

**Research Advisory Committee on  
Gulf War Veterans' Illnesses (RACGWVI)  
— PubMed Research Citations  
Concerning Long Haul COVID-19  
July, August, September 2022**

Prepared by Staff of the RACGWVI.

## **RACGWVI: Long Haul COVID-19 — PubMed Citations for July, Aug, Sept 2022**

The following is a selection of published research projects that focus on Long Haul COVID-19 for the months of July, August and September 2022.

This research alert supports the RACGWVI recommendation three, “Initiate research on the relationship between COVID-19, long-haul COVID-19, and their impact on GWI” of the four recommendations presented to the Secretary of Veterans Affairs. For further VA research updates please visit, VA RESEARCH CURRENTS — Research News from the U.S. Department of Veterans Affairs. [VA Research Currents - Home](#)

Please note, due to the evolving nature of COVID-19 (SARS-CoV-2) the terms Long, Long Haul, Post-acute and Post-acute Sequelae (PASC) all refer to the same long-term, multi-symptom illness caused by COVID-19 infection. Ref. [Long COVID or Post-acute Sequelae ...](#)

### **Hyperlinks Guide:**

**Table of Contents:** Each title in the table of contents is linked to that corresponding abstract. Click on the desired title to go to that page (e.g.,).

**Article Title:** The title on each page (excluding table of contents), links to the abstract at PubMed.

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## **Long COVID after breakthrough SARS-CoV-2 infection**

Nat Med. 2022 Jul;28(7):1461-1467. doi: [10.1038/s41591-022-01840-0](https://doi.org/10.1038/s41591-022-01840-0). Epub 2022 May 25.

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### **Abstract**

The post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection—also referred to as Long COVID—have been described, but whether breakthrough SARS-CoV-2 infection (BTI) in vaccinated people results in post-acute sequelae is not clear. In this study, we used the US Department of Veterans Affairs national healthcare databases to build a cohort of 33,940 individuals with BTI and several controls of people without evidence of SARS-CoV-2 infection, including contemporary ( $n = 4,983,491$ ), historical ( $n = 5,785,273$ ) and vaccinated ( $n = 2,566,369$ ) controls. At 6 months after infection, we show that, beyond the first 30 days of illness, compared to contemporary controls, people with BTI exhibited a higher risk of death (hazard ratio (HR) = 1.75, 95% confidence interval (CI): 1.59, 1.93) and incident post-acute sequelae (HR = 1.50, 95% CI: 1.46, 1.54), including cardiovascular, coagulation and hematologic, gastrointestinal, kidney, mental health, metabolic, musculoskeletal and neurologic disorders. The results were consistent in comparisons versus the historical and vaccinated controls. Compared to people with SARS-CoV-2 infection who were not previously vaccinated ( $n = 113,474$ ), people with BTI exhibited lower risks of death (HR = 0.66, 95% CI: 0.58, 0.74) and incident post-acute sequelae (HR = 0.85, 95% CI: 0.82, 0.89). Altogether, the findings suggest that vaccination before infection confers only partial protection in the post-acute phase of the disease; hence, reliance on it as a sole mitigation strategy may not optimally reduce long-term health consequences of SARS-CoV-2 infection. The findings emphasize the need for continued optimization of strategies for primary prevention of BTI and will guide development of post-acute care pathways for people with BTI.

**Long COVID: What We Know Now**

Am J Nurs. 2022 Jul 1;122(7):20-22. doi: [10.1097/01.NAJ.0000842232.15530.f1](https://doi.org/10.1097/01.NAJ.0000842232.15530.f1).

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**Abstract**

A growing population struggles with ongoing health problems.

**Long COVID: aiming for a consensus**

Lancet Respir Med. 2022 Jul;10(7):632-634. doi: [10.1016/S2213-2600\(22\)00135-7](https://doi.org/10.1016/S2213-2600(22)00135-7). Epub 2022 May 4.

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**No abstract available**



**ESCMID rapid guidelines for assessment and management of long COVID**

Clin Microbiol Infect. 2022 Jul;28(7):955-972. doi: [10.1016/j.cmi.2022.02.018](https://doi.org/10.1016/j.cmi.2022.02.018). Epub 2022 Feb 17.

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**Abstract**

**Scope:** The aim of these guidelines is to provide evidence-based recommendations for the assessment and management of individuals with persistent symptoms after acute COVID-19 infection and to provide a definition for this entity, termed 'long COVID'.

**Methods:** We performed a search of the literature on studies addressing epidemiology, symptoms, assessment, and treatment of long COVID. The recommendations were grouped by these headings and by organ systems for assessment and treatment. An expert opinion definition of long COVID is provided. Symptoms were reviewed by a search of the available literature. For assessment recommendations, we aimed to perform a diagnostic meta-analysis, but no studies provided relevant results. For treatment recommendations we performed a systematic review of the literature in accordance with the PRISMA statement. We aimed to evaluate patient-related outcomes, including quality of life, return to baseline physical activity, and return to work. Quality assessment of studies included in the systematic review is provided according to study design.

**Recommendations:** Evidence was insufficient to provide any recommendation other than conditional guidance. The panel recommends considering routine blood tests, chest imaging, and pulmonary functions tests for patients with persistent respiratory symptoms at 3 months. Other tests should be performed mainly to exclude other conditions according to symptoms. For management, no evidence-based recommendations could be provided. Physical and respiratory rehabilitation should be considered. On the basis of limited evidence, the panel suggests designing high-quality prospective clinical studies/trials, including a control group, to further evaluate the assessment and management of individuals with persistent symptoms of COVID-19.

**Proposed subtypes of post-COVID-19 syndrome (or long-COVID) and their respective potential therapies**

Rev Med Virol. 2022 Jul;32(4):e2315. doi: [10.1002/rmv.2315](https://doi.org/10.1002/rmv.2315). Epub 2021 Dec 9.

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**Abstract**

The effects of coronavirus disease 2019 (COVID-19), a highly transmissible infectious respiratory disease that has initiated an ongoing pandemic since early 2020, do not always end in the acute phase. Depending on the study referred, about 10%-30% (or more) of COVID-19 survivors may develop long-COVID or post-COVID-19 syndrome (PCS), characterised by persistent symptoms (most commonly fatigue, dyspnoea, and cognitive impairments) lasting for 3 months or more after acute COVID-19. While the pathophysiological mechanisms of PCS have been extensively described elsewhere, the subtypes of PCS have not. Owing to its highly multifaceted nature, this review proposes and characterises six subtypes of PCS based on the existing literature. The subtypes are non-severe COVID-19 multi-organ sequelae (NSC-MOS), pulmonary fibrosis sequelae (PFS), myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS), post-intensive care syndrome (PICS) and medical or clinical sequelae (MCS). Original studies supporting each of these subtypes are documented in this review, as well as their respective symptoms and potential interventions. Ultimately, the subtyping proposed herein aims to provide better clarity on the current understanding of PCS.

## Identifying who has long COVID in the USA: a machine learning approach using N3C data

Lancet Digit Health. 2022 Jul;4(7):e532-e541. doi: [10.1016/S2589-7500\(22\)00048-6](https://doi.org/10.1016/S2589-7500(22)00048-6). Epub 2022 May 16.

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### Abstract

**Background:** Post-acute sequelae of SARS-CoV-2 infection, known as long COVID, have severely affected recovery from the COVID-19 pandemic for patients and society alike. Long COVID is characterised by evolving, heterogeneous symptoms, making it challenging to derive an unambiguous definition. Studies of electronic health records are a crucial element of the US National Institutes of Health's RECOVER Initiative, which is addressing the urgent need to understand long COVID, identify treatments, and accurately identify who has it—the latter is the aim of this study.

**Methods:** Using the National COVID Cohort Collaborative's (N3C) electronic health record repository, we developed XGBoost machine learning models to identify potential patients with long COVID. We defined our base population (n=1 793 604) as any non-deceased adult patient (age ≥18 years) with either an International Classification of Diseases-10-Clinical Modification COVID-19 diagnosis code (U07.1) from an inpatient or emergency visit, or a positive SARS-CoV-2 PCR or antigen test, and for whom at least 90 days have passed since COVID-19 index date. We examined demographics, health-care utilisation, diagnoses, and medications for 97 995 adults with COVID-

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19. We used data on these features and 597 patients from a long COVID clinic to train three machine learning models to identify potential long COVID among all patients with COVID-19, patients hospitalised with COVID-19, and patients who had COVID-19 but were not hospitalised. Feature importance was determined via Shapley values. We further validated the models on data from a fourth site.

**Findings:** Our models identified, with high accuracy, patients who potentially have long COVID, achieving areas under the receiver operator characteristic curve of 0·92 (all patients), 0·90 (hospitalised), and 0·85 (non-hospitalised). Important features, as defined by Shapley values, include rate of health-care utilisation, patient age, dyspnoea, and other diagnosis and medication information available within the electronic health record.

**Interpretation:** Patients identified by our models as potentially having long COVID can be interpreted as patients warranting care at a specialty clinic for long COVID, which is an essential proxy for long COVID diagnosis as its definition continues to evolve. We also achieve the urgent goal of identifying potential long COVID in patients for clinical trials. As more data sources are identified, our models can be retrained and tuned based on the needs of individual studies.

**Registered clinical trials investigating treatment of long COVID: a scoping review and recommendations for research**

Infect Dis (Lond). 2022 Jul;54(7):467-477. doi: [10.1080/23744235.2022.2043560](https://doi.org/10.1080/23744235.2022.2043560). Epub 2022 Mar 14.

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**Abstract**

**Background:** A considerable proportion of individuals report persistent, debilitating and disparate symptoms despite resolution of acute COVID-19 infection (i.e. long COVID). Numerous registered clinical trials investigating treatment of long COVID are expected to be completed in 2021-2022. The aim of this review is to provide a scope of the candidate treatments for long COVID. A synthesis of ongoing long COVID clinical trials can inform methodologic approaches for future studies and identify key research vistas.

**Methods:** Scoping searches were conducted on multiple national and international clinical trial registries. Interventional trials testing treatments for long COVID were selected. The search timeline was from database inception to 28 July 2021.

**Results:** This scoping review included 59 clinical trial registration records from 22 countries with a total projected enrolment of 6718. Considerable heterogeneity was exhibited amongst component records with respect to the characterization of long COVID (i.e. name, symptoms- including frequency, intensity, trajectory and duration- mode of ascertainment, and definition of acute phase). In addition, the majority of proposed interventions were non-pharmacological and either targeted multiple long COVID symptoms simultaneously, or focussed on treatment of respiratory/pulmonary sequelae. Multiple interventions targeted inflammation, as well as tissue oxygenation and cellular recovery, and several interventions were repurposed from analogous conditions.

**Conclusions:** The results of this scoping review investigating ongoing clinical trials testing candidate treatments for long COVID suggest that a greater degree of definitional stringency and

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homogeneity is needed insofar as the characterization of long COVID and inclusion/exclusion criteria.

## Neuropsychologic Profiles and Cerebral Glucose Metabolism in Neurocognitive Long COVID Syndrome

J Nucl Med. 2022 Jul;63(7):1058-1063. doi: [10.2967/jnumed.121.262677](https://doi.org/10.2967/jnumed.121.262677). Epub 2021 Oct 14.

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### Abstract

During the coronavirus disease 2019 (COVID-19) pandemic, Long COVID syndrome, which impairs patients through cognitive deficits, fatigue, and exhaustion, has become increasingly relevant. Its underlying pathophysiology, however, is unknown. In this study, we assessed cognitive profiles and regional cerebral glucose metabolism as a biomarker of neuronal function in outpatients with long-term neurocognitive symptoms after COVID-19. Methods: Outpatients seeking neurologic counseling with neurocognitive symptoms persisting for more than 3 mo after polymerase chain reaction (PCR)-confirmed COVID-19 were included prospectively between June 16, 2020, and January 29, 2021. Patients ( $n = 31$ ; age,  $53.6 \pm 2.0$  y) in the long-term phase after COVID-19 ( $202 \pm 58$  d after positive PCR) were assessed with a neuropsychologic test battery. Cerebral 18F-FDG PET imaging was performed in 14 of 31 patients. Results: Patients self-reported impaired attention, memory, and multitasking abilities (31/31), word-finding difficulties (27/31), and fatigue (24/31). Twelve of 31 patients could not return to the previous level of independence/employment. For all cognitive domains, average group results of the neuropsychologic test battery showed no impairment, but deficits ( $z$  score  $< -1.5$ ) were present on a single-patient level mainly in the domain of visual memory (in 7/31; other domains  $\leq 2/31$ ). Mean Montreal Cognitive Assessment performance (27/30 points) was above the cutoff value for detection of cognitive impairment ( $< 26$  points), although 9 of 31 patients performed slightly below this level (23-25 points). In the subgroup of patients who underwent 18F-FDG PET, we found no significant changes of regional cerebral glucose metabolism. Conclusion: Long COVID patients self-report uniform symptoms hampering their ability to work in a relevant fraction. However, cognitive testing showed minor impairments only on a single-patient level approximately 6 mo after the infection, whereas functional imaging revealed no distinct pathologic changes. This clearly deviates from previous findings in subacute COVID-19 patients, suggesting that underlying neuronal causes are different and possibly related to the high prevalence of fatigue.

**Big data and long COVID**

Lancet Digit Health. 2022 Jul;4(7):e477. doi: [10.1016/S2589-7500\(22\)00113-3](https://doi.org/10.1016/S2589-7500(22)00113-3).

The Lancet Digital Health

PMID: 35750397 PMCID: PMC9214483 DOI: [10.1016/S2589-7500\(22\)00113-3](https://doi.org/10.1016/S2589-7500(22)00113-3)

No abstract available



**Evidence for impaired chronotropic responses to and recovery from 6-minute walk test in women with post-acute COVID-19 syndrome**

Exp Physiol. 2022 Jul;107(7):722-732. doi: [10.1113/EP089965](https://doi.org/10.1113/EP089965). Epub 2021 Nov 17.

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**Abstract**

**New findings:** What is the central question of this study? Are chronotropic responses to a 6-minute walk test different in women with post-acute coronavirus disease 2019 (COVID-19) syndrome compared with control subjects? What is the main finding and its importance? Compared with control subjects, the increase in heart rate was attenuated and recovery delayed after a 6-minute walk test in participants after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Women reporting specific symptoms at time of testing had greater impairments compared with control subjects and SARS-CoV-2 participants not actively experiencing these symptoms. Such alterations have potential to constrain not only exercise tolerance but also participation in free-living physical activity in women during post-acute recovery from COVID-19.

**Abstract:** The short-term cardiopulmonary manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are well defined. However, the implications of cardiopulmonary sequelae, persisting beyond acute illness, on physical function are largely unknown. Herein, we characterized heart rate responses to and recovery from a 6-minute walk test (6MWT) in women ~3 months after mild-to-moderate SARS-CoV-2 infection compared with non-infected control subjects. Forty-five women (n = 29 SARS-CoV-2; n = 16 controls; age = 56 ± 11 years; body mass index = 25.8 ± 6.0 kg/m<sup>2</sup>) completed pulmonary function testing and a 6MWT. The SARS-CoV-2 participants demonstrated reduced total lung capacity (84 ± 8 vs. 93 ± 13%; P = 0.006), vital capacity (87 ± 10 vs. 93 ± 10%; P = 0.040), functional residual capacity (75 ± 16 vs. 88 ± 16%; P = 0.006) and residual volume (76 ± 18 vs. 93 ± 22%; P = 0.001) compared with control subjects. No between-group differences were observed in 6MWT distance (P = 0.194); however, the increase in heart rate with exertion was attenuated among SARS-CoV-2 participants compared with control subjects (+52 ± 20 vs. +65 ± 18 beats/min; P = 0.029). The decrease in heart rate was also delayed for minutes 1-5 of recovery among SARS-CoV-2 participants (all P < 0.05). Women reporting specific symptoms at the time of testing had greater impairments compared with control subjects and SARS-CoV-2 participants not actively experiencing these symptoms. Our findings provide evidence for marked differences in chronotropic responses to and recovery from a 6MWT in women several months after acute SARS-CoV-2 infection.

**Post-COVID-19 Depressive Symptoms: Epidemiology, Pathophysiology, and Pharmacological Treatment**

CNS Drugs. 2022 Jul;36(7):681-702. doi: [10.1007/s40263-022-00931-3](https://doi.org/10.1007/s40263-022-00931-3). Epub 2022 Jun 21.

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**Abstract**

The Coronavirus Disease 2019 (COVID-19) pandemic is still spreading worldwide over 2 years since its outbreak. The psychopathological implications in COVID-19 survivors such as depression, anxiety, and cognitive impairments are now recognized as primary symptoms of the "post-acute COVID-19 syndrome." Depressive psychopathology was reported in around 35% of patients at short, medium, and long-term follow-up after the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection. Post-COVID-19 depressive symptoms are known to increase fatigue and affect neurocognitive functioning, sleep, quality of life, and global functioning in COVID-19 survivors. The psychopathological mechanisms underlying post-COVID-19 depressive symptoms are mainly related to the inflammation triggered by the peripheral immune-inflammatory response to the viral infection and to the persistent psychological burden during and after infection. The large number of SARS-CoV-2-infected patients and the high prevalence of post-COVID-19 depressive symptoms may significantly increase the pool of people suffering from depressive disorders. Therefore, it is essential to screen, diagnose, treat, and monitor COVID-19 survivors' psychopathology to counteract the depression disease burden and related years of life lived with disability. This paper reviews the current literature in order to synthesize the available evidence regarding epidemiology, clinical features, neurobiological underpinning, and pharmacological treatment of post-COVID-19 depressive symptoms.

**Cardiometabolic syndrome - an emergent feature of Long COVID?**

Nat Rev Immunol. 2022 Jul;22(7):399-400. doi: [10.1038/s41577-022-00739-8](https://doi.org/10.1038/s41577-022-00739-8).

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**Abstract**

Large-scale clinical studies on the post-infectious impacts of SARS-CoV-2 have suggested that patients who have recovered from acute infection have increased risk for cardiometabolic syndrome-associated morbidities such as diabetes, chronic kidney disease and heart failure. Initial studies have taken the first steps towards unravelling the molecular processes that may be driving these findings, including the role of immune and inflammatory factors, but a comprehensive aetiology remains unclear. Given that cardiometabolic syndrome progression in patients with Long COVID may pose a significant global health and economic burden post pandemic, there is an emergent need to identify therapeutic targets and treatment options.

**Adjuncts to treatments for long COVID**

Br J Community Nurs. 2022 Jul 2;27(7):318-319. doi: [10.12968/bjcn.2022.27.7.318](https://doi.org/10.12968/bjcn.2022.27.7.318).

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**No abstract available**

**Mast cell activation syndrome and the link with long COVID**

Br J Hosp Med (Lond). 2022 Jul 2;83(7):1-10. doi: [10.12968/hmed.2022.0123](https://doi.org/10.12968/hmed.2022.0123). Epub 2022 Jul 26.

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**Abstract**

Mast cells are innate immune cells found in connective tissues throughout the body, most prevalent at tissue-environment interfaces. They possess multiple cell-surface receptors which react to various stimuli and, after activation, release many mediators including histamine, heparin, cytokines, prostaglandins, leukotrienes and proteases. In mast cell activation syndrome, excessive amounts of inflammatory mediators are released in response to triggers such as foods, fragrances, stress, exercise, medications or temperature changes. Diagnostic markers may be difficult to assess because of their rapid degradation; these include urinary N-methyl histamine, urinary prostaglandins D2, DM and F2 $\alpha$  and serum tryptase (which is stable) in the UK. Self-management techniques, medications and avoiding triggers may improve quality of life. Treatments include mast cell mediator blockers, mast cell stabilisers and anti-inflammatory agents. 'Long COVID' describes post-COVID-19 syndrome when symptoms persist for more than 12 weeks after initial infection with no alternative diagnosis. Both mast cell activation syndrome and long COVID cause multiple symptoms. It is theorised that COVID-19 infection could lead to exaggeration of existing undiagnosed mast cell activation syndrome, or could activate normal mast cells owing to the persistence of viral particles. Other similarities include the relapse-remission cycle and improvements with similar treatments. Importantly, however, aside from mast cell disorders, long COVID could potentially be attributed to several other conditions.

**Association between D-dimer levels and post-acute sequelae of SARS-CoV-2 in patients from a tertiary care center**

Biomark Med. 2022 Jul 5. doi: [10.2217/bmm-2022-0050](https://doi.org/10.2217/bmm-2022-0050). Online ahead of print.

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**Abstract**

Background: Post-acute sequelae of SARS-CoV-2 (PASC) is becoming an important concern in SARS-CoV-infected people. The pathophysiology behind PASC is unknown, and much study should be carried out to check the D-dimer levels in the PASC population. Methodology: In COVID-19 patients, the D-dimer level was checked during admission and discharge, and a follow-up study was carried out after 3 and 6 months of discharge. The results were compared with the appropriate statistical tests. Results: Patients had a high D-dimer value than the normal range, and the elevated D-dimer value continued to increase up to 6 months. Conclusion: Persistence of PASC has a direct correlation with increased D-dimer values. D-dimer can be used as biomarker in PASC patients.

**Prevalence and risk factors of post-COVID-19 condition in adults and children at 6 and 12 months after hospital discharge: a prospective, cohort study in Moscow (StopCOVID)**

BMC Med. 2022 Jul 6;20(1):244. doi: [10.1186/s12916-022-02448-4](https://doi.org/10.1186/s12916-022-02448-4).

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## RACGWVI: Long Haul COVID-19 — PubMed Citations for July, Aug, Sept 2022

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### Abstract

**Background:** Previous studies assessing the prevalence of COVID-19 sequelae in adults and children were performed in the absence of an agreed definition. We investigated prevalence of post-COVID-19 condition (PCC) (WHO definition), at 6- and 12-months follow-up, amongst previously hospitalised adults and children and assessed risk factors.

**Methods:** Prospective cohort study of children and adults with confirmed COVID-19 in Moscow, hospitalised between April and August, 2020. Two follow-up telephone interviews, using the



## **RACGWVI: Long Haul COVID-19 — PubMed Citations for July, Aug, Sept 2022**

International Severe Acute Respiratory and Emerging Infection Consortium survey, were performed at 6 and 12 months after discharge.

**Results:** One thousand thirteen of 2509 (40%) of adults and 360 of 849 (42%) of children discharged participated in both the 6- and 12-month follow-ups. PCC prevalence was 50% (95% CI 47-53) in adults and 20% (95% CI 16-24) in children at 6 months, with decline to 34% (95% CI 31-37) and 11% (95% CI 8-14), respectively, at 12 months. In adults, female sex was associated with PCC at 6- and 12-month follow-up (OR 2.04, 95% CI 1.57 to 2.65) and (OR 2.04, 1.54 to 2.69), respectively. Pre-existing hypertension (OR 1.42, 1.04 to 1.94) was associated with post-COVID-19 condition at 12 months. In children, neurological comorbidities were associated with PCC both at 6 months (OR 4.38, 1.36 to 15.67) and 12 months (OR 8.96, 2.55 to 34.82) while allergic respiratory diseases were associated at 12 months (OR 2.66, 1.04 to 6.47).

**Conclusions:** Although prevalence of PCC declined one year after discharge, one in three adults and one in ten children experienced ongoing sequelae. In adults, females and persons with pre-existing hypertension, and in children, persons with neurological comorbidities or allergic respiratory diseases are at higher risk of PCC.

## Deriving and validating a risk prediction model for long COVID-19: protocol for an observational cohort study using linked Scottish data

BMJ Open. 2022 Jul 6;12(7):e059385. doi: [10.1136/bmjopen-2021-059385](https://doi.org/10.1136/bmjopen-2021-059385).

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### Abstract

**Introduction:** COVID-19 is commonly experienced as an acute illness, yet some people continue to have symptoms that persist for weeks, or months (commonly referred to as 'long-COVID'). It remains unclear which patients are at highest risk of developing long-COVID. In this protocol, we describe plans to develop a prediction model to identify individuals at risk of developing long-COVID.

**Methods and analysis:** We will use the national Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) platform, a population-level linked dataset of routine electronic healthcare data from 5.4 million individuals in Scotland. We will identify potential indicators for long-COVID by identifying patterns in primary care data linked to information from out-of-hours general practitioner encounters, accident and emergency visits, hospital admissions, outpatient visits, medication prescribing/dispensing and mortality. We will investigate the potential indicators of long-COVID by performing a matched analysis between those with a positive reverse transcriptase PCR (RT-PCR) test for SARS-CoV-2 infection and two control groups: (1) individuals with at least one negative RT-PCR test and never tested positive; (2) the general population (everyone who did not test positive) of Scotland. Cluster analysis will then be used to determine the final definition of the outcome measure for long-COVID. We will then derive, internally and externally validate a prediction model to identify the epidemiological risk factors associated with long-COVID.

**Ethics and dissemination:** The EAVE II study has obtained approvals from the Research Ethics Committee (reference: 12/SS/0201), and the Public Benefit and Privacy Panel for Health and Social Care (reference: 1920-0279). Study findings will be published in peer-reviewed journals and presented at conferences. Understanding the predictors for long-COVID and identifying the patient groups at greatest risk of persisting symptoms will inform future treatments and preventative strategies for long-COVID.

**COVID fog demystified**

Cell. 2022 Jul 7;185(14):2391-2393. doi: [10.1016/j.cell.2022.06.020](https://doi.org/10.1016/j.cell.2022.06.020). Epub 2022 Jun 15.

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**Abstract**

Acute mild respiratory SARS-CoV-2 infection can lead to a more chronic cognitive syndrome known as "COVID fog." New findings from Fernández-Castañeda et al. reveal how glial dysregulation and consequent neural circuit dysfunction may contribute to cognitive impairments in long COVID.

## **Long COVID and its Management**

Int J Biol Sci. 2022 Jul 11;18(12):4768-4780. doi: [10.7150/ijbs.75056](https://doi.org/10.7150/ijbs.75056). eCollection 2022.

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### **Abstract**

The pandemic of COVID-19 is the biggest public health crisis in 21st Century. Besides the acute symptoms after infection, patients and society are also being challenged by the long-term health complications associated with COVID-19, commonly known as long COVID. While health professionals work hard to find proper treatments, large amount of knowledge has been accumulated in recent years. In order to deal with long COVID efficiently, it is important for people to keep up with current progresses and take proactive actions on long COVID. For this purpose, this review will first introduce the general background of long COVID, and then discuss its risk factors, diagnostic indicators and management strategies. This review will serve as a useful resource for people to understand and prepare for long COVID that will be with us in the foreseeable future.

**At the Root of 3 "Long" Diseases: Persistent Antigens Inflicting Chronic Damage on the Brain and Other Organs in Gulf War Illness, Long-COVID-19, and Chronic Fatigue Syndrome**

Neurosci Insights. 2022 Jul 22; 17:26331055221114817. doi: [10.1177/26331055221114817](https://doi.org/10.1177/26331055221114817). eCollection 2022.

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**Abstract**

Several foreign antigens such as those derived from viruses and bacteria have been linked to long-term deleterious effects on the brain and other organs; yet, health outcomes subsequent to foreign antigen exposure vary depending in large part on the host's immune system, in general, and on human leukocyte antigen (HLA) composition, in particular. Here we first provide a brief description of 3 conditions characterized by persistent long-term symptoms, namely long-COVID-19, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and Gulf War Illness (GWI), followed by a brief overview of the role of HLA in the immune response to foreign antigens. We then discuss our Persistent Antigen (PA) hypothesis and highlight associations between antigen persistence due to HLA-antigen incongruence and chronic health conditions in general and the 3 "long" diseases above in particular. This review is not intended to cover the breadth and depth of symptomatology of those diseases but is specifically focused on the hypothesis that the presence of persistent antigens underlies their pathogenesis.

**Symptoms and risk factors for long COVID in non-hospitalized adults**

Nat Med. 2022 Aug;28(8):1706-1714. doi: [10.1038/s41591-022-01909-w](https://doi.org/10.1038/s41591-022-01909-w). Epub 2022 Jul 25.

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**Abstract**

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is associated with a range of persistent symptoms impacting everyday functioning, known as post-COVID-19 condition or long COVID. We undertook a retrospective matched cohort study using a UK-based primary care database, Clinical Practice Research Datalink Aurum, to determine symptoms that are associated with confirmed SARS-CoV-2 infection beyond 12 weeks in non-hospitalized adults and the risk factors associated with developing persistent symptoms. We selected 486,149 adults with confirmed SARS-CoV-2 infection and 1,944,580 propensity score-matched adults with no recorded evidence of SARS-CoV-2 infection. Outcomes included 115 individual symptoms, as well as long COVID, defined as a composite outcome of 33 symptoms by the World Health Organization clinical case definition. Cox proportional hazards models were used to estimate adjusted hazard ratios (aHRs) for the outcomes. A total of 62 symptoms were significantly associated with SARS-CoV-2 infection after 12 weeks. The largest aHRs were for anosmia (aHR 6.49, 95% CI 5.02-8.39), hair loss (3.99, 3.63-4.39), sneezing (2.77, 1.40-5.50), ejaculation difficulty (2.63, 1.61-4.28) and reduced libido (2.36, 1.61-3.47). Among the cohort of patients infected with SARS-CoV-2, risk factors for long COVID included female sex, belonging to an ethnic minority, socioeconomic deprivation, smoking, obesity and a wide range of comorbidities. The risk of developing long COVID was also found to be increased along a gradient of decreasing age. SARS-CoV-2 infection is associated with a plethora of symptoms that are associated with a range of sociodemographic and clinical risk factors.

**Long COVID-19: The Need for an Interdisciplinary Approach**

Clin Geriatr Med. 2022 Aug;38(3):533-544. doi: [10.1016/j.cger.2022.03.005](https://doi.org/10.1016/j.cger.2022.03.005). Epub 2022 Mar 21.

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**Abstract**

Long coronavirus disease 2019 (COVID-19) is characterized by persistent COVID-19 symptoms that last for at least 2 months. In the elderly population, apart from the typical symptoms (fatigue, cough, or dyspnea), unspecific symptoms coexist (functional deterioration, cognitive impairment, or delirium) that can mitigate the prevalence of this syndrome in this age group. Its main consequence is the functional decline, leading to sarcopenia, frailty, and disability, in addition to the nutritional and cognitive disorders. Thus, a multicomponent and individualized program (exercise, diet, cognitive stimulation) should be designed for older people with persistent COVID, where new technologies could be useful.



**Long-COVID, Metabolic and Endocrine Disease**

Horm Metab Res. 2022 Aug;54(8):562-566. doi: [10.1055/a-1878-9307](https://doi.org/10.1055/a-1878-9307). Epub 2022 Jun 20.

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**Abstract**

In the aftermath of the corona pandemic, long-COVID or post-acute COVID-19 syndrome still represents a great challenge, and this topic will continue to represent a significant health problem in the coming years. At present, the impact of long-COVID on our health system cannot be fully assessed but according to current studies, up to 40% of people who have been infected with SARS-CoV-2 suffer from clinically relevant symptoms of long-COVID syndrome several weeks to months after the acute phase. The main symptoms are chronic fatigue, dyspnea, and various cognitive symptoms. Initial studies have shown that people with overweight and diabetes mellitus have a higher risk of developing long-COVID associated symptoms. Furthermore, repeated treatment of acute COVID-19 and long-COVID with steroids can contribute to long-term metabolic and endocrine disorders. Therefore, a structured program with rehabilitation and physical activity as well as optimal dietary management is of utmost importance, especially for patients with metabolic diseases and/or long-COVID. Furthermore, the removal of autoantibodies and specific therapeutic apheresis procedures could lead to a significant improvement in the symptoms of long-COVID in individual patients.

## **The Impact of Long COVID-19 on Muscle Health**

Clin Geriatr Med. 2022 Aug;38(3):545-557. doi: [10.1016/j.cger.2022.03.004](https://doi.org/10.1016/j.cger.2022.03.004). Epub 2022 Mar 21.

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### **Abstract**

COVID-19 negatively impacts several organs and systems weeks or months after initial diagnosis. Skeletal muscle can be affected, leading to fatigue, lower mobility, weakness, and poor physical performance. Older adults are at increased risk of developing musculoskeletal symptoms during long COVID. Systemic inflammation, physical inactivity, and poor nutritional status are some of the mechanisms leading to muscle dysfunction in individuals with long COVID. Current evidence suggests that long COVID negatively impacts body composition, muscle function, and quality of life. Muscle mass and function assessments can contribute toward the identification, diagnosis, and management of poor muscle health resulting from long COVID.

**Post-Acute COVID-19 Syndrome for Anesthesiologists: A Narrative Review and a Pragmatic Approach to Clinical Care**

J Cardiothorac Vasc Anesth. 2022 Aug;36(8 Pt A):2727-2737. doi: [10.1053/j.jvca.2021.09.051](https://doi.org/10.1053/j.jvca.2021.09.051). Epub 2021 Oct 3.

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**Abstract**

Post-acute coronavirus disease 2019 (COVID-19) syndrome is a novel, poorly understood clinical entity with life-impacting ramifications. Patients with this syndrome, also known as "COVID-19 long-haulers," often present with nonspecific ailments involving more than one body system. The most common complaints include dyspnea, fatigue, brain fog, and chest pain. There currently is no single agreed-upon definition for post-acute COVID-19 syndrome, but most agree that criterion for this syndrome is the persistence of mental and physical health consequences after initial infection. Given the millions of acute infections in the United States over the course of the pandemic, perioperative providers will encounter these patients in clinical practice in growing numbers. Symptoms of the COVID-19 long-haulers should not be minimized, as these patients are at higher risk for postoperative respiratory complications and perioperative mortality for up to seven weeks after initial illness. Instead, a cautious multidisciplinary preoperative evaluation should be performed. Perioperative care should be viewed through the prism of best practices already in use, such as avoidance of benzodiazepines in patients with cognitive impairment and use of lung-protective ventilation. Recommendations especially relevant to the COVID-19 long-haulers include assessment of critical care myopathies and neuropathies to determine suitable neuromuscular blocking agents and reversal, preoperative workup of insidious cardiac or pulmonary pathologies in previously healthy patients, and, thorough medication review, particularly of anticoagulation regimens and chronic steroid use. In this article, the authors define the syndrome, synthesize the available scientific evidence, and make pragmatic suggestions regarding the perioperative clinical care of COVID-19 long-haulers.

**Aromatherapy blend of thyme, orange, clove bud, and frankincense boosts energy levels in post-COVID-19 female patients: A randomized, double-blinded, placebo controlled clinical trial**

Complement Ther Med. 2022 Aug; 67:102823. doi: [10.1016/j.ctim.2022.102823](https://doi.org/10.1016/j.ctim.2022.102823). Epub 2022 Mar 25.

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**Abstract**

**Background:** A large proportion of individuals who have recovered from an acute COVID-19 infection continue to experience symptoms months later. Post-acute COVID-19 (long-haul COVID-19) can range from serious complications to quality of life symptoms such as fatigue or insomnia. The purpose of this study was to evaluate the potential for inhalation of essential oils to improve energy levels among otherwise healthy female survivors of acute COVID-19 who experience a lack of energy more than five months after recovery. This study was conducted in the United States in late 2021.

**Method:** This was a randomized double blind, placebo controlled trial to evaluate the potential for inhalation of Longevity™, a proprietary essential oil blend manufactured by Young Living Essential Oils (Lehi, Utah, USA), on energy levels among female survivors of COVID-19 who continue to experience fatigue more than 5 months recovery from the acute infection. Forty women were randomized to two groups: intervention and placebo. Both groups inhaled the assigned product twice daily for fourteen consecutive days. Fatigue scores were measured using the Multidimensional Fatigue Symptom Inventory (MFSI). Secondary outcomes included scores on each of the MFSI's ten subscales.

**Results:** Individuals who inhaled the essential oil blend for 2 weeks had significantly lower fatigue scores after controlling for baseline scores, employment status, BMI, olfactory function, and time since diagnosis, with a large effect size ( $F(1,39) = 6.15, p = .020, \text{partial } \eta^2 = 0.198$ ). Subscale analysis identified subscales of vigor, as well as global, behavioral, general, and mental fatigue as benefiting from the intervention. This study provides evidence that a proprietary aromatherapy blend can significantly improve energy levels among women who are experiencing fatigue after recovering from COVID-19.

**Muscle fatigability and post-acute COVID-19 syndrome: A case study**

Physiol Rep. 2022 Aug;10(16):e15391. doi: [10.14814/phy2.15391](https://doi.org/10.14814/phy2.15391).

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**Abstract**

The acute phase of COVID-19 has been well studied, however with increasing post-acute COVID-19 syndrome, much is unknown about its long-term effects. A common symptom in both the acute and post-acute phases has been fatigue, assessed predominantly qualitatively. Here we present a case study objectively assessing neuromuscular fatigability in a young male (27 year, 1.85 m, 78 kg) who continues to experience COVID-19 related fatigue and cognitive dysfunction, including other symptoms, 12+ months post-infection. Prior to infection, he was part of a neuromuscular study forming the basis of our pre-COVID-19 results. The study was repeated 12 months post-COVID-19 infection. Muscle strength, endurance, torque steadiness, voluntary activation, twitch properties, electromyography, and compound muscle action potential were obtained and compared pre- and post-COVID-19. All measurements were done using a dorsiflexion dynamometer in which the participant also was asked to produce a one-minute fatiguing maximal voluntary contraction. Muscle strength, voluntary activation, and fatigability (slope of torque) showed no meaningful differences, suggesting intrinsic neuromuscular properties are not affected. However, torque steadiness was impaired three-fold in the post- compared with pre-COVID-19 test. The participant also reported a higher level of perceived exertion subjectively and a continued complaint of fatigue. These findings indicate that muscle fatigability in post-acute COVID-19 syndrome may not be a limitation of the muscle and its activation, but a perceptual disconnect caused by cognitive impairments relating to physical efforts. This case report suggests the potential value of larger studies designed to assess these features in post-acute COVID-19 syndrome.

## **Long COVID headache**

J Headache Pain. 2022 Aug 1;23(1):93. doi: [10.1186/s10194-022-01450-8](https://doi.org/10.1186/s10194-022-01450-8).

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### **Abstract**

Headache is among the most frequent symptoms persisting or newly developing after coronavirus disease 2019 (COVID-19) as part of the so-called long COVID syndrome. The knowledge on long COVID headache is still limited, however growing evidence is defining the features of this novel condition, in particular regarding clinical characteristics, some pathophysiological mechanisms and first treatment recommendations. Long COVID headache can present in the form of worsening of a preexisting primary headache, or, more specifically, in the form of a new (intermittent or daily) headache starting during the acute infection or after a delay. It often presents together with other long COVID symptoms, most frequently with hyposmia. It can manifest with a migrainous or, more frequently, with a tension-type-like phenotype. Persistent activation of the immune system and trigeminovascular activation are thought to play a role. As there are virtually no treatment studies, treatment currently is largely guided by the existing guidelines for primary headaches with the corresponding phenotype. The present report, a collaborative work of the international group of the Junior Editorial Board of The Journal of Headache and Pain aims to summarize the most recent evidence about long COVID headache and suggests approaches to the diagnosis and treatment of this disorder.

**Long COVID endotheliopathy: hypothesized mechanisms and potential therapeutic approaches**

J Clin Invest. 2022 Aug 1;132(15):e161167. doi: [10.1172/JCI161167](https://doi.org/10.1172/JCI161167).

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**Abstract**

SARS-CoV-2-infected individuals may suffer a multi-organ system disorder known as "long COVID" or post-acute sequelae of SARS-CoV-2 infection (PASC). There are no standard treatments, the pathophysiology is unknown, and incidence varies by clinical phenotype. Acute COVID-19 correlates with biomarkers of systemic inflammation, hypercoagulability, and comorbidities that are less prominent in PASC. Macrovascular thrombosis, a hallmark of acute COVID-19, is less frequent in PASC. Female sex at birth is associated with reduced risk for acute COVID-19 progression, but with increased risk of PASC. Persistent microvascular endotheliopathy associated with cryptic SARS-CoV-2 tissue reservoirs has been implicated in PASC pathology. Autoantibodies, localized inflammation, and reactivation of latent pathogens may also be involved, potentially leading to microvascular thrombosis, as documented in multiple PASC tissues. Diagnostic assays illuminating possible therapeutic targets are discussed.

**European Respiratory Society statement on long COVID follow-up**

Eur Respir J. 2022 Aug 4;60(2):2102174. doi: [10.1183/13993003.02174-2021](https://doi.org/10.1183/13993003.02174-2021). Print 2022 Aug.

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**Abstract**

Patients diagnosed with coronavirus disease 2019 (COVID-19) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection frequently experience symptom burden post-acute infection or post-hospitalisation. We aimed to identify optimal strategies for follow-up care that may positively impact the patient's quality of life (QoL). A European Respiratory Society (ERS) Task Force convened and prioritised eight clinical questions. A targeted search of the literature defined the timeline of "long COVID" as 1-6 months post-infection and identified clinical evidence in the follow-up of patients. Studies meeting the inclusion criteria report an association of characteristics of acute infection with persistent symptoms, thromboembolic events in the follow-up period, and evaluations of pulmonary physiology and imaging. Importantly, this statement reviews QoL consequences, symptom burden, disability and home care follow-up. Overall, the evidence for follow-up care for patients with long COVID is limited.



**Screening and assessment for post-acute COVID-19 syndrome (PACS), guidance by personal pilots and support with individual digital trainings within intersectoral care: a study protocol of a randomized controlled trial**

BMC Infect Dis. 2022 Aug 15;22(1):693. doi: [10.1186/s12879-022-07584-z](https://doi.org/10.1186/s12879-022-07584-z).

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**Abstract**

**Background:** Because the clinical patterns and symptoms that persist after a COVID-19 infection are diverse, a diagnosis of post-acute COVID-19 syndrome (PACS) is difficult to implement. The current research project therefore aims to evaluate the feasibility and the practicability of a comprehensive, interdisciplinary, and cross-sectoral treatment program consisting of a low-threshold online screening and holistic assessment for PACS. Furthermore, it aims to evaluate digital interventions and the use of so-called personal guides that may help to facilitate the recovery of PACS.

**Methods:** This German study consists of a low-threshold online screening for PACS where positively screened participants will be supported throughout by personal pilots. The personal pilots are aimed at empowering patients and helping them to navigate through the study and different treatment options. Patients will then be randomly assigned either to an intervention group (IG) or an active control group (ACG). The IG will receive a comprehensive assessment of physiological and psychological functioning to inform future treatment. The ACG does not receive the assessment but both groups will receive a treatment consisting of an individual digital treatment program (digital intervention platform and an intervention via a chatbot). This digital intervention is based on the needs identified during the assessment for participants in the IG. Compared to that, the ACG will receive a more common digital treatment program aiming to reduce PACS symptoms. Importantly, a third comparison group (CompG) will be recruited that does not receive any treatment. A propensity score matching will take place, ensuring comparability between the participants. Primary endpoints of the study are symptom reduction and return to work. Secondary outcomes comprise, for example, social participation and activities in daily life. Furthermore, the feasibility and applicability of the online screening tool, the holistic assessment, digital trainings, and personal pilots will be evaluated.

**Discussion:** This is one of the first large-scale studies to improve the diagnosis and the care of patients with PACS by means of empowerment. It is to be evaluated whether the methods utilized can be used for the German and international population. Trial registration [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT05238415; date of registration: February 14, 2022.

**Possible long COVID healthcare pathways: a scoping review**

BMC Health Serv Res. 2022 Aug 23;22(1):1076. doi: [10.1186/s12913-022-08384-6](https://doi.org/10.1186/s12913-022-08384-6).

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**Abstract**

**Background:** Individuals of all ages and with all degrees of severity of the coronavirus disease (COVID) can suffer from persisting or reappearing symptoms called long COVID. Long COVID involves various symptoms, such as shortness of breath, fatigue, or organ damage. The growing number of long COVID cases places a burden on the patients and the broader economy and, hence, has gained more weight in political decisions. This scoping review aimed to give an overview of recommendations about possible long COVID healthcare pathways and requirements regarding decision-making and communication for healthcare professionals.

**Methods:** A systematic search in four databases and biweekly update-hand searches were conducted. In addition to guidelines and reviews, expert opinions in consensus statements or clinical perspectives were also considered. Data were systematically extracted and subsequently narratively and graphically summarised.

**Results:** Fourteen references, five guidelines, four reviews, one consensus paper, and four clinical perspectives were included. The evidence recommended that most long COVID-related healthcare should be in primary care. Patients with complex symptoms should be referred to specialized long COVID outpatient assessment clinics. In contrast, patients with one dominant symptom should be directed to the respective specialist for a second assessment. Depending on the patients' needs, further referral options include, e.g. rehabilitation or non-medical health services. Self-management and good communication between healthcare professionals and patients are crucial aspects of the long COVID management recommendations.

**Conclusions:** The quality of the included guidelines and reviews is limited in the methods applied due to the novelty of this topic and the associated urgency for research. Hence, an update review with more rigorous data is recommended. Furthermore, the systematic collection of real-world data on long COVID surveillance needs to be set up soon to gather further information on the duration and severity of long COVID and thereby facilitate long COVID care planning.

## **Long-COVID in immunocompromised children**

Eur J Pediatr. 2022 Sep;181(9):3501-3509. doi: [10.1007/s00431-022-04561-1](https://doi.org/10.1007/s00431-022-04561-1). Epub 2022 Jul 14.

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### **Abstract**

Coronavirus disease 2019 (COVID-19) can lead to an illness characterized by persistent symptoms which affect various organs and systems, known as long-COVID. This study aimed to assess the prevalence and clinical characteristics of long-COVID in children with immunodeficiency, in comparison to those without. A self-constructed questionnaire was created, which included questions regarding the child's general health, the course of their COVID-19, their symptoms of long-COVID and its impact on their daily functioning, the diagnosis of multisystem inflammatory syndrome (MIS-C), and vaccination status. The questionnaire was completed by parents of 147 children - 70 children with a diagnosis of immunodeficiency (47.6%) and 77 who were immunocompetent (52.4%). Immunocompetent children were more significantly affected by long-COVID than those immunocompromised. Its prevalence in the first 12-week post-infection was 60.0% and 35.7% in these groups, respectively. Beyond this period, these percentages had dropped to 34.6% and 11.43%, respectively. Children who were immunocompetent reported more often symptoms of fatigue, reduced exercise tolerance, and difficulty concentrating. Meanwhile, there was a slight increase in complaints of gastrointestinal symptoms in immunocompromised patients. The risk of developing long-COVID increased with age and COVID-19 severity in both groups. Furthermore, the daily activities of immunocompetent children were limited more frequently (41.8%) than for those who were immunocompromised (25%).

**Conclusions:** Although immunocompromised children experienced long-COVID, its prevalence and impact on daily functioning were significantly lower than among immunocompetent children. However, as the pathomechanisms of long-COVID are not yet fully understood, it is not currently possible to fully explain these findings.

**What is known:** Long COVID is characterized by persistent symptoms following COVID-19, which can affect various tissues and organs, as well as mental health. • Due to the similar course of COVID-19 - mainly mild or asymptomatic - among children with and without immunodeficiency, the question arises, over whether the prevalence and severity of long-COVID is also similar in both groups.

**What is new:** Immunocompromised children also suffer from long-COVID, but the prevalence is significantly lower than in the immunocompetent group of children. • The potential causes of less frequent and milder long-COVID in this group may be the milder course of COVID-19 and the state of reduced immunity protecting against neuroinflammation.

**Cross-talk between SARS-CoV-2 infection and the insulin/IGF signaling pathway: Implications for metabolic diseases in COVID-19 and for post-acute sequelae of SARS-CoV-2 infection**

Metabolism. 2022 Sep;134:155267. doi: [10.1016/j.metabol.2022.155267](https://doi.org/10.1016/j.metabol.2022.155267). Epub 2022 Jul 25.

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**No abstract available**

**An Insight Into Pathophysiology, Epidemiology, and Management of Cardiovascular Complications of SARS-CoV-2 Infection, Post-acute COVID Syndrome, and COVID Vaccine**

Crit Pathw Cardiol. 2022 Sep 1;21(3):123-129. doi: [10.1097/HPC.0000000000000290](https://doi.org/10.1097/HPC.0000000000000290). Epub 2022 Apr 28.

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**Abstract**

Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic health emergency in March 2020. Elderly patients and those with pre-existing medical conditions including cardiovascular disease are at increased risk of developing severe disease. Not only is the viral infection with SARS-CoV-2 associated with higher mortality in patients with underlying cardiovascular disease, but development of cardiovascular complications is also common in patients with COVID-19. Even after recovery from the acute illness, post-acute COVID syndrome with cardiopulmonary manifestations can occur in some patients. Additionally, there are rare but increasingly recognized adverse events, including cardiovascular side effects, reported with currently available COVID-19 vaccines. In this review, we discuss the most common cardiovascular complications of SARS-CoV-2 and COVID-19 vaccines, cardiopulmonary manifestations of post-acute COVID syndrome and the current evidence-based guidance on the management of such complications.

**Vasospastic Angina: A Cause of Post-acute COVID-19 Syndrome**

Intern Med. 2022 Sep 1;61(17):2693-2695. doi: [10.2169/internalmedicine.0137-22](https://doi.org/10.2169/internalmedicine.0137-22). Epub 2022 Jun 28.

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**No abstract available**

## Long COVID-19 Liver Manifestation in Children

J Pediatr Gastroenterol Nutr. 2022 Sep 1;75(3):244-251. doi: [10.1097/MPG.0000000000003521](https://doi.org/10.1097/MPG.0000000000003521). Epub 2022 Aug 9.

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### Abstract

**Objectives:** Severe acute respiratory syndrome coronavirus 2, the novel coronavirus responsible for coronavirus disease (COVID-19), has been a major cause of morbidity and mortality worldwide. Gastrointestinal and hepatic manifestations during acute disease have been reported extensively in the literature. Post-COVID-19 cholangiopathy has been increasingly reported in adults. In children, data are sparse. Our aim was to describe pediatric patients who recovered from COVID-19 and later presented with liver injury.

**Methods:** This is a retrospective case series study of pediatric patients with post-COVID-19 liver manifestations. We collected data on demographics, medical history, clinical presentation, laboratory results, imaging, histology, treatment, and outcome.

**Results:** We report 5 pediatric patients who recovered from COVID-19 and later presented with liver injury. Two types of clinical presentation were distinguishable. Two infants aged 3 and 5 months, previously healthy, presented with acute liver failure that rapidly progressed to liver transplantation. Their liver explant showed massive necrosis with cholangiolar proliferation and lymphocytic infiltrate. Three children, 2 aged 8 years and 1 aged 13 years, presented with hepatitis with cholestasis. Two children had a liver biopsy significant for lymphocytic portal and parenchyma inflammation, along with bile duct proliferations. All 3 were started on steroid treatment; liver enzymes improved, and they were weaned successfully from treatment. For all 5 patients, extensive etiology workup for infectious and metabolic etiologies was negative.

**Conclusions:** We report 2 distinct patterns of potentially long COVID-19 liver manifestations in children with common clinical, radiological, and histopathological characteristics after a thorough workup excluded other known etiologies.

**The long COVID syndrome: A conundrum for the allergist/immunologist**

Allergy Asthma Proc. 2022 Sep 1;43(5):368-374. doi: [10.2500/aap.2022.43.220059](https://doi.org/10.2500/aap.2022.43.220059).

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**Abstract**

Background: The long coronavirus disease 2019 (COVID-19) syndrome includes a group of patients who, after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exhibit lingering mild-to-moderate symptoms and develop medical complications that can have lasting health problems. Objective: The purpose of this report was to examine the current body of evidence that deals with the relationship of COVID-19 infection with the long COVID syndrome to define the possible immunologic mechanisms involved in the pathogenesis of long COVID and to describe potential strategies for the diagnosis and clinical management of the condition. Methods: Extensive research was conducted in medical literature data bases by applying terms such as long COVID, post-COVID-19 condition, pathogenesis of long COVID, management of the long COVID syndrome. Results: The post-COVID conditions, a more recent and less anxiety-inducing term for the patient than long COVID or "long haul," is an umbrella term for a wide range of physical and mental health symptoms similar to those seen in patients with the myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), experienced by some patients and are present  $\geq 4$  weeks after SARS-CoV-2 infection. Although the precise reason why long COVID develops is unknown, one of the major causes is thought to be related to chronic inflammation with overproduction of inflammatory cytokines responsible for the symptoms of the disorder. Conclusion: Long COVID is a growing burden for millions of patients, health-care providers, and global health-care systems, and is a particular challenge for the allergist/immunologist. Many survivors of COVID-19 struggle with multiple symptoms, increased disability, reduced function, and poor quality of life. The allergist/immunologist can assist the total health-care team's efforts in providing a comprehensive and coordinated approach to the management of these patients by promoting comprehensive vaccination and rehabilitation and social services that focus on improving physical, mental, and social well-being, and by establishing partnerships with specialists and other health-care professionals who can provide behavioral, lifestyle, and integrative approaches that may have much to offer in helping patients cope with their symptoms.



**A Review of Respiratory Post-Acute Sequelae of COVID-19 (PASC) and the Potential Benefits of Pulmonary Rehabilitation**

R I Med J (2013). 2022 Sep 1;105(7):11-15 [www.rimed.org/rimedicaljournal/2022/09/2022-09-11-covid-simon.pdf](http://www.rimed.org/rimedicaljournal/2022/09/2022-09-11-covid-simon.pdf).

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**Abstract**

With the SARS-CoV-2 pandemic continuing into its third year, the number of patients who survive acute COVID-19 infection but go on to develop long-term symptoms is increasing daily. Those individuals who experience one or more of a variety of persistent symptoms post-COVID-19 are now diagnosed with the syndrome called post-acute sequelae of COVID-19 (PASC), often colloquially called "Long COVID." This article discusses relevant research and current hypotheses regarding the pathophysiology and management of respiratory symptoms of PASC, in order to provide primary care physicians with context for management of this heterogeneous population. We focus on the growing body of research that supports the use of pulmonary rehabilitation for patients with PASC to improve symptoms and quality of life.

## Follow-Up of a Cohort of Patients with Post-Acute COVID-19 Syndrome in a Belgian Family Practice

Viruses. 2022 Sep 9;14(9):2000. doi: [10.3390/v14092000](https://doi.org/10.3390/v14092000).

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### Abstract

Fifty-five patients who suffered from COVID-19, who were still very ill after several months, with extreme fatigue, effort exhaustion, brain fog, anomia, memory disorder, anosmia, dysgeusia, and other multi-systemic health problems have been followed in a family practice setting between May 2021 and July 2022. Data extracted from the medical records of the 55 patients (40 women), mean age 42.4 (12 to 79 years), and a qualitative study of 6 of them using a semi-open-ended questionnaire allowed to highlight the clinical picture described by WHO as post-acute COVID-19 syndrome (PACS) also known as long COVID. We used brain single-photon emission computed tomography (SPECT-CT) in thirty-two patients with a high severity index and a highly impaired functional status, demonstrating vascular encephalopathy in twenty nine patients and supporting the hypothesis of a persistent cerebral vascular flow disorder in post COVID-19 condition. The patients will benefit from the consortium COVID Human Genetic Effort ([covidhge.com](https://covidhge.com)) to explore the genetic and immunological basis of their problem, as 23/55 cases don't have immunological certainty of a COVID-19 infection. There is no known verified treatment. Analyzing the data from the first 52 patients, three categories of patients emerged over time: 16 patients made a full recovery after 6-8 months, 15 patients were able to return to life and work after 12-18 months with some sequelae, both groups being considered cured. In the third group, 21 patients are still very ill and unable to resume their work and life after 18 months. The biopsychosocial consequences on patients' lives are severe and family doctors are left out in the cold. It is necessary to test the reproducibility of this description, conducted on a small number of patients. Nevertheless, identifying, monitoring and supporting these patients is a necessity in family medicine.

## The Fatigue-Related Symptoms Post-Acute SARS-CoV-2: A Preliminary Comparative Study

Int J Environ Res Public Health. 2022 Sep 16;19(18):11662. doi: [10.3390/ijerph191811662](https://doi.org/10.3390/ijerph191811662).

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### Abstract

A sizeable sub-group of individuals continue to experience persistent debilitating symptoms post-acute SARS-CoV-2. Although these can vary from person to person, fatigue appears to be the most common symptom. Post-viral fatigue has been documented in conditions such as influenza, infectious mononucleosis and more recently chronic fatigue syndrome (CFS). The current study uses measures that successfully describe the fatigue-related symptoms associated with CFS to investigate the fatigue experienced post-acute SARS-CoV-2. Twenty-six volunteers were recruited from Long COVID support groups active on social media. Data were collected anonymously using an online survey platform. These data were compared to pre-pandemic data from non-fatigued and CFS groups. The post-acute SARS-CoV-2 volunteers reported significantly higher levels of fatigue and cognitive difficulties than the non-fatigued controls. They also report more individual symptoms (such as lack of concentration) and problems with sleep quality. There was a similarity between the post-acute SARS-CoV-2 volunteers and the CFS group in terms of levels of depression, perceived stress, emotional distress and cognitive difficulties. Although this was a small-scale study, it demonstrates the range of symptoms experienced post-acute SARS-CoV-2. In addition, the similarities between this group and CFS suggests the need for further research into the mechanisms at play here, the need to identify those at risk of long-term symptoms and the development of possible interventions.

## Protection of vaccination versus hybrid immunity against infection with COVID-19 Omicron variants among Health-Care Workers

Vaccine. 2022 Sep 19; S0264-410X(22)01150-1. doi: [10.1016/j.vaccine.2022.09.042](https://doi.org/10.1016/j.vaccine.2022.09.042). Online ahead of print.

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### Abstract

**Background aim:** The Omicron COVID-19 variants BA.1\* and BA.2\* evade immune system leading to increased transmissibility and breakthrough infections. We aim to test the hypothesis that immunity achieved post COVID-19 infection combined with vaccination (hybrid immunity), is more effective against Omicron infection than vaccination alone in a health-care setting.

**Methods:** Data on regular pre-emptive PCR testing from all Health-Care Workers (HCWs) at Laiko University Hospital from 29th December 2020, date on which the national COVID-19 immunization program began in Greece, until 24th May 2022, were retrospectively collected and recorded. The infection rate was calculated after December 21st, 2021, when Omicron was the predominant circulating variant in Greece, as the total number of infections (positive PCR COVID-19 test regardless of symptoms) divided by the total person-months at risk.

**Results:** Of 1,305 vaccinated HCWs who were included in the analysis [median age of 47 (IQR: 36, 56) years, 66.7 % women], 13 % and 87 % had received 2 or 3 vaccine doses (full and booster vaccination), respectively. A COVID-19 infection had occurred in 135 of 1,305 of participants prior to Omicron predominance. Of those 135 HCWs with hybrid immunity only 13 (9.6 %) were re-infected. Of the 154 and 1,016 HCWs with full and booster vaccination-induced immunity, respectively, 71 (46.1 %, infection rate 13.4/100 person-months) and 448 (44.1 %, infection rate 12.2/100 person-months) were infected during the follow up period. No association between gender or age and COVID-19 infection was found and none of the participants had a severe infection or died.

**Conclusions:** Hybrid immunity confers higher protection by almost 5-fold compared to full or booster vaccination for COVID-19 infection with the Omicron variant among HCWs who are at high risk of exposure. This may inform public health policies on how to achieve optimal immunity in terms of the timing and mode of vaccination.

## Long-term comprehensive cardiopulmonary phenotyping of COVID-19

Respir Res. 2022 Sep 21;23(1):263. doi: [10.1186/s12931-022-02173-9](https://doi.org/10.1186/s12931-022-02173-9).

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### Abstract

**Background:** Persistent symptoms after initial COVID-19 infection are common and are frequently referred to by the umbrella terms "post-COVID syndrome" and "long COVID". The sheer number of affected patients pose an increasing challenge to healthcare systems worldwide. To date, our understanding of the pathophysiology of the post-COVID syndrome remains poor and the extent to which persistent cardiopulmonary abnormalities contribute to the symptom complex is unclear. We sought to determine the presence and impact of cardiopulmonary sequelae after COVID-19 in longitudinal assessment.

**Methods:** We report on 71 patients who underwent comprehensive, longitudinal testing in regular intervals for up to 12 months after their initial COVID-19 diagnosis. Testing included pulmonary function testing, cardiopulmonary exercise testing, dedicated left and right heart echocardiography, lung ultrasonography, and cardiac MRI.

**Results:** Our results demonstrate that subjective quality of life after COVID-19 (EQ-5D visual acuity scale, VAS, 67.4 for patients treated as outpatient, 79.2 for patients admitted to the general floor, 71.8 for patients treated in an ICU) is not related to the severity of the initial infection. Maximal exercise capacity is also reduced (VO<sub>2</sub>max 79% predicted, SD ± 19%); however, this is driven in large parts by patients who had initially required ICU-level of care. The degree of objective reduction in exertion did not correlate with quality of life scores. Pulmonary function testing revealed mild and persistent reduction in DLCO over the first 12 months without significant restrictive or obstructive lung disease. Left and right heart function was intact with good RV function and intact RV/PA coupling, imaging findings suggestive of myocarditis were uncommon (7% of patients).

**Conclusion:** A reduction in exercise capacity after COVID-19 is common, but is most prominent in patients previously treated in the ICU and more likely related to deconditioning or fatigue than to cardiopulmonary impairment. Subjective quality of life scores are independent of the severity of initial infection and do not correlate with objective measures of cardiopulmonary function. In our cohort, persistent cardiopulmonary impairment after COVID-19 was uncommon. The post-COVID syndrome is unlikely to be the result of cardiopulmonary sequelae and may reflect a post-ICU syndrome in some. Trial registration Registered on [clinicaltrials.gov](https://clinicaltrials.gov) (NCT04442789), Date: June 23, 2020.

**Proteomics of fibrin amyloid microclots in long COVID/post-acute sequelae of COVID-19 (PASC) shows many entrapped pro-inflammatory molecules that may also contribute to a failed fibrinolytic system**

Cardiovasc Diabetol. 2022 Sep 21;21(1):190. doi: [10.1186/s12933-022-01623-4](https://doi.org/10.1186/s12933-022-01623-4).

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**Abstract**

**Background:** Post-acute sequelae of COVID-19 (PASC), also now known as long COVID, has become a major global health and economic burden. Previously, we provided evidence that there is a significant insoluble fibrin amyloid microclot load in the circulation of individuals with long COVID, and that these microclots entrap a substantial number of inflammatory molecules, including those that might prevent clot breakdown. Scientifically, the most challenging aspect of this debilitating condition is that traditional pathology tests such as a serum CRP (C-reactive protein) may not show any significant abnormal inflammatory markers, albeit these tests measure only the soluble inflammatory molecules. Elevated, or abnormal soluble biomarkers such as IL-6, D-Dimer or fibrinogen indicate an increased risk for thrombosis or a host immune response in COVID-19. The absence of biomarkers in standard pathology tests, result in a significant amount of confusion for patients and clinicians, as patients are extremely sick or even bed-ridden but with no regular identifiable reason for their disease. Biomarkers that are currently available cannot detect the molecules present in the microclots we identified and are therefore unable to confirm their presence or the mechanisms that drive their formation.

**Methods:** Here we analysed the protein content of double-digested microclots of 99 long COVID patients and 29 healthy controls. The patients suffering from long COVID reported their symptoms through a questionnaire completed by themselves or their attending physician.

**Results:** Our long COVID cohort's symptoms were found to be in line with global findings, where the most prevalent symptoms were constant fatigue (74%), cognitive impairment (71%) and depression and anxiety (30%). Our most noteworthy findings were a reduced level of plasma Kallikrein compared to our controls, an increased level of platelet factor 4 (PF4) von Willebrand factor (VWF), and a marginally increased level of  $\alpha$ -2 antiplasmin ( $\alpha$ -2-AP). We also found a significant presence of antibodies entrapped inside these microclots.

**Conclusion:** Our results confirm the presence of pro-inflammatory molecules that may also contribute to a failed fibrinolysis phenomenon, which could possibly explain why individuals with

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long COVID suffer from chronic fatigue, dyspnoea, or cognitive impairment. In addition, significant platelet hyperactivation was noted. Hyperactivation will result in the granular content of platelets being shed into the circulation, including PF4. Overall, our results provide further evidence of both a failed fibrinolytic system in long COVID/PASC and the entrapment of many proteins whose presence might otherwise go unrecorded. These findings might have significant implications for individuals with pre-existing comorbidities, including cardiovascular disease and type 2 diabetes.

**Long COVID symptoms in exposed and infected children, adolescents and their parents one year after SARS-CoV-2 infection: A prospective observational cohort study**

EBioMedicine. 2022 Sep 22; 84:104245. doi: [10.1016/j.ebiom.2022.104245](https://doi.org/10.1016/j.ebiom.2022.104245). Online ahead of print.

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**Abstract**

**Background:** Long COVID in children and adolescents remains poorly understood due to a lack of well-controlled studies with long-term follow-up. In particular, the impact of the family context on persistent symptoms following SARS-CoV-2 infection remains unknown. We examined long COVID symptoms in a cohort of infected children, adolescents, and adults and their exposed but non-



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infected household members approximately 1 year after infection and investigated clustering of persistent symptoms within households.

**Methods:** 1267 members of 341 households (404 children aged <14 years, 140 adolescents aged 14-18 years and 723 adults) were categorized as having had either a SARS-CoV-2 infection or household exposure to SARS-CoV-2 without infection, based on three serological assays and history of laboratory-confirmed infection. Participants completed questionnaires assessing the presence of long COVID symptoms 11-12 months after infection in the household using online questionnaires.

**Findings:** The prevalence of moderate or severe persistent symptoms was statistically significantly higher in infected than in exposed women (36.4% [95% CI: 30.7-42.4%] vs 14.2% [95% CI: 8.7-21.5%]), infected men (22.9% [95% CI: 17.9-28.5%] vs 10.3% [95% CI: 5.8-16.9%]) and infected adolescent girls (32.1% 95% CI: 17.2-50.5%] vs 8.9% [95%CI: 3.1-19.8%]). However, moderate or severe persistent symptoms were not statistically more common in infected adolescent boys aged 14-18 (9.7% [95% CI: 2.8-23.6%] or in infected children <14 years (girls: 4.3% [95% CI: 1.2-11.0%]; boys: 3.7% [95% CI: 1.1-9.6%]) than in their exposed counterparts (adolescent boys: 0.0% [95% CI: 0.0-6.7%]; girls < 14 years: 2.3% [95% CI: 0.7-6.1%]; boys < 14 years: 0.0% [95% CI: 0.0-2.0%]). The number of persistent symptoms reported by individuals was associated with the number of persistent symptoms reported by their household members (IRR=1.11, p=.005, 95% CI [1.03-1.20]).

**Interpretation:** In this controlled, multi-centre study, infected men, women and adolescent girls were at increased risk of negative outcomes 11-12 months after SARS-CoV-2 infection. Amongst non-infected adults, prevalence of negative outcomes was also high. Prolonged symptoms tended to cluster within families, suggesting family-level interventions for long COVID could prove useful.

**Lowered oxygen saturation and increased body temperature in acute COVID-19 largely predict chronic fatigue syndrome and affective symptoms due to Long COVID: A precision nomothetic approach**

Acta Neuropsychiatr. 2022 Sep 22;1-12. doi: [10.1017/neu.2022.21](https://doi.org/10.1017/neu.2022.21). Online ahead of print.

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**Abstract**

**Background:** Long coronavirus disease 2019 (LC) is a chronic sequel of acute COVID-19. The exact pathophysiology of the affective, chronic fatigue and physiosomatic symptoms (labelled as "physio-affective phenome") of LC has remained elusive.

**Objective:** The current study aims to delineate the effects of oxygen saturation (SpO<sub>2</sub>) and body temperature during the acute phase on the physio-affective phenome of LC.

**Method:** We recruited 120 LC patients and 36 controls. For all participants, we assessed the lowest SpO<sub>2</sub> and peak body temperature during acute COVID-19, and the Hamilton Depression and Anxiety Rating Scale (HAMD/HAMA) and Fibro Fatigue (FF) scales 3-4 months later.

**Results:** Lowered SpO<sub>2</sub> and increased body temperature during the acute phase and female sex predict 60.7% of the variance in the physio-affective phenome of LC. Using unsupervised learning techniques, we were able to delineate a new endophenotype class, which comprises around 26.7% of the LC patients and is characterised by very low SpO<sub>2</sub> and very high body temperature, and depression, anxiety, chronic fatigue, and autonomic and gastro-intestinal symptoms scores. Single latent vectors could be extracted from both biomarkers, depression, anxiety and FF symptoms or from both biomarkers, insomnia, chronic fatigue, gastro-intestinal and autonomic symptoms.

**Conclusion:** The newly constructed endophenotype class and pathway phenotypes indicate that the physio-affective phenome of LC is at least in part the consequence of the pathophysiology of acute COVID-19, namely the combined effects of lowered SpO<sub>2</sub>, increased body temperature and the associated immune-inflammatory processes and lung lesions.

**Incidence of post-COVID syndrome and associated symptoms in outpatient care in Bavaria, Germany: a retrospective cohort study using routinely collected claims data**

BMJ Open. 2022 Sep 22;12(9):e064979. doi: [10.1136/bmjopen-2022-064979](https://doi.org/10.1136/bmjopen-2022-064979).

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**Abstract**

**Objectives:** To estimate the treatment incidence of post-COVID syndrome (postinfectious sequelae present at least 12 weeks following infection) in the context of ambulatory care in Bavaria, Germany, and to establish whether related diagnoses occur more frequently than in patients with no known history of COVID-19.

**Design:** Retrospective cohort analysis of routinely collected claims data.

**Setting:** Ambulatory care in Bavaria, Germany, observed from January 2020 to March 2022 (data accessed May 2022).

**Participants:** 391 990 patients with confirmed COVID-19 diagnosis, 62 659 patients with other respiratory infection and a control group of 659 579 patients with no confirmed or suspected diagnosis of COVID-19.

**Primary and secondary outcome measures:** Primary outcome is diagnosis of post-COVID syndrome documented in ambulatory care. Secondary outcomes are: chronic fatigue syndrome, psychological disorder, fatigue, mild cognitive impairment, disturbances of taste and smell, dyspnoea, pulmonary embolism and myalgia.

**Results:** Among all patients with confirmed COVID-19, 14.2% (95% CI 14.0% to 14.5%) received a diagnosis of a post-COVID syndrome, and 6.7% (95% CI 6.5% to 6.9%) received the diagnosis in at least two quarterly periods during a 2-year follow-up. Compared with patients with other respiratory infections and with controls, patients with COVID-19 more frequently received a variety of diagnoses including chronic fatigue syndrome (1.6% vs 0.6% and 0.3%, respectively), fatigue (13.3% vs 9.2% and 6.0%), dyspnoea (9.9% vs 5.1% and 3.2%) and disturbances of taste and smell (3.2% vs 1.2% and 0.5%). The treatment incidence of post-COVID syndrome was highest among adults aged 40-59 (19.0%) and lowest among children aged below 12 years (2.6%).

**Conclusions:** Our results demonstrate a moderately high incidence of post-COVID syndrome 2 years after COVID-19 diagnosis. There is an urgent need to find efficient and effective solutions to help patients with dyspnoea, fatigue, cognitive impairment and loss of smell. Guidelines and treatment algorithms, including referral criteria, and occupational and physical therapy, require prompt and coherent implementation.

**Long covid-an update for primary care**

BMJ. 2022 Sep 22;378:e072117. doi: [10.1136/bmj-2022-072117](https://doi.org/10.1136/bmj-2022-072117).

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**No abstract available**

## Circulating anti-nuclear autoantibodies in COVID-19 survivors predict long-COVID symptoms

Eur Respir J. 2022 Sep 22;2200970. doi: [10.1183/13993003.00970-2022](https://doi.org/10.1183/13993003.00970-2022). Online ahead of print.

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### Abstract

**Background:** Autoimmunity has been reported in patients with severe COVID-19. We investigated whether antinuclear/extractable-nuclear antibodies (ANAs) were present up to a year after infection, and if they were associated with the development of clinically relevant Post-Acute Sequelae of COVID-19 (PASC) symptoms.

**Methods:** A rapid assessment line immunoassay was used to measure circulating levels of ANA/ENAs in 106 convalescent COVID-19 patients with varying acute phase severities at 3, 6, and 12 months post-recovery. Patient-reported fatigue, cough, and dyspnea were recorded at each timepoint. Multivariable logistic regression model and receiver-operating curves (ROC) were used to test the association of autoantibodies with patient-reported outcomes and pro-inflammatory cytokines.

**Results:** Compared to age- and sex-matched healthy controls (n=22) and those who had other respiratory infections (n=34), patients with COVID-19 had higher detectable ANAs at 3 months post-recovery (p<0.001). The mean number of ANA autoreactivities per individual decreased from 3 to 12 months (3.99 to 1.55) with persistent positive titers associated with fatigue, dyspnea, and cough severity. Antibodies to U1-snRNP and anti-SS-B/La were both positively associated with persistent symptoms of fatigue (p<0.028, AUC=0.86) and dyspnea (p<0.003, AUC=0.81). Pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF $\alpha$ ) and C-reactive protein predicted the elevated ANAs at 12 months. TNF $\alpha$ , D-dimer, and IL-1 $\beta$  had the strongest association with symptoms at 12 months. Regression analysis showed TNF $\alpha$  predicted fatigue ( $\beta$ =4.65, p=0.004) and general symptomatology ( $\beta$ =2.40, p=0.03) at 12 months.

**Interpretation:** Persistently positive ANAs at 12 months post-COVID are associated with persisting symptoms and inflammation (TNF $\alpha$ ) in a subset of COVID-19 survivors. This finding indicates the need for further investigation into the role of autoimmunity in PASC.

**Incidence of post-COVID syndrome and associated symptoms in outpatient care in Bavaria, Germany: a retrospective cohort study using routinely collected claims data**

BMJ Open. 2022 Sep 22;12(9):e064979. doi: [10.1136/bmjopen-2022-064979](https://doi.org/10.1136/bmjopen-2022-064979).

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**Abstract**

**Objectives:** To estimate the treatment incidence of post-COVID syndrome (postinfectious sequelae present at least 12 weeks following infection) in the context of ambulatory care in Bavaria, Germany, and to establish whether related diagnoses occur more frequently than in patients with no known history of COVID-19.

**Design:** Retrospective cohort analysis of routinely collected claims data.

**Setting:** Ambulatory care in Bavaria, Germany, observed from January 2020 to March 2022 (data accessed May 2022).

**Participants:** 391 990 patients with confirmed COVID-19 diagnosis, 62 659 patients with other respiratory infection and a control group of 659 579 patients with no confirmed or suspected diagnosis of COVID-19.

**Primary and secondary outcome measures:** Primary outcome is diagnosis of post-COVID syndrome documented in ambulatory care. Secondary outcomes are: chronic fatigue syndrome, psychological disorder, fatigue, mild cognitive impairment, disturbances of taste and smell, dyspnoea, pulmonary embolism and myalgia.

**Results:** Among all patients with confirmed COVID-19, 14.2% (95% CI 14.0% to 14.5%) received a diagnosis of a post-COVID syndrome, and 6.7% (95% CI 6.5% to 6.9%) received the diagnosis in at least two quarterly periods during a 2-year follow-up. Compared with patients with other respiratory infections and with controls, patients with COVID-19 more frequently received a variety of diagnoses including chronic fatigue syndrome (1.6% vs 0.6% and 0.3%, respectively), fatigue (13.3% vs 9.2% and 6.0%), dyspnoea (9.9% vs 5.1% and 3.2%) and disturbances of taste and smell (3.2% vs 1.2% and 0.5%). The treatment incidence of post-COVID syndrome was highest among adults aged 40-59 (19.0%) and lowest among children aged below 12 years (2.6%).

**Conclusions:** Our results demonstrate a moderately high incidence of post-COVID syndrome 2 years after COVID-19 diagnosis. There is an urgent need to find efficient and effective solutions to help patients with dyspnoea, fatigue, cognitive impairment and loss of smell. Guidelines and treatment algorithms, including referral criteria, and occupational and physical therapy, require prompt and coherent implementation.

**Glycyrrhizin and boswellic acids, the golden nutraceuticals: multitargeting for treatment of mild-moderate COVID-19 and prevention of post-COVID cognitive impairment**

Inflammopharmacology. 2022 Sep 22;1-16. doi: [10.1007/s10787-022-01062-3](https://doi.org/10.1007/s10787-022-01062-3). Online ahead of print.

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**Abstract**

Breakthrough infections have been reported in fully vaccinated persons. Furthermore, rebound symptoms have been reported following the new FDA granted emergency use to combat SARS-CoV-2. Glycyrrhizin (GR) and boswellic acids (BAs) combination has been shown to have highly successful actions against COVID-19 in our recent clinical trial. However, the study is limited by the small sample size, and therefore, the aim of this article is to comprehensively evaluate recent evidence on the efficacy of GR and BAs in preventing the development of COVID-19 in patients with mild and moderate infections and in preventing post-COVID-19 cognitive impairment, which is the most important symptom after recovery from Covid-19 disease. We have reviewed and discussed information published since the outbreak of the COVID-19 pandemic until July 2022 on preclinical (in vivo, in vivo and bioinformatics) and clinical studies related to the antiviral, anti-inflammatory and immunomodulatory activity of Gr and BAs. Sixteen studies were performed to determine the efficacy of GR against SARS-CoV-2. Ten studies were used primarily for in vitro and in vivo assays and six used molecular docking studies. However, the antiviral activity of BAs against SARS-CoV-2 was determined in only five studies using molecular modeling and bioinformatics. All these studies confirmed that GR n and BAs have strong antiviral activity and can be used as a therapeutic agent for COVID-19 and as a protective agent against SARS-CoV-2. They may act by inhibiting the main protease SARS-CoV-2 (Mpro) responsible for replication and blocking spike protein-mediated cell entry. Only seven rigorously designed clinical trials regarding the usefulness of GR, BAs or their combinations in the treatment of COVID-19 have been published as of July 2022. Although there is no clinical study regarding the treatment of cognitive impairment after COVID-19 that has been published so far, several preclinical and clinical studies have demonstrated the potential effect of GR and BAs in the prevention and treatment of cognitive impairment by inhibiting the activity of several molecules that activate inflammatory signaling pathway. In conclusion, the findings of our study documented the beneficial use of GR and BAs to treat SARS-CoV-2 and its variants and prevent post-COVID cognitive impairment. However, it warrants further studies with a larger randomized sample size to ensure that the studies have sufficient evidence of benefits against COVID-19 and post-COVID-19 symptoms.

## **An international study of post-COVID sleep health**

Sleep Health. 2022 Sep 23; S2352-7218(22)00112-7. doi: [10.1016/j.sleh.2022.06.011](https://doi.org/10.1016/j.sleh.2022.06.011). Online ahead of print.

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### **Abstract**

**Objectives:** COVID-19 has infected millions of people worldwide, with growing evidence that individuals with a history of infection may continue to show persistent post-COVID symptoms (long COVID). The aim of this study was to investigate sleep health in an international sample of individuals who reported previously testing positive for COVID-19.

**Design:** Cross-sectional.

**Setting:** Online survey distributed online between March and June 2021.

**Participants:** A total of 1001 individuals who reported a positive diagnosis of COVID-19 across different geographical regions, including North and South America, Sub-Saharan Africa, and Europe.

**Measurements:** Self-reported sleep health, using the Regulatory Satisfaction Alertness Timing Efficiency Duration scale, as recalled before a COVID-19 diagnosis and also reported currently.

**Results:** Individuals reported worse overall current sleep health, with lower ratings across the 6 dimensions of sleep health (sleep regularity, satisfaction, alertness, timing, efficiency, and duration) compared to their ratings as recalled before COVID-19 infection. Greater severity of COVID-19 symptoms was the strongest predictor of poor current sleep health ( $P < .001$ ), independent of demographics, presence of a pre-existing chronic health condition, and time since infection. Poor current sleep health was associated with poorer current quality of life ( $P < .001$ ).

**Conclusions:** Poor current sleep health is evident in individuals with a history of COVID-19, particularly those with more severe symptoms at the time of their COVID-19 infection and is associated with a poorer quality of life. Clinicians and researchers should assess sleep health in COVID-19 patients and investigate long-term associations with their mental and physical health, as well as potential benefits of improving sleep in this population.



**Guidelines for diagnosing 'long Covid' in patients living with postacute sequelae of COVID-19 (PASC)**

Evid Based Nurs. 2022 Sep 23; ebnurs-2022-103538. doi: [10.1136/ebnurs-2022-103538](https://doi.org/10.1136/ebnurs-2022-103538). Online ahead of print.

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**A distinct symptom pattern emerges for COVID-19 long-haul: a nationwide study**

Sci Rep. 2022 Sep 23;12(1):15905. doi: [10.1038/s41598-022-20214-7](https://doi.org/10.1038/s41598-022-20214-7).

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**Abstract**

Long-haul COVID-19, also called post-acute sequelae of SARS-CoV-2 (PASC), is a new illness caused by SARS-CoV-2 infection and characterized by the persistence of symptoms. The purpose of this cross-sectional study was to identify a distinct and significant temporal pattern of PASC symptoms (symptom type and onset) among a nationwide sample of PASC survivors (n = 5652). The sample was randomly sorted into two independent samples for exploratory (EFA) and confirmatory factor analyses (CFA). Five factors emerged from the EFA: (1) cold and flu-like symptoms, (2) change in smell and/or taste, (3) dyspnea and chest pain, (4) cognitive and visual problems, and (5) cardiac symptoms. The CFA had excellent model fit ( $\chi^2 = 513.721$ ,  $df = 207$ ,  $p < 0.01$ ,  $TLI = 0.952$ ,  $CFI = 0.964$ ,  $RMSEA = 0.024$ ). These findings demonstrate a novel symptom pattern for PASC. These findings can enable nurses in the identification of at-risk patients and facilitate early, systematic symptom management strategies for PASC.

**Systemic antibody responses against human microbiota flagellins are overrepresented in chronic fatigue syndrome patients**

Sci Adv. 2022 Sep 23;8(38):eabq2422. doi: [10.1126/sciadv.abq2422](https://doi.org/10.1126/sciadv.abq2422). Epub 2022 Sep 23.

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**Abstract**

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating disease with an unclear etiology and pathogenesis. Both an involvement of the immune system and gut microbiota dysbiosis have been implicated in its pathophysiology. However, potential interactions between adaptive immune responses and the microbiota in ME/CFS have been incompletely characterized. Here, we profiled antibody responses of patients with severe ME/CFS and healthy controls against microbiota and viral antigens represented as a phage-displayed 244,000 variant library. Patients with severe ME/CFS exhibited distinct serum antibody epitope repertoires against flagellins of Lachnospiraceae bacteria. Training machine learning algorithms on this antibody-binding data demonstrated that immune responses against gut microbiota represent a unique layer of information beyond standard blood tests, providing improved molecular diagnostics for ME/CFS. Together, our results point toward an involvement of the microbiota-immune axis in ME/CFS and lay the foundation for comparative studies with inflammatory bowel diseases and illnesses characterized by long-term fatigue symptoms, including post-COVID-19 syndrome.

## Creative Long Covid: A qualitative exploration of the experience of Long Covid through the medium of creative narratives

Health Expect. 2022 Sep 23. doi: [10.1111/hex.13602](https://doi.org/10.1111/hex.13602). Online ahead of print.

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### Abstract

**Background:** Healthcare is witnessing a new disease with the emergence of Long Covid; a condition which can result in myriad symptoms, varying in frequency and severity. As new data are emerging to help inform treatment guidelines, the perspectives of those living with Long Covid are essential in informing healthcare practice. The research aimed to collect the narratives of people living with Long Covid to better understand the lived experience of this condition. In attempting to narrate complex or traumatic experiences the arts and humanities can offer alternative ways of expressing embodied narratives, representing rich sources of meaning. Therefore, the research specifically sought to elicit creative expressions from participants with lived experience of Long Covid.

**Methods:** Data were collected via an online repository where participants could submit their pieces of creative writing. Data were collected between August 2021 and January 2022 and a total of 28 submissions were received from participants. These were mostly written creative narratives. However, a small number were submitted as audio or video files of spoken word poetry or songs. Data collection was stopped once data saturation was achieved.

**Results:** The submissions were subjected to thematic analysis and five themes were generated. These five themes are Identity, social relationships, symptoms, interaction with healthcare systems and time. The results provide an insight into the experience of Long Covid as detailed by the participants' creative narratives.

**Conclusion:** The results from this study provide a unique insight into the lived experience of Long Covid. In relation to clinical practice, the results suggest that adjustment reaction and loss of sense of self could be added as common symptoms.

**Patient and public contribution:** Before undertaking the research, Long Covid community groups were contacted to discuss the potential value of this study and it was widely supported. One of the leading Long Covid support groups was also involved in disseminating information regarding the project. As part of ongoing work within this project, members of the team are actively disseminating the results within Long Covid communities and seeking to develop arts-based workshops specifically for people with Long Covid.

**Neurological post-acute sequelae of SARS-CoV-2 infection (PASC)**

Psychiatry Clin Neurosci. 2022 Sep 23. doi: [10.1111/pcn.13481](https://doi.org/10.1111/pcn.13481). Online ahead of print.

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**Abstract**

The novel corona virus infectious disease, COVID-19, caused by SARS-CoV-2, can have two phases: acute (generally 4 weeks after onset) and chronic (> 4 weeks after onset). Both phases include a wide variety of signs and symptoms including neurological and psychiatric symptoms. The signs and symptoms that are considered sequelae of COVID-19 are termed post-COVID condition, long COVID-19, and post-acute sequelae of SARS-CoV-2 infection (PASC). PASC symptoms include fatigue, dyspnea, palpitation, dysosmia, sub-fever, hypertension, alopecia, sleep problems, loss of concentration, amnesia, numbness, pain, gastrointestinal symptoms, depression, and anxiety. Because the specific pathophysiology of PASC has not yet been clarified, there are no definite criteria of the condition, hence the World Health Organization's definition is quite broad. Consequently, it is difficult to correctly diagnose PASC. Approximately 50% of patients may show at least one PASC symptom up to 12 months after COVID-19 infection; however, the exact prevalence of PASC has not been determined. Despite extensive research in progress worldwide, there are currently no clear diagnostic methodologies or treatments for PASC. In this review, we discuss the currently available information on PASC and highlight the neurological sequelae of COVID-19 infection. Furthermore, we provide clinical suggestions for diagnosing and caring for PASC patients based on our outpatient clinic experience. This article is protected by copyright. All rights reserved.

## COVID Symptoms, Symptom Clusters, and Predictors for Becoming a Long-Hauler Looking for Clarity in the Haze of the Pandemic

Clin Nurs Res. 2022 Sep 24;10547738221125632. doi: [10.1177/10547738221125632](https://doi.org/10.1177/10547738221125632). Online ahead of print.

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### Abstract

Post-acute sequelae of SARS-CoV-2 (PASC) is defined as persistent symptoms after apparent recovery from acute COVID-19 infection, also known as COVID-19 long-haul. We performed a retrospective review of electronic health records (EHR) from the University of California COVID Research Data Set (UC CORDS), a de-identified EHR of PCR-confirmed SARS-CoV-2-positive patients in California. The purposes were to (1) describe the prevalence of PASC, (2) describe COVID-19 symptoms and symptom clusters, and (3) identify risk factors for PASC. Data were subjected to non-negative matrix factorization to identify symptom clusters, and a predictive model of PASC was developed. PASC prevalence was 11% (277/2,153), and of these patients, 66% (183/277) were considered asymptomatic at days 0-30. Five PASC symptom clusters emerged and specific symptoms at days 0-30 were associated with PASC. Women were more likely than men to develop PASC, with all age groups and ethnicities represented. PASC is a public health priority.

**Long-term neuromuscular consequences of SARS-Cov-2 and their similarities with myalgic encephalomyelitis/chronic fatigue syndrome: results of the retrospective CoLGEM study**

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**Abstract**

**Background:** Patients with long-COVID often complain of continuous fatigue, myalgia, sleep problems, cognitive dysfunction, and post-exertional malaise. No data are available on EMG recording of evoked myopotentials (M-waves) or exercise-induced alterations in long-COVID patients, providing evidence of muscle membrane fatigue. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) develops in more than half of patients after an infectious disease, particularly viral diseases. A large proportion (around 70%) of these patients have neuromuscular disorders with M-wave alterations during and after exercise. Our hypothesis was that M-wave alterations would be also found in long-COVID patients, in association with neuromuscular symptoms, similar to ME/CFS.

**Methods:** This retrospective observational CoLGEM (Covid LonG Encéphalomyelite Myalgique) study compared 59 patients with long-COVID and 55 ME/CFS patients with a history of severe infection who presented before the COVID pandemic. All of these patients underwent the same protocol consisting of a questionnaire focusing on neural and neuromuscular disorders and M-wave recording in the rectus femoris muscle before, during, and 10 min after a progressive cycling exercise. Maximal handgrip strength (MHGS) and maximal exercise power were also measured. The frequency of symptoms and magnitude of M-wave changes in the two groups were compared using non-parametric and parametric tests.

**Results:** The frequency of fatigue, myalgia, sleep problems, cognitive dysfunction, and post-exertional malaise as well as the magnitude of exercise-induced M-wave alterations were the same in the two groups. By contrast, digestive problems were less present in long-COVID. M-wave alterations were greater in ME/CFS patients as in those with long-COVID when the highest muscle strength and highest exercise performance were measured.

**Conclusions:** These high clinical and biological similarities between long-COVID and ME/CFS support the hypothesis that SARS-Cov-2 infection can cause ME/CFS symptoms. Trial registration Registered retrospectively.

## Alleviation of Post-COVID-19 Cognitive Deficits by Treatment with EGb 761®: A Case Series

Am J Case Rep. 2022 Sep 26; 23:e937094. doi: [10.12659/AJCR.937094](https://doi.org/10.12659/AJCR.937094).

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### Abstract

**BACKGROUND** Cognitive symptoms persisting longer than 3 months after infection, such as memory loss, or difficulties concentrating, have been reported in up to one-third of patients after COVID-19. Evidence-based therapeutic interventions to treat post-COVID-19 symptoms (also called "Long-COVID symptoms") have not yet been established, and the treating physicians must rely on conjecture to help patients. Based on its mechanism of action and its efficacy in treating cognitive impairment, as well as its good tolerability, the Ginkgo biloba special extract EGb 761 has been suggested as a remedy to alleviate cognitive post-COVID-19 symptoms. In many studies, EGb 761 has been demonstrated to protect endothelial cells, to have potent anti-inflammatory effects, and to enhance neuroplasticity. **CASE REPORT** Here, we report for the first time the application of EGb 761 in the therapy of post-COVID-19-related cognitive deficits. Three women and 2 men, aged 26 to 59 years (average age 34.6 years), presented with concentration and attention deficits, cognitive deficiencies, and/or fatigue 9-35 weeks after infection. A daily dose of 2×80 mg of EGb 761 did not cause any detectable adverse effects, and it substantially improved or completely restored cognitive deficits and, when initially present, also other symptoms, such as fatigue and hyposmia, within an observation period of up to 6 months. **CONCLUSIONS** Our observations support the hypothesis that EGb 761 might be a low-risk treatment option for post-COVID-19 patients with cognitive symptoms. Moreover, we derive recommendations for randomized controlled clinical trials to confirm efficacy in that indication.



**Remdesivir resistance in transplant recipients with persistent COVID-19**

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**Abstract**

New mutations conferring resistance to SARS-CoV-2 therapeutics have important clinical implications. We describe the first cases of an independently acquired V792I RNA-dependent RNA polymerase mutation developing in renal transplant recipients after remdesivir exposure. Our work underscores the need for augmented efforts to identify concerning mutations and address their clinical implications.

**A Delphi consensus statement for the management of post-COVID interstitial lung disease**

Expert Rev Respir Med. 2022 Sep 26. doi: [10.1080/17476348.2022.2128770](https://doi.org/10.1080/17476348.2022.2128770). Online ahead of print.

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**Abstract**

**Introduction:** As millions of people worldwide recover from COVID-19, a substantial proportion continue to have persistent symptoms, pulmonary function abnormalities, and radiological findings suggestive of post-COVID interstitial lung disease (ILD). To date, there is limited scientific evidence on the management of post-COVID ILD, necessitating a consensus-based approach.

**Areas covered:** A panel of experts in pulmonology and thoracic radiology was constituted. Key questions regarding the management of post-COVID ILD were identified. A search was performed on PubMed and EMBASE and updated till 1st March 2022. The relevant literature regarding the

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epidemiology, pathophysiology, diagnosis and treatment of post-COVID ILD was summarized. Subsequently, suggestions regarding the management of these patients were framed, and a consensus was obtained using the Delphi approach. Those suggestions which were approved by over 80% of the panelists were accepted. The final document was approved by all panel members.

**Expert opinion:** Dedicated facilities should be established for the care of patients with post-COVID ILD. Symptom screening, pulmonary function testing, and thoracic imaging have a role in the diagnosis. The pharmacologic and non-pharmacologic options for the management of post-COVID ILD are discussed. Further research into the pathophysiology and management of post-COVID ILD will improve our understanding of this condition.