يهدف هذا المشروع إلى تقليل العبء العالمي الهائل لـ PASC من خلال البحث والسياسات، وبالتالي تحسين جودة الحياة للأفراد المتضررين وتعزيز أنظمة الصحة العالمية.

الكلمات المفتاحية: كوفيد الطويل، PASC، الفيزيولوجيا المرضية، الرعاية متعددة التخصصات، العدالة الصحية