

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

Prepared by Staff of the RACGWVI.

RACGWVI: Long Haul COVID-19 — PubMed Citations for Jan, Feb, March 2022

The following is a list of published research projects that focus on Long Haul COVID-19 for the months of January, February and March 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., Understanding Long Covid: Nosology, social attitudes and stigma, page 5).

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

DOI: Selecting the digital object identifier (DOI) will link to the article publication website.

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The contested meaning of "long COVID" - Patients, doctors, and the politics of subjective evidence

Soc Sci Med. 2022 Jan; 292:114619. doi: [10.1016/j.socscimed.2021.114619](https://doi.org/10.1016/j.socscimed.2021.114619). Epub 2021 Nov 30.

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Abstract

In our article, we reconstruct how the patient-made term "long COVID" was able to become a widely accepted concept in public discourses. While the condition was initially invisible to the public eye, we show how the mobilization of subjective evidence online, i.e., the dissemination of reports on the different experiences of lasting symptoms, was able to transform the condition into a crucial feature of the coronavirus pandemic. We explore how stakeholders used the term "long COVID" in online media and in other channels to create their illness and group identity, but also to demarcate the personal experience and experiential knowledge of long COVID from that of other sources. Our exploratory study addresses two questions. Firstly, how the mobilization of subjective evidence leads to the recognition of long COVID and the development of treatment interventions in medicine; and secondly, what distinguishes these developments from other examples of subjective evidence mobilization. We argue that the long COVID movement was able to fill crucial knowledge gaps in the pandemic discourses, making long COVID a legitimate concern of official measures to counter the pandemic. By first showing how illness experiences were gathered that defied official classifications of COVID-19, we show how patients made the "long COVID" term. Then we compare the clinical and social identity of long COVID to that of chronic fatigue syndrome (ME/CFS), before we examine the social and epistemic processes at work in the digital and medial discourses that have transformed how the pandemic is perceived through the lens of long COVID. Building on this, we finally demonstrate how the alignment of medical professionals as patients with the movement has challenged the normative role of clinical evidence, leading to new forms of medical action to tackle the pandemic.

Associations of Post-Acute COVID syndrome with physiological and clinical measures 10 months after hospitalization in patients of the first wave

Eur J Intern Med. 2022 Jan; 95:50-60. doi: 10.1016/j.ejim.2021.10.031. Epub 2021 Nov 25.

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Abstract

Background: For a better understanding of the factors underlying the Post-Acute COVID Syndrome, we studied the relationship between symptoms and functional alterations in COVID-19 patients 10 months after hospitalization.

Methods: One-hundred-one patients hospitalized between March 1st and June 30th 2020 participated in a follow-up visit for an assessment of clinical history, comorbidities, lung function, physical capacity and symptoms, including the SGRQ for health-related quality of life, PHQ-9-D for depression, and SOMS-2 J for somatoform disorders. Data were analyzed by univariate comparisons and multiple logistic regression analyses.

Results: Median age was 60 years, 42% were female, 76% had at least one comorbidity, the median length of the hospital stay was 8 days, 19% had been on the ICU. The most prevalent symptoms included shortness of breath (49%), fatigue (49%) and cognitive impairment (39%). Signs of major depression (PHQ-9-D ≥ 10) occurred in 28%/2% ($p < 0.05$) of patients with/without self-reported cognitive impairment, with median total SGRQ score being 25.4/5.3 ($p < 0.05$). There were associations between shortness of breath and BMI, SGRQ and hemoglobin levels; between fatigue, SGRQ and PHQ-9-D; and between cognitive impairment and PHQ-9-D ($p < 0.05$ each) but not with lung function or physical capacity. Characteristics of the acute disease were not related to symptoms.

Conclusions: The findings demonstrate that 10 months after discharge from a hospital stay due to COVID-19, the percentages of patients with symptoms were high. Symptoms showed a consistent pattern but could not be attributed to altered lung function or physical capacity. Our results suggest a role for alternative etiologies including psychosocial factors.

Depression pandemic and cardiovascular risk in the COVID-19 era and long COVID syndrome: Gender makes a difference

Trends Cardiovasc Med. 2022 Jan;32(1):12-17. doi: [10.1016/j.tcm.2021.09.009](https://doi.org/10.1016/j.tcm.2021.09.009). Epub 2021 Oct 5.

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Abstract

The ongoing COVID-19 pandemic highlighted a significant interplay between cardiovascular disease (CVD), COVID-19 related inflammatory status, and depression. Cardiovascular (CV) injury is responsible for a substantial percentage of COVID-19 deaths while COVID-19 social restrictions emerged as a non-negligible risk factor for CVD as well as a variety of mental health issues, and in particular, depression. Inflammation seems to be a shared condition between these two disorders. Gender represents a potential modifying factor both in CVD and depression, as well as in COVID-19 short- and long-term outcomes, particularly in cases involving long-term COVID complications. Results from emerging studies indicate that COVID-19 pandemic affected male and female populations in different ways. Women seem to experience less severe short-term complications but suffer worse long-term COVID complications, including depression, reduced physical activity, and deteriorating lifestyle habits, all of which may impact CV risk. Here, we summarize the current state of knowledge about the interplay between COVID-19, depression, and CV risk in women.

Long COVID following mild SARS-CoV-2 infection: characteristic T cell alterations and response to antihistamines

J Investig Med. 2022 Jan;70(1):61-67. doi: [10.1136/jim-2021-002051](https://doi.org/10.1136/jim-2021-002051). Epub 2021 Oct 5.

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Abstract

Long COVID is characterized by the emergence of multiple debilitating symptoms following SARS-CoV-2 infection. Its etiology is unclear and it often follows a mild acute illness. Anecdotal reports of gradual clinical responses to histamine receptor antagonists (HRAs) suggest a histamine-dependent mechanism that is distinct from anaphylaxis, possibly mediated by T cells, which are also regulated by histamine. T cell perturbations have been previously reported in post-viral syndromes, but the T cell landscape in patients who have recovered from mild COVID-19 and its relationship to both long COVID symptoms and any symptomatic response to HRA remain underexplored. We addressed these questions in an observational study of 65 individuals who had recovered from mild COVID-19. Participants were surveyed between 87 and 408 days after the onset of acute symptoms; none had required hospitalization, 16 had recovered uneventfully, and 49 had developed long COVID. Symptoms were quantified using a structured questionnaire and T cell subsets enumerated in a standard diagnostic assay. Patients with long-COVID had reduced CD4+ and CD8+ effector memory (EM) cell numbers and increased PD-1 (programmed cell death protein 1) expression on central memory (CM) cells, whereas the asymptomatic participants had reduced CD8+ EM cells only and increased CD28 expression on CM cells. 72% of patients with long COVID who received HRA reported clinical improvement, although T cell profiling did not clearly distinguish those who responded to HRA. This study demonstrates that T cell perturbations persist for several months after mild COVID-19 and are associated with long COVID symptoms.

Understanding Long Covid: Nosology, social attitudes and stigma

Brain Behav Immun. 2022 Jan; 99:17-24. doi: [10.1016/j.bbi.2021.09.012](https://doi.org/10.1016/j.bbi.2021.09.012). Epub 2021 Sep 23.

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Abstract

The debate around Long Covid has so far shown resistance to accept parallels between Long Covid and a set of existing conditions which have historically been subject to stigma. This resistance risks endorsing the stigma associated with such existing conditions, and as such, these dynamics of stigma ought to be dismantled in order to facilitate the development of effective clinical resources for all such implicated conditions. As well as affecting proceedings at the structural level, I discuss how the aforementioned problems also risk affecting patients at the personal level by motivating the reconfiguration and restriction of patient illness narratives. The problems I identify therefore risk affecting both collective and individual understanding of Long Covid.

Long COVID: cognitive complaints (brain fog) and dysfunction of the cingulate cortex

J Neurol. 2022 Jan;269(1):44-46. doi: [10.1007/s00415-021-10655-x](https://doi.org/10.1007/s00415-021-10655-x). Epub 2021 Jun 18.

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Abstract

Many patients who have suffered from acute COVID infections have long-lasting symptoms affecting several organs including the brain. This long COVID status can include "brain fog" and cognitive deficits that can disturb activities of daily living and can delay complete recovery. Here, we report two cases of neurological long COVID with abnormal FDG PET findings marked by hypometabolic regions of the cingulate cortex.

Caspases and therapeutic potential of caspase inhibitors in moderate-severe SARS-CoV-2 infection and long COVID

Allergy. 2022 Jan;77(1):118-129. doi: 10.1111/all.14907. Epub 2021 Jun 2.

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Abstract

Background: COVID-19 can present with lymphopenia and extraordinary complex multiorgan pathologies that can trigger long-term sequela.

Aims: Given that inflammasome products, like caspase-1, play a role in the pathophysiology of a number of co-morbid conditions, we investigated caspases across the spectrum of COVID-19 disease.

Materials & methods: We assessed transcriptional states of multiple caspases and using flow cytometry, the expression of active caspase-1 in blood cells from COVID-19 patients in acute and convalescent stages of disease. Non-COVID-19 subject presenting with various comorbid conditions served as controls.

Results: Single-cell RNA-seq data of immune cells from COVID-19 patients showed a distinct caspase expression pattern in T cells, neutrophils, dendritic cells, and eosinophils compared with controls. Caspase-1 was upregulated in CD4+ T-cells from hospitalized COVID-19 patients compared with unexposed controls. Post-COVID-19 patients with lingering symptoms (long-haulers) also showed upregulated caspase-1 activity in CD4+ T-cells that ex vivo was attenuated with a select pan-caspase inhibitor. We observed elevated caspase-3/7 levels in red blood cells from COVID-19 patients compared with controls that was reduced following caspase inhibition.

Discussion: Our preliminary results suggest an exuberant caspase response in COVID-19 that may facilitate immune-related pathological processes leading to severe outcomes. Further clinical correlations of caspase expression in different stages of COVID-19 will be needed.

Conclusion: Pan-caspase inhibition could emerge as a therapeutic strategy to ameliorate or prevent severe COVID-19.

Editorial commentary: Long COVID-19: A tangled web of lungs, heart, mind, and gender

Trends Cardiovasc Med. 2022 Jan; 32(1):18-19. doi: [10.1016/j.tcm.2021.10.004](https://doi.org/10.1016/j.tcm.2021.10.004). Epub 2021 Oct 19.

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No abstract available

Kidney in the net of acute and long-haul coronavirus disease 2019: a potential role for lipid mediators in causing renal injury and fibrosis

Curr Opin Nephrol Hypertens. 2022 Jan 1; 31(1):36-46. doi: [10.1097/MNH.0000000000000750](https://doi.org/10.1097/MNH.0000000000000750).

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Abstract

Purpose of review: Severe COVID-19 disease is often complicated by acute kidney injury (AKI), which may transition to chronic kidney disease (CKD). Better understanding of underlying mechanisms is important in advancing therapeutic approaches.

Recent findings: SARS-CoV-2-induced endothelial injury initiates platelet activation, platelet-neutrophil partnership and release of neutrophil extracellular traps. The resulting thromboinflammation causes ischemia-reperfusion (I/R) injury to end organs. Severe COVID-19 induces a lipid-mediator storm with massive increases in thromboxane A2 (TxA2) and PGD2, which promote thromboinflammation and apoptosis of renal tubular cells, respectively, and thereby enhance renal fibrosis. COVID-19-associated AKI improves rapidly in the majority. However, 15-30% have protracted renal injury, raising the specter of transition from AKI to CKD.

Summary: In COVID-19, the lipid-mediator storm promotes thromboinflammation, ischemia-reperfusion injury and cytotoxicity. The thromboxane A2 and PGD2 signaling presents a therapeutic target with potential to mitigate AKI and transition to CKD. Ramatroban, the only dual antagonist of the thromboxane A2/TP α and PGD2/DPr2 signaling could potentially mitigate renal injury in acute and long-haul COVID. Urgent studies targeting the lipid-mediator storm are needed to potentially reduce the heavy burden of kidney disease emerging in the wake of the current pandemic.

Long-term complications of COVID-19

Am J Physiol Cell Physiol. 2022 Jan 1; 322(1):C1-C11. doi: 10.1152/ajpcell.00375.2021. Epub 2021 Nov 24.

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Abstract

SARS-CoV-2 has rapidly spread across the globe and infected hundreds of millions of people worldwide. As our experience with this virus continues to grow, our understanding of both short-term and long-term complications of infection with SARS-CoV-2 continues to grow as well. Just as there is heterogeneity in the acute infectious phase, there is heterogeneity in the long-term complications seen following COVID-19 illness. The purpose of this review article is to present the current literature with regards to the epidemiology, pathophysiology, and proposed management algorithms for the various long-term sequelae that have been observed in each organ system following infection with SARS-CoV-2. We will also consider future directions, with regards to newer variants of the virus and their potential impact on the long-term complications observed.

Determinants of COVID-19-Related Length of Hospital Stays and Long COVID in Ghana: A Cross-Sectional Analysis

Int J Environ Res Public Health. 2022 Jan 4;19(1):527. doi: 10.3390/ijerph19010527.

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Abstract

Objectives: There is paucity of data on determinants of length of COVID-19 admissions and long COVID, an emerging long-term sequel of COVID-19, in Ghana. Therefore, this study identified these determinants and discussed their policy implications.

Method: Data of 2334 patients seen at the main COVID-19 treatment centre in Ghana were analysed in this study. Their characteristics, such as age, education level and comorbidities, were examined as explanatory variables. The dependent variables were length of COVID-19 hospitalisations and long COVID. Negative binomial and binary logistic regressions were fitted to investigate the determinants.

Result: The regression analyses showed that, on average, COVID-19 patients with hypertension and diabetes mellitus spent almost 2 days longer in hospital ($p = 0.00$, 95% CI = 1.42-2.33) and had 4 times the odds of long COVID (95% CI = 1.61-10.85, $p = 0.003$) compared to those with no comorbidities. In addition, the odds of long COVID decreased with increasing patient's education level (primary OR = 0.73, $p = 0.02$; secondary/vocational OR = 0.26, $p = 0.02$; tertiary education OR = 0.23, $p = 0.12$).

Conclusion: The presence of hypertension and diabetes mellitus determined both length of hospitalisation and long COVID among patients with COVID-19 in Ghana. COVID-19 prevention and management policies should therefore consider these factors.

Double-blind placebo-controlled randomized clinical trial to assess the efficacy of montelukast in mild to moderate respiratory symptoms of patients with long COVID: E-SPERANZA COVID Project study protocol

Trials. 2022 Jan 6;23(1):19. doi: 10.1186/s13063-021-05951-w.

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic continues to affect the globe. After 18 months of the SARS-CoV-2 emergence, clinicians have clearly defined a subgroup of patients with lasting, disabling symptoms. While big strides have been made in understanding the acute phase of SARS-CoV-2 infection, the pathophysiology of long COVID is still largely unknown, and evidence-based, effective treatments for this condition remain unavailable.

Objectives: To evaluate the efficacy of 10 mg oral montelukast every 24 h versus placebo in improving quality of life associated with mild to moderate respiratory symptoms in patients with long COVID as measured with the COPD Assessment Test (CAT) questionnaire. The secondary objectives will evaluate the effect of montelukast versus placebo on improving exercise capacity, COVID-19 symptoms (asthenia, headache, mental confusion or brain fog, ageusia, and anosmia), oxygen desaturation during exertion, functional status, and mortality.

Methods and analysis: Phase III, randomized, double-blind clinical trial. We will include 18- to 80-year-old patients with SARS-CoV-2 infection and mild to moderate respiratory symptoms lasting more than 4 weeks. Participants will be randomly allocated in a 1:1 ratio to the intervention (experimental treatment with 10 mg/day montelukast) or the control group (placebo group), during a 28-day treatment. Follow-up will finish 56 days after the start of treatment. The primary outcome will be health-related quality of life associated with respiratory symptoms according to the COPD Assessment Test 4 weeks after starting the treatment. The following are the secondary outcomes: (a) exercise capacity and oxygen saturation (1-min sit-to-stand test); (b) Post-COVID-19 Functional Status Scale; (c) other symptoms: asthenia, headache, mental confusion (brain fog), ageusia, and anosmia (Likert scale); (d) use of healthcare resources; (e) mortality; (f) sick leave duration in days; and (g) side effects of montelukast.

RACGWVI: Long Haul COVID-19 — PubMed Citations for Jan, Feb, March 2022

Ethics and dissemination: This study has been approved by the Clinical Research Ethics Committee of the IDIAPJGol (reference number 21/091-C). The trial results will be published in open access, peer-reviewed journals and explained in webinars to increase awareness and understanding about long COVID among primary health professionals.

Inappropriate sinus tachycardia in post-COVID-19 syndrome

Sci Rep. 2022 Jan 7;12(1):298. doi: 10.1038/s41598-021-03831-6.

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Abstract

Inappropriate sinus tachycardia (IST) is a common observation in patients with post-COVID-19 syndrome (PCS) but has not yet been fully described to date. To investigate the prevalence and the mechanisms underlying IST in a prospective population of PCS patients. Consecutive patients admitted to the PCS Unit between June and December 2020 with a resting sinus rhythm rate ≥ 100 bpm were prospectively enrolled in this study and further examined by an orthostatic test, 2D echocardiography, 24-h ECG monitoring (heart rate variability was a surrogate for cardiac autonomic activity), quality-of-life and exercise capacity testing, and blood sampling. To assess cardiac autonomic function, a 2:1:1 comparative sub-analysis was conducted against both fully recovered patients with previous SARS-CoV-2 infection and individuals without prior SARS-CoV-2 infection. Among 200 PCS patients, 40 (20%) fulfilled the diagnostic criteria for IST (average age of 40.1 ± 10 years, 85% women, 83% mild COVID-19). No underlying structural heart disease, pro-inflammatory state, myocyte injury, or hypoxia were identified. IST was accompanied by a decrease in most heart rate variability parameters, especially those related to cardiovagal tone: pNN50 (cases 3.2 ± 3 vs. recovered 10.5 ± 8 vs. non-infected 17.3 ± 10 ; $p < 0.001$) and HF band (246 ± 179 vs. 463 ± 295 vs. 1048 ± 570 , respectively; $p < 0.001$). IST is prevalent condition among PCS patients. Cardiac autonomic nervous system imbalance with decreased parasympathetic activity may explain this phenomenon.

Risk factors and incidence of long-COVID syndrome in hospitalized patients: does remdesivir have a protective effect?

QJM. 2022 Jan 9;114(12):865-871. doi: 10.1093/qjmed/hcab297.

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Abstract

Background: The definition of 'long-COVID syndrome' (LCS) is still debated and describes the persistence of symptoms after viral clearance in hospitalized or non-hospitalized patients affected by coronavirus disease 2019 (COVID-19).

Aim: In this study, we examined the prevalence and the risk factors of LCS in a cohort of patients with previous COVID-19 and followed for at least 6 months of follow-up.

Design: We conducted a prospective study including all hospitalized patients affected by COVID-19 at our center of Infectious Diseases (Vercelli, Italy) admitted between 10 March 2020 and 15 January 2021 for at least 6 months after discharge. Two follow-up visits were performed: after 1 and 6 months after hospital discharge. Clinical, laboratory and radiological data were recorded at each visit.

Results: A total of 449 patients were included in the analysis. The LCS was diagnosed in 322 subjects at Visit 1 (71.7%) and in 206 at Visit 2 (45.9); according to the post-COVID-19 functional status scale we observed 147 patients with values 2-3 and 175 with values >3 at Visit 1; at Visit 2, 133 subjects had the score between 2-3 and 73 > 3. In multivariate analysis, intensive care unit (ICU) admission (OR = 2.551; 95% CI = 1.998-6.819; P = 0.019), time of hospitalization (OR = 2.255; 95% CI = 1.018-6.992; P = 0.016) and treatment with remdesivir (OR = 0.641; 95% CI = 0.413-0.782; P < 0.001) were independent predictors of LCS.

Conclusions: Treatment with remdesivir leads to a 35.9% reduction in LCS rate in follow-up. Severity of illness, need of ICU admission and length of hospital stay were factor associated with the persistence of PCS at 6 months of follow-up.

Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection

Front Immunol. 2022 Jan 10; 12:746021. doi: [10.3389/fimmu.2021.746021](https://doi.org/10.3389/fimmu.2021.746021). eCollection 2021.

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Abstract

The recent COVID-19 pandemic is a treatment challenge in the acute infection stage but the recognition of chronic COVID-19 symptoms termed post-acute sequelae SARS-CoV-2 infection (PASC) may affect up to 30% of all infected individuals. The underlying mechanism and source of this distinct immunologic condition three months or more after initial infection remains elusive. Here, we investigated the presence of SARS-CoV-2 S1 protein in 46 individuals. We analyzed T-cell, B-cell, and monocytic subsets in both severe COVID-19 patients and in patients with post-acute sequelae of COVID-19 (PASC). The levels of both intermediate (CD14+, CD16+) and non-classical monocyte (CD14Lo, CD16+) were significantly elevated in PASC patients up to 15 months post-acute infection compared to healthy controls ($P=0.002$ and $P=0.01$, respectively). A statistically significant number of non-classical monocytes contained SARS-CoV-2 S1 protein in both severe ($P=0.004$) and PASC patients ($P=0.02$) out to 15 months post-infection. Non-classical monocytes were sorted from PASC patients using flow cytometric sorting and the SARS-CoV-2 S1 protein was confirmed by mass spectrometry. Cells from 4 out of 11 severe COVID-19 patients and 1 out of 26 PASC patients contained ddPCR+ peripheral blood mononuclear cells, however, only fragmented SARS-CoV-2 RNA was found in PASC patients. No full length sequences were identified, and no sequences that could account for the observed S1 protein were identified in any patient. That non-classical monocytes may be a source of inflammation in PASC warrants further study.

Exploring the Neuropsychiatric Sequelae of Perceived COVID-19 Exposure in College Students: A Pilot Digital Phenotyping Study

Front Psychiatry. 2022 Jan 10; 12:788926. doi: 10.3389/fpsy.2021.788926. eCollection 2021.

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Abstract

The urgency to understand the long-term neuropsychiatric sequela of COVID-19, a part of the Post-Acute COVID-19 Syndrome (PACS), is expanding as millions of infected individuals experience new unexplained symptoms related to mood, anxiety, insomnia, headache, pain, and more. Much research on PACS involves cross sectional surveys which limits ability to understand the dynamic trajectory of this emerging phenomenon. In this secondary analysis, we analyzed data from a 4-week observational digital phenotyping study using the mindLAMP app for 695 college students with elevated stress who specified if they were exposed to COVID-19. Students also completed a biweekly survey of clinical assessments to obtain active data. Additionally, passive data streams like GPS, accelerometer, and screen state were extracted from phone sensors and through features the group built. Three hundred and eighty-second number participants successfully specified their COVID-19 exposure and completed the biweekly survey. From active smartphone data, we found significantly higher scores for the Prodromal Questionnaire (PQ) and the Pittsburgh Sleep Quality Index (PSQI) for students reporting exposure to COVID-19 compared to those who were not ($p < 0.05$). Additionally, we found significantly decreased sleep duration as captured from the smartphone via passive data for the COVID-19 exposed group ($p < 0.05$). No significant differences were detected for other surveys or passive sensors. Smartphones can capture both self-reported symptoms and behavioral changes related to PACS. Our results around changes in sleep highlight how digital phenotyping methods can be used in a scalable and accessible manner toward better capturing the evolving phenomena of PACS. The present study further provides a foundation for future research to implement improving digital phenotyping methods.

Post-sequelae symptoms and comorbidities after COVID-19

J Med Virol. 2022 Jan 14. doi: [10.1002/jmv.27586](https://doi.org/10.1002/jmv.27586). Online ahead of print.

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Abstract

The frequency, severity, and forms of symptoms months after coronavirus 2019 (COVID-19) are poorly understood, especially in community settings. To better understand and characterize symptoms months after community-based COVID-19, a retrospective cohort analysis was conducted. Three hundred and twenty-eight consecutive persons with a positive test for SARS-CoV-2 in the Johns Hopkins Health System, Maryland, March-May 2020, were selected for the study. Symptom occurrence and severity were measured through questionnaires. Of 328 persons evaluated, a median of 242 days (109-478 days) from the initial positive SARS-CoV-2 test, 33.2% reported not being fully recovered and 4.9% reported symptoms that constrained daily activities. Compared to those who reported being fully recovered, those with post-acute sequelae were more likely to report a prior history of heart attack ($p < 0.01$). Among those reporting long-term symptoms, men and women were equally represented (men = 34.8%, women = 34.6%), but only women reported symptoms that constrained daily activities, and 56% of them were caregivers. The types of new or persistent symptoms varied, and for many, included a deviation from prior COVID-19 health, such as being less able to exercise, walk, concentrate, or breathe. A limitation is that self-report of symptoms might be biased and/or caused by factors other than COVID-19. Overall, even in a community setting, symptoms may persist months after COVID-19 reducing daily activities including caring for dependents.

Stellate ganglion block reduces symptoms of Long COVID: A case series

J Neuroimmunol. 2022 Jan 15; 362:577784. doi: 10.1016/j.jneuroim.2021.577784. Epub 2021 Dec 8.

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Abstract

After recovering from COVID-19, a significant proportion of symptomatic and asymptomatic individuals develop Long COVID. Fatigue, orthostatic intolerance, brain fog, anosmia, and ageusia/dysgeusia in Long COVID resemble "sickness behavior," the autonomic nervous system response to pro-inflammatory cytokines (Dantzer et al., 2008). Aberrant network adaptation to sympathetic/parasympathetic imbalance is expected to produce long-standing dysautonomia. Cervical sympathetic chain activity can be blocked with local anesthetic, allowing the regional autonomic nervous system to "reboot." In this case series, we successfully treated two Long COVID patients using stellate ganglion block, implicating dysautonomia in the pathophysiology of Long COVID and suggesting a novel treatment.

Trigger point injections and dry needling can be effective in treating long COVID syndrome-related myalgia: a case report

J Med Case Rep. 2022 Jan 17;16(1):31. doi: 10.1186/s13256-021-03239-w.

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Abstract

Introduction: Myofascial pain is a complex health condition that affects the majority of the general population. Myalgia has been recognized as a symptom of long COVID syndrome. The treatment for long COVID syndrome-related myalgia lacks research. Dry needling is a technique that involves the insertion of a needle into the tissue of, or overlaying, a pain point. Wet needling is the addition of an injection of an analgesic substance such as lidocaine while performing needling. Both dry and wet needling have are practiced as treatment modalities for myofascial pain. Limited literature exists to define long COVID syndrome-related myalgia and its relation to myofascial pain, or to examine the utility of needling techniques for this pain. We report a case of dry and wet needling as effective treatments for long COVID-related myofascial pain.

Case presentation: A 59-year-old, previously healthy Hispanic male with no comorbid conditions was diagnosed with COVID-19 pneumonia. The patient suffered moderate disease without hypoxia and was never hospitalized. Three months later, the patient continued to suffer from symptoms such as exertional dyspnea, "brain fog," and myalgia. An extensive multisystem workup revealed normal cardiac, pulmonary, and end organ functions. The patient was then diagnosed with long COVID syndrome. The nature and chronicity of the patient's myalgia meet the criteria for myofascial pain. Both wet and dry needling were used to treat the patient's myofascial pain, with good short- and long-term therapeutic effects.

Conclusions: COVID-19 infection has been shown to exacerbate preexisting myofascial pain syndrome. Our case report indicates that long COVID syndrome-related myalgia is likely a form of new-onset myofascial pain. Additionally, both wet and dry needling can be utilized as an effective treatment modality for this pain syndrome, with short- and long-term benefits.

Evolution of anti-SARS-CoV-2 immune response in a cohort of French healthcare workers followed for 7 months

Infect Dis Now. 2022 Jan 18; S2666-9919(22)00004-5. doi: 10.1016/j.idnow.2022.01.004. Online ahead of print.

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Abstract

Objectives: We aimed to understand the immune response among healthcare workers (HCWs) following SARS-CoV-2 infection, and to determine the infection prevalence during the first wave of the pandemic among workers in our hospital.

Methods: Determination of the serological status against SARS-CoV-2 (nucleocapsid) was offered to all HCWs. All HCWs with positive SARS-CoV-2 serology were proposed to be included in a longitudinal medical and serological follow-up (anti-spike) for 7 months.

Results: We included 3,062 HCWs; 256 (8.4%) were positive for anti-SARS-CoV-2 nucleocapsid IgG. Among them, early decrease in the anti-nucleocapsid antibody index was observed between the first (S1) and second (S2) serology samplings in 208 HCWs (84.2%). The initial anti-nucleocapsid IgG index seemed to be related to the HCWs' age. Seventy-four HCWs were included in the 7-month cohort study. Among them, 69 (90.5%) had detectable anti-spike IgG after 7 months and 24 (32.4%) reported persistent symptoms consistent with post-acute COVID-19 syndrome diagnosis.

Conclusion: The prevalence of serological positivity among HCWs was 6.7%. Infection should be followed by vaccination because of antibody decrease.

Multiple early factors anticipate post-acute COVID-19 sequelae

Cell. 2022 Jan 25; S0092-8674(22)00072-1. doi: [10.1016/j.cell.2022.01.014](https://doi.org/10.1016/j.cell.2022.01.014). Online ahead of print.

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Abstract

Post-acute sequelae of COVID-19 (PASC) represent an emerging global crisis. However, quantifiable risk factors for PASC and their biological associations are poorly resolved. We executed a deep multi-omic, longitudinal investigation of 309 COVID-19 patients from initial diagnosis to convalescence (2-3 months later), integrated with clinical data and patient-reported symptoms. We resolved four PASC-anticipating risk factors at the time of initial COVID-19 diagnosis: type 2 diabetes, SARS-CoV-2 RNAemia, Epstein-Barr virus viremia, and specific auto-antibodies. In patients with gastrointestinal PASC, SARS-CoV-2-specific and CMV-specific CD8+ T cells exhibited unique dynamics during recovery from COVID-19. Analysis of symptom-associated immunological signatures revealed coordinated immunity polarization into four endotypes, exhibiting divergent acute severity and PASC. We find that immunological associations between PASC factors diminish over time, leading to distinct convalescent immune states. Detectability of most PASC factors at COVID-19 diagnosis emphasizes the importance of early disease measurements for understanding emergent chronic conditions and suggests PASC treatment strategies.¹⁴ December 2021, Accepted 19 January 2022, Available online 25 January 2022.

Cerebrospinal fluid findings in COVID-19: a multicenter study of 150 lumbar punctures in 127 patients

J Neuroinflammation. 2022 Jan 20;19(1):19. doi: [10.1186/s12974-021-02339-0](https://doi.org/10.1186/s12974-021-02339-0).

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Abstract

Background: Comprehensive data on the cerebrospinal fluid (CSF) profile in patients with COVID-19 and neurological involvement from large-scale multicenter studies are missing so far.

Objective: To analyze systematically the CSF profile in COVID-19.

Methods: Retrospective analysis of 150 lumbar punctures in 127 patients with PCR-proven COVID-19 and neurological symptoms seen at 17 European university centers **RESULTS:** The most frequent pathological finding was blood-CSF barrier (BCB) dysfunction (median QAlb 11.4 [6.72-50.8]), which was present in 58/116 (50%) samples from patients without pre-/coexisting CNS diseases (group I). QAlb remained elevated > 14d (47.6%) and even > 30d (55.6%) after neurological onset. CSF total protein was elevated in 54/118 (45.8%) samples (median 65.35 mg/dl [45.3-240.4]) and strongly correlated with QAlb. The CSF white cell count (WCC) was increased in 14/128 (11%) samples (mostly lympho-monocytic; median 10 cells/ μ l, > 100 in only 4). An albuminocytological dissociation (ACD) was found in 43/115 (37.4%) samples. CSF L-lactate was increased in 26/109 (24%; median 3.04 mmol/l [2.2-4]). CSF-IgG was elevated in 50/100 (50%), but was of peripheral origin, since QIgG was normal in almost all cases, as were QIgA and QIgM. In 58/103 samples (56%) pattern 4 oligoclonal bands (OCB) compatible with systemic inflammation were present, while CSF-restricted OCB were found in only 2/103 (1.9%). SARS-CoV-2-CSF-PCR was negative in 76/76 samples. Routine CSF findings were normal in 35%. Cytokine levels were frequently elevated in the CSF (often associated with BCB dysfunction) and serum, partly remaining positive at high levels for weeks/months (939 tests). Of note, a positive SARS-CoV-2-IgG-antibody index (AI) was found in 2/19 (10.5%) patients which was associated with unusually high WCC in both of them and a strongly increased interleukin-6 (IL-6) index in one (not tested in the other). Anti-neuronal/anti-glia autoantibodies were mostly absent in the CSF and serum (1509 tests). In samples from patients with pre-/coexisting CNS disorders (group II [N = 19]; including multiple sclerosis, JC-virus-associated immune reconstitution inflammatory syndrome, HSV/VZV encephalitis/meningitis, CNS lymphoma, anti-Yo syndrome, subarachnoid hemorrhage), CSF findings were mostly representative of the respective disease.

Conclusions: The CSF profile in COVID-19 with neurological symptoms is mainly characterized by BCB disruption in the absence of intrathecal inflammation, compatible with cerebrospinal endotheliopathy. Persistent BCB dysfunction and elevated cytokine levels may contribute to both acute symptoms and 'long COVID'. Direct infection of the CNS with SARS-CoV-2, if occurring at all, seems to be rare. Broad differential diagnostic considerations are recommended to avoid misinterpretation of treatable coexisting neurological disorders as complications of COVID-19.

SEattle-based Research of Chinese Herbs for COVID-19 Study: A Whole Health Perspective on Chinese Herbal Medicine for Symptoms that may be Related to COVID-19

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Abstract

Introduction: East Asian Medicine (EAM) is a Whole System medicine that includes Chinese herbal medicine (CHM). Chinese herbal medicine has been utilized to reduce symptom burden in infectious disease, with notable theoretical reformulations during pandemics of the 3rd, 13th, and 17th centuries. Today, Licensed Acupuncturists trained in CHM have utilized it to treat symptoms and sequelae of COVID-19. However, little is known about its use or efficacy by the public and health practitioners. Understanding and evaluating whole medicine systems of healthcare is inherently complex; there is international consensus for a descriptive, pragmatic approach. We are conducting a feasibility pilot study using a prospective, pragmatic, observational design using Whole Health and Whole Person perspectives. The complexity of COVID-19 reflects the impact on multiple homeoregulatory systems and provides a unique opportunity to assess the impact of interventions such as EAM on whole health. Observation of these EAM encounters will provide valuable qualitative and quantitative data on the interface of an extant Whole System medicine with a novel complex illness as a precursor to a randomized clinical trial.

Methods: This ongoing study observes a CHM clinic offering telehealth consultations to a diverse patient population since April, 2020. Patients who report symptoms potentially related to COVID-19 disease are consented for standardized collection and analysis of demographic and clinical data from each clinical encounter.

Results: To date, 61 patients engaged in 195 consultations (mean 3.3) with 49 reporting symptom resolution sufficient to complete treatment, and 4 withdrawals. Just over half (62%) were female, with an average age of 45.7 years. A wide variety of CHM formulas and EAM dietary and lifestyle modifications were provided.

Discussion: Adequate recruitment and retention suggest feasibility of the intervention and data collection. The rich dataset may facilitate the construction of Whole Health models of CHM's clinical impact, as well as integrative inquiry into CHM's effects on symptoms.

Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome

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Abstract

Background: Long-term complications after COVID-19 are common, but the potential cause for persistent symptoms after viral clearance remains unclear.

Objective: To investigate whether gut microbiome composition is linked to post-acute COVID-19 syndrome (PACS), defined as at least one persistent symptom 4 weeks after clearance of the SARS-CoV-2 virus.

Methods: We conducted a prospective study of 106 patients with a spectrum of COVID-19 severity followed up from admission to 6 months and 68 non-COVID-19 controls. We analysed serial faecal microbiome of 258 samples using shotgun metagenomic sequencing, and correlated the results with persistent symptoms at 6 months.

Results: At 6 months, 76% of patients had PACS and the most common symptoms were fatigue, poor memory and hair loss. Gut microbiota composition at admission was associated with occurrence of PACS. Patients without PACS showed recovered gut microbiome profile at 6 months comparable to that of non-COVID-19 controls. Gut microbiome of patients with PACS were characterised by higher levels of *Ruminococcus gnavus*, *Bacteroides vulgatus* and lower levels of *Faecalibacterium prausnitzii*. Persistent respiratory symptoms were correlated with opportunistic gut pathogens, and neuropsychiatric symptoms and fatigue were correlated with nosocomial gut pathogens, including *Clostridium innocuum* and *Actinomyces naeslundii* (all $p < 0.05$). Butyrate-producing bacteria, including *Bifidobacterium pseudocatenulatum* and *Faecalibacterium prausnitzii* showed the largest inverse correlations with PACS at 6 months.

Conclusion: These findings provided observational evidence of compositional alterations of gut microbiome in patients with long-term complications of COVID-19. Further studies should investigate whether microbiota modulation can facilitate timely recovery from post-acute COVID-19 syndrome.

Post-acute COVID-19 syndrome in patients after 12 months from COVID-19 infection in Korea

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Abstract

Background: As the coronavirus disease 2019 (COVID-19) pandemic continues to progress, awareness about its long-term impacts has been growing. To date, studies on the long-term course of symptoms, factors associated with persistent symptoms, and quality of life after 12 months since recovery from acute COVID-19 have been limited.

Methods: A prospective online survey (First: September 8, 2020-September 10, 2020; Second: May 26, 2021-June 1, 2021) was conducted on recovered patients who were previously diagnosed with COVID-19 between February 13, 2020 and March 13, 2020 at Kyungpook National University Hospital. Responders aged between 17 and 70 years were included in the study. Overall, 900 and 241 responders were followed up at 6 and 12 months after recovery from COVID-19 in the first and second surveys, respectively. Clinical characteristics, self-reported persistent symptoms, and EuroQol-5-dimension (EQ5D) index score were investigated for evaluating quality of life.

Results: The median period from the date of the first symptom onset or COVID-19 diagnosis to the time of the survey was 454 (interquartile range [IQR] 451-458) days. The median age of the responders was 37 (IQR 26.0-51.0) years, and 164 (68.0%) responders were women. Altogether, 11 (4.6%) responders were asymptomatic, and 194 (80.5%), 30 (12.4%), and 6 (2.5%) responders had mild, moderate, and severe illness, respectively. Overall, 127 (52.7%) responders still experienced COVID-19-related persistent symptoms and 12 (5.0%) were receiving outpatient treatment for such symptoms. The main symptoms were difficulty in concentration, cognitive dysfunction, amnesia, depression, fatigue, and anxiety. Considering the EQ5D index scores, only 59.3% of the responders did not have anxiety or depression. Older age, female sex, and disease severity were identified as risk factors for persistent neuropsychiatric symptoms.

Conclusion: COVID-19-related persistent symptoms improved over time; however, neurological symptoms can last longer than other symptoms. Continuous careful observation of symptom improvement and multidisciplinary integrated research on recovered COVID-19 patients are required.

What should a family physician know about nutrition and physical exercise rehabilitation' advices to communicate to "long-term COVID-19" patients?

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Abstract

In real practice, there is a paradox in the management of patients with "long-term Covid-19". Indeed, Family physicians (FPs) are on the front line in the management process of these patients. For "long-term Covid-19" patients, and according to the World Health Organization guideline, the cardiopulmonary rehabilitation (CPR) should be provided not only at tertiary- or secondary- care, but mainly at primary-care with a real implication of FPs. However, specific guidelines/recommendations were addressed for FPs. Therefore, an alternative including the CPR minimal advice that a FP should provide to "long-term Covid-19" patients, seems to be necessary to respond to the needs of FPs to face their involvement with "long-term Covid-19" patients. Thus, this paper aimed to report the CPR "minimal advice" that should be provided by FPs managing "long-term Covid-19" patients with incapacity (i.e.; alteration of the cardiorespiratory and muscular chain). According to the authors, FPs should be more cautious in the prescription of exercise and nutrition program and informed about the minimal advices related to nutritional and physical exercise rehabilitation guidelines when taking care of "long-term Covid-19" patients, and how these guidelines can relieve the mental and physical problems, improve immunity, and accelerate the recovery process of the patients. With the occurrence of new variants of the severe acute respiratory syndrome coronavirus 2, the nutritional and exercise rehabilitation guidelines implemented by FPs become indispensable to promote the recovery of Covid-19 patients and support a return to normal life.

Case Report: Overlap Between Long COVID and Functional Neurological Disorders

Front Neurol. 2022 Jan 28; 12:811276. doi: 10.3389/fneur.2021.811276. eCollection 2021.

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Abstract

Long lasting symptoms have been reported in a considerable proportion of patients after a severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection. This condition, defined as either "post-acute coronavirus disease (COVID)," "long COVID," or "long-haul COVID," has also been described in outpatients and in individuals who are asymptomatic during the acute infection. A possible overlap exists between this condition and the functional neurological disorders (FNDs). We report a 23-year-old man who developed, after asymptomatic COVID-19, a complex symptomatology characterized by fatigue, episodic shortness of breath, nocturnal tachycardia, and chest pain. He also complained of attention and memory difficulties, fluctuating limb dysesthesia, and weakness of his left arm. After neurological examination, a diagnosis of FND was made. Notably, the patient was also evaluated at a post-COVID center and received a diagnosis of long COVID-19 syndrome. After 4 months of psychoanalytic psychotherapy and targeted physical therapy in our center for FNDs, dysesthesia and motor symptoms had resolved, and the subjective cognitive complaints had improved significantly. However, the patient had not fully recovered as mild symptoms persisted limiting physical activities. Long-term post COVID symptoms and FNDs may share underlying biological mechanisms, such as stress and inflammation. Our case suggests that functional symptoms may coexist with the long COVID symptoms and may improve with targeted interventions. In patients presenting with new fluctuating symptoms after SARS-CoV-2 infection, the diagnosis of FNDs should be considered, and the positive clinical signs should be carefully investigated.

"LONG COVID"-A hypothesis for understanding the biological basis and pharmacological treatment strategy

Pharmacol Res Perspect. 2022 Feb; 10(1): e00911. doi: 10.1002/prp2.911.

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Abstract

Infection of humans with SARS-CoV-2 virus causes a disease known colloquially as "COVID-19" with symptoms ranging from asymptomatic to severe pneumonia. Initial pathology is due to the virus binding to the ACE-2 protein on endothelial cells lining blood vessels and entering these cells in order to replicate. Viral replication causes oxidative stress due to elevated levels of reactive oxygen species. Many (~60%) of the infected people appear to have eliminated the virus from their body after 28 days and resume normal activity. However, a significant proportion (~40%) experience a variety of symptoms (loss of smell and/or taste, fatigue, cough, aching pain, "brain fog," insomnia, shortness of breath, and tachycardia) after 12 weeks and are diagnosed with a syndrome named "LONG COVID." Longitudinal clinical studies in a group of subjects who were infected with SARS-CoV-2 have been compared to a non-infected matched group of subjects. A cohort of infected subjects can be identified by a battery of cytokine markers to have persistent, low level grade of inflammation and often self-report two or more troubling symptoms. There is no drug that will relieve their symptoms effectively. It is hypothesized that drugs that activate the intracellular transcription factor, nuclear factor erythroid-derived 2-like 2 (NRF2) may increase the expression of enzymes to synthesize the intracellular antioxidant, glutathione that will quench free radicals causing oxidative stress. The hormone melatonin has been identified as an activator of NRF2 and a relatively safe chemical for most people to ingest chronically. Thus, it is an option for consideration of re-purposing studies in "LONG COVID" subjects experiencing insomnia, depression, fatigue, and "brain fog" but not tachycardia. Appropriately designed clinical trials are required to evaluate melatonin.

Pathological sequelae of long-haul COVID

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Abstract

The world continues to contend with successive waves of coronavirus disease 2019 (COVID-19), fueled by the emergence of viral variants. At the same time, persistent, prolonged and often debilitating sequelae are increasingly recognized in convalescent individuals, named 'post-COVID-19 syndrome' or 'long-haul COVID'. Clinical symptomatology includes fatigue, malaise, dyspnea, defects in memory and concentration and a variety of neuropsychiatric syndromes as the major manifestations, and several organ systems can be involved. The underlying pathophysiological mechanisms are poorly understood at present. This Review details organ-specific sequelae of post-COVID-19 syndromes and examines the underlying pathophysiological mechanisms available so far, elaborating on persistent inflammation, induced autoimmunity and putative viral reservoirs. Finally, we propose diagnostic strategies to better understand this heterogeneous disorder that continues to afflict millions of people worldwide.

Antihistamines for Postacute Sequelae of SARS-CoV-2 Infection

J Nurse Pract. 2022 Feb 7. doi: [10.1016/j.nurpra.2021.12.016](https://doi.org/10.1016/j.nurpra.2021.12.016). Online ahead of print.

Melissa D Pinto, Natalie Lambert, Charles A Downs, Heather Abraham, Thomas D Hughes, Amir M Rahmani, Candace W Burton, Rana Chakraborty

Abstract

Postacute sequelae of SARS-CoV2 (PASC) infection is an emerging global health crisis, variably affecting millions worldwide. PASC has no established treatment. We describe 2 cases of PASC in response to opportune administration of over-the-counter antihistamines, with significant improvement in symptoms and ability to perform activities of daily living. Future studies are warranted to understand the potential role of histamine in the pathogenesis of PASC and explore the clinical benefits of antihistamines in the treatment of PASC.

Long-term cardiovascular outcomes of COVID-19

Nat Med. 2022 Feb 7. doi: [10.1038/s41591-022-01689-3](https://doi.org/10.1038/s41591-022-01689-3). Online ahead of print.

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Abstract

The cardiovascular complications of acute coronavirus disease 2019 (COVID-19) are well described, but the post-acute cardiovascular manifestations of COVID-19 have not yet been comprehensively characterized. Here we used national healthcare databases from the US Department of Veterans Affairs to build a cohort of 153,760 individuals with COVID-19, as well as two sets of control cohorts with 5,637,647 (contemporary controls) and 5,859,411 (historical controls) individuals, to estimate risks and 1-year burdens of a set of pre-specified incident cardiovascular outcomes. We show that, beyond the first 30 d after infection, individuals with COVID-19 are at increased risk of incident cardiovascular disease spanning several categories, including cerebrovascular disorders, dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure and thromboembolic disease. These risks and burdens were evident even among individuals who were not hospitalized during the acute phase of the infection and increased in a graded fashion according to the care setting during the acute phase (non-hospitalized, hospitalized and admitted to intensive care). Our results provide evidence that the risk and 1-year burden of cardiovascular disease in survivors of acute COVID-19 are substantial. Care pathways of those surviving the acute episode of COVID-19 should include attention to cardiovascular health and disease.

Clinical patterns of somatic symptoms in patients suffering from post-acute long COVID: a systematic review

Eur J Clin Microbiol Infect Dis. 2022 Feb 10;1-31. doi: 10.1007/s10096-022-04417-4. Online ahead of print.

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Abstract

Background: Long COVID-19 may affect patients after hospital discharge.

Aims: This study aims to describe the burden of the long-term persistence of clinical symptoms in COVID-19 patients.

Methods: We conducted a systematic review by using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline. The PubMed and Google Scholar databases were searched for studies that included information on the prevalence of somatic clinical symptoms lasting at least 4 weeks after the onset of a PCR- or serology-confirmed diagnosis of COVID-19. The prevalence of persisting clinical symptoms was assessed and risk factors were described when investigated. Psychological symptoms and cognitive disorders were not evaluated in this study.

Results: Thirty-seven articles met the inclusion criteria. Eighteen studies involved in-patients only with a duration of follow-up of either less than 12 weeks, 12 weeks to 6 months, or more. In these studies, fatigue (16-64%), dyspnea (15-61%), cough (2-59%), arthralgia (8-55%), and thoracic pain (5-62%) were the most frequent persisting symptoms. In nineteen studies conducted in a majority of out-patients, the persistence of these symptoms was lower and 3% to 74% of patients reported prolonged smell and taste disorders. The main risk factors for persisting symptoms were being female, older, having comorbidities and severity at the acute phase of the disease.

Conclusion: COVID-19 patients should have access to dedicated multidisciplinary healthcare allowing a holistic approach. Effective outpatient care for patients with long-COVID-19 requires coordination across multiple sub-specialties, which can be proposed in specialized post-COVID units.

Endocrine Follow-up During Post-Acute COVID-19: Practical Recommendations Based on Available Clinical Evidence

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Abstract

Objective: COVID-19 affects multiple endocrine organ systems during the disease course. However, follow-up data post-COVID-19 is scarce; hitherto available limited data suggest that most of the biochemical endocrine dysfunctions observed during acute phase of COVID-19 tend to improve after recovery. Hence, we aim to provide a rational approach toward endocrine follow-up of patients during post-acute COVID-19.

Methods: We performed a literature review across PubMed/MEDLINE database looking into the effects of COVID-19 on endocrine system and subsequent long-term endocrine sequelae. Accordingly, we have presented a practical set of recommendations regarding endocrine follow-up post-acute COVID-19.

Results: COVID-19 can lead to new-onset hyperglycemia/diabetes mellitus or worsening of dysglycemia in patients with preexisting diabetes mellitus. Hence, those with preexisting diabetes mellitus should ensure optimum glycemic control in the post-COVID-19 period. New-onset diabetes mellitus has been described post-acute COVID-19; hence, a selected group of patients (aged <70 years and those requiring intensive care unit admission) may be screened for the same at 3 months. Thyroid dysfunction (euthyroid sick syndrome and atypical thyroiditis) and adrenal insufficiency have been described in COVID-19; however, thyroid/adrenal functions usually normalize on follow-up; hence, widespread screening post-acute COVID-19 should not be recommended. Pituitary apoplexy and male hypogonadism have rarely been documented in COVID-19; therefore, appropriate follow-up may be undertaken as per clinical context. Hypocalcemia during COVID-19 is not uncommon; however, routine estimation of serum calcium post-COVID-19 is not warranted.

Conclusion: The recommendations herein provide a rational approach that would be expected to guide physicians to better delineate and manage the endocrine sequelae during post-acute COVID-19.

Intravenous immunoglobulin: A potential treatment for the post-acute sequelae of SARS-Cov-2 infection?

Bosn J Basic Med Sci. 2022 Feb 12. doi: [10.17305/bjbms.2021.6901](https://doi.org/10.17305/bjbms.2021.6901). Online ahead of print.

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No abstract available

Metabolic rewiring and serotonin depletion in patients with postacute sequelae of COVID-19

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No abstract available

Endothelial dysfunction in COVID-19: A potential predictor of long-COVID?

Int J Cardiol. 2022 Feb 15; 349:155-156. doi: [10.1016/j.ijcard.2021.11.051](https://doi.org/10.1016/j.ijcard.2021.11.051). Epub 2021 Nov 24.

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No abstract available

A Novel Glucocorticoid and Androgen Receptor Modulator Reduces Viral Entry and Innate Immune Inflammatory Responses in the Syrian Hamster Model of SARS-CoV-2 Infection

Front Immunol. 2022 Feb 16; 13:811430. doi: [10.3389/fimmu.2022.811430](https://doi.org/10.3389/fimmu.2022.811430). eCollection 2022.

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Abstract

Despite significant research efforts, treatment options for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remain limited. This is due in part to a lack of therapeutics that increase host defense to the virus. Replication of SARS-CoV-2 in lung tissue is associated with marked infiltration of macrophages and activation of innate immune inflammatory responses that amplify tissue injury. Antagonists of the androgen (AR) and glucocorticoid (GR) receptors have shown efficacy in models of COVID-19 and in clinical studies because the cell surface proteins required for viral entry, angiotensin converting enzyme 2 (ACE2) and the transmembrane protease, serine 2 (TMPRSS2), are transcriptionally regulated by these receptors. We postulated that the GR and AR modulator, PT150, would reduce infectivity of SARS-CoV-2 and prevent inflammatory lung injury in the Syrian golden hamster model of COVID-19 by down-regulating expression of critical genes regulated through these receptors. Animals were infected intranasally with 2.5×10^4 TCID50/ml equivalents of SARS-CoV-2 (strain 2019-nCoV/USA-WA1/2020) and PT150 was administered by oral gavage at 30 and 100 mg/Kg/day for a total of 7 days. Animals were examined at 3, 5 and 7 days post-infection (DPI) for lung histopathology, viral load and production of proteins regulating the progression of SARS-CoV-2 infection. Results indicated that oral administration of PT150 caused a dose-dependent decrease in replication of SARS-CoV-2 in lung, as well as in expression of ACE2 and TMPRSS2. Lung hypercellularity and infiltration of macrophages and CD4+ T-cells were dramatically decreased in PT150-treated animals, as was tissue damage and expression of IL-6. Molecular docking studies suggest that PT150 binds to the co-activator interface of the ligand-binding domain of both AR and GR, thereby acting as an allosteric modulator and transcriptional repressor of these receptors. Phylogenetic analysis of AR and GR revealed a high degree of sequence identity maintained across multiple species, including humans, suggesting that the mechanism of action and therapeutic efficacy observed in Syrian hamsters would likely be predictive of positive outcomes in patients. PT150 is therefore a strong candidate for further clinical development for the treatment of COVID-19 across variants of SARS-CoV-2.

A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications

Biochem J. 2022 Feb 17;479(4):537-559. doi: 10.1042/BCJ20220016.

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Abstract

Post-acute sequelae of COVID (PASC), usually referred to as 'Long COVID' (a phenotype of COVID-19), is a relatively frequent consequence of SARS-CoV-2 infection, in which symptoms such as breathlessness, fatigue, 'brain fog', tissue damage, inflammation, and coagulopathies (dysfunctions of the blood coagulation system) persist long after the initial infection. It bears similarities to other post-viral syndromes, and to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Many regulatory health bodies still do not recognize this syndrome as a separate disease entity, and refer to it under the broad terminology of 'COVID', although its demographics are quite different from those of acute COVID-19. A few years ago, we discovered that fibrinogen in blood can clot into an anomalous 'amyloid' form of fibrin that (like other β -rich amyloids and prions) is relatively resistant to proteolysis (fibrinolysis). The result, as is strongly manifested in platelet-poor plasma (PPP) of individuals with Long COVID, is extensive fibrin amyloid microclots that can persist, can entrap other proteins, and that may lead to the production of various autoantibodies. These microclots are more-or-less easily measured in PPP with the stain thioflavin T and a simple fluorescence microscope. Although the symptoms of Long COVID are multifarious, we here argue that the ability of these fibrin amyloid microclots (fibrinaloids) to block up capillaries, and thus to limit the passage of red blood cells and hence O₂ exchange, can actually underpin the majority of these symptoms. Consistent with this, in a preliminary report, it has been shown that suitable and closely monitored 'triple' anticoagulant therapy that leads to the removal of the microclots also removes the other symptoms. Fibrin amyloid microclots represent a novel and potentially important target for both the understanding and treatment of Long COVID and related disorders.

Persistent post-discharge symptoms after COVID-19 in rheumatic and musculoskeletal diseases

Rheumatol Adv Pract. 2022 Feb 17;6(1): rkac008. doi: 10.1093/rap/rkac008. eCollection 2022.

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Abstract

Objectives: We aimed to describe persistent symptoms and sequelae in patients with rheumatic and musculoskeletal diseases (RMD) after admission owing to coronavirus disease 2019 (COVID-19), assessing the role of autoimmune rheumatic diseases (ARDs) compared with non-autoimmune rheumatic and musculoskeletal diseases (NARDs) on persistent symptoms and sequelae.

Methods: We performed an observational study including RMD patients who attended a rheumatology clinic in Madrid and required admission owing to COVID-19 (between March and May 2020) and survived. The study began at discharge and ran until October 2020. Main outcomes were persistence of symptoms and sequelae related to COVID-19. The independent variable was the RMD group (ARD and NARD). Covariates included sociodemographics, clinical and treatment data. We ran a multivariate logistic regression model to assess the risk of the main outcomes by RMD group.

Results: We included 105 patients, of whom 51.5% had ARD and 68.57% reported at least one persistent symptom. The most frequent symptoms were dyspnoea, fatigue and chest pain. Sequelae were recorded in 31 patients. These included lung damage in 10.4% of patients, lymphopenia in 10%, a central retinal vein occlusion and an optic neuritis. Two patients died. Eleven patients required re-admission owing to COVID-19 problems (16.7% ARD vs 3.9% NARD; $P = 0.053$). No statistically significant differences were found between RMD groups in the final models.

Conclusion: Many RMD patients have persistent symptoms, as in other populations. Lung damage is the most frequent sequela. Compared with NARD, ARD does not seem to differ in terms of persistent symptoms or consequences, although ARD might have more re-admissions owing to COVID-19.

Neurological manifestations of long-COVID syndrome: a narrative review

Ther Adv Chronic Dis. 2022 Feb 17; 13:20406223221076890. doi: 10.1177/20406223221076890. eCollection 2022.

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Abstract

Accumulating evidence points toward a very high prevalence of prolonged neurological symptoms among coronavirus disease 2019 (COVID-19) survivors. To date, there are no solidified criteria for 'long-COVID' diagnosis. Nevertheless, 'long-COVID' is conceptualized as a multi-organ disorder with a wide spectrum of clinical manifestations that may be indicative of underlying pulmonary, cardiovascular, endocrine, hematologic, renal, gastrointestinal, dermatologic, immunological, psychiatric, or neurological disease. Involvement of the central or peripheral nervous system is noted in more than one-third of patients with antecedent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, while an approximately threefold higher incidence of neurological symptoms is recorded in observational studies including patient-reported data. The most frequent neurological manifestations of 'long-COVID' encompass fatigue; 'brain fog'; headache; cognitive impairment; sleep, mood, smell, or taste disorders; myalgias; sensorimotor deficits; and dysautonomia. Although very limited evidence exists to date on the pathophysiological mechanisms implicated in the manifestation of 'long-COVID', neuroinflammatory and oxidative stress processes are thought to prevail in propagating neurological 'long-COVID' sequelae. In this narrative review, we sought to present a comprehensive overview of our current understanding of clinical features, risk factors, and pathophysiological processes of neurological 'long-COVID' sequelae. Moreover, we propose diagnostic and therapeutic algorithms that may aid in the prompt recognition and management of underlying causes of neurological symptoms that persist beyond the resolution of acute COVID-19. Furthermore, as causal treatments for 'long-COVID' are currently unavailable, we propose therapeutic approaches for symptom-oriented management of neurological 'long-COVID' symptoms. In addition, we emphasize that collaborative research initiatives are urgently needed to expedite the development of preventive and therapeutic strategies for neurological 'long-COVID' sequelae.

Autonomic neuropathy as post-acute sequela of SARS-CoV-2 infection: a case report

J Neurovirol. 2022 Feb 18; 1-4. doi: [10.1007/s13365-022-01056-5](https://doi.org/10.1007/s13365-022-01056-5). Online ahead of print.

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Abstract

Symptoms of autonomic dysfunction, particularly those of orthostatic intolerance, continue to represent a major component of the currently recognized post-acute sequelae of SARS-CoV-2 infections. Different pathophysiologic mechanisms can be involved in the development of orthostatic intolerance including hypovolemia due to gastrointestinal dysfunction, fatigue-associated deconditioning, and hyperadrenergic state due to pandemic-related anxiety. Additionally, there has been a well-established association of a common primary autonomic disorder like postural orthostatic tachycardia syndrome, a subtype of orthostatic intolerance, with antecedent viral infections. Here we report a case of neuropathic type postural orthostatic tachycardia syndrome as a form of autonomic neuropathy that developed following COVID-19 infection.

Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus

Eur Heart J. 2022 Feb 18; ehac031. doi: [10.1093/eurheartj/ehac031](https://doi.org/10.1093/eurheartj/ehac031). Online ahead of print.

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Abstract

Emerging as a new epidemic, long COVID or post-acute sequelae of coronavirus disease 2019 (COVID-19), a condition characterized by the persistence of COVID-19 symptoms beyond 3 months, is anticipated to substantially alter the lives of millions of people globally. Cardiopulmonary symptoms including chest pain, shortness of breath, fatigue, and autonomic manifestations such as postural orthostatic tachycardia are common and associated with significant disability, heightened anxiety, and public awareness. A range of cardiovascular (CV) abnormalities has been reported among patients beyond the acute phase and include myocardial inflammation, myocardial infarction, right ventricular dysfunction, and arrhythmias. Pathophysiological mechanisms for delayed complications are still poorly understood, with a dissociation seen between ongoing symptoms and objective measures of cardiopulmonary health. COVID-19 is anticipated to alter the long-term trajectory of many chronic cardiac diseases which are abundant in those at risk of severe disease. In this review, we discuss the definition of long COVID and its epidemiology, with an emphasis on cardiopulmonary symptoms. We further review the pathophysiological mechanisms underlying acute and chronic CV injury, the range of post-acute CV sequelae, and impact of COVID-19 on multiorgan health. We propose a possible model for referral of post-COVID-19 patients to cardiac services and discuss future directions including research priorities and clinical trials that are currently underway to evaluate the efficacy of treatment strategies for long COVID and associated CV sequelae.

Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of One-Year Follow-Up Studies on Post-COVID Symptoms

Pathogens. 2022 Feb 19; 11(2):269. doi: 10.3390/pathogens11020269.

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Abstract

Emerging evidence has shown that COVID-19 survivors could suffer from persistent symptoms. However, it remains unclear whether these symptoms persist over the longer term. This study aimed to systematically synthesise evidence on post-COVID symptoms persisting for at least 12 months. We searched PubMed and Embase for papers reporting at least one-year follow-up results of COVID-19 survivors published by 6 November 2021. Random-effects meta-analyses were conducted to estimate pooled prevalence of specific post-COVID symptoms. Eighteen papers that reported one-year follow-up data from 8591 COVID-19 survivors were included. Fatigue/weakness (28%, 95% CI: 18-39), dyspnoea (18%, 95% CI: 13-24), arthromyalgia (26%, 95% CI: 8-44), depression (23%, 95% CI: 12-34), anxiety (22%, 95% CI: 15-29), memory loss (19%, 95% CI: 7-31), concentration difficulties (18%, 95% CI: 2-35), and insomnia (12%, 95% CI: 7-17) were the most prevalent symptoms at one-year follow-up. Existing evidence suggested that female patients and those with more severe initial illness were more likely to suffer from the sequelae after one year. This study demonstrated that a sizeable proportion of COVID-19 survivors still experience residual symptoms involving various body systems one year later. There is an urgent need for elucidating the pathophysiologic mechanisms and developing and testing targeted interventions for long-COVID patients.

Symptoms After COVID-19 Vaccination in Patients with Post-Acute Sequelae of SARS-CoV-2

J Gen Intern Med. 2022 Feb 22; 1-4. doi: [10.1007/s11606-022-07443-2](https://doi.org/10.1007/s11606-022-07443-2). Online ahead of print.

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No abstract available

Long-term follow-up of dynamic brain changes in patients recovered from COVID-19 without neurological manifestations

JCI Insight. 2022 Feb 22;7(4): e155827. doi: 10.1172/jci.insight.155827.

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Abstract

BACKGROUND: After the initial surge in COVID-19 cases, large numbers of patients were discharged from a hospital without assessment of recovery. Now, an increasing number of patients report postacute neurological sequelae, known as "long COVID" - even those without specific neurological manifestations in the acute phase.

METHODS: Dynamic brain changes are crucial for a better understanding and early prevention of "long COVID." Here, we explored the cross-sectional and longitudinal consequences of COVID-19 on the brain in 34 discharged patients without neurological manifestations. Gray matter morphology, cerebral blood flow (CBF), and volumes of white matter tracts were investigated using advanced magnetic resonance imaging techniques to explore dynamic brain changes from 3 to 10 months after discharge.

RESULTS: Overall, the differences of cortical thickness were dynamic and finally returned to the baseline. For cortical CBF, hypoperfusion in severe cases observed at 3 months tended to recover at 10 months. Subcortical nuclei and white matter differences between groups and within subjects showed various trends, including recoverable and long-term unrecovered differences. After a 10-month recovery period, a reduced volume of nuclei in severe cases was still more extensive and profound than that in mild cases.

CONCLUSION: Our study provides objective neuroimaging evidence for the coexistence of recoverable and long-term unrecovered changes in 10-month effects of COVID-19 on the brain. The remaining potential abnormalities still deserve public attention, which is critically important for a better understanding of "long COVID" and early clinical guidance toward complete recovery.

Long COVID 12 months after discharge: persistent symptoms in patients hospitalised due to COVID-19 and patients hospitalised due to other causes-a multicentre cohort study

BMC Med. 2022 Feb 23; 20(1):92. doi: 10.1186/s12916-022-02292-6.

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Abstract

Background: Long-term-specific sequelae or persistent symptoms (SPS) after hospitalisation due to COVID-19 are not known. The aim of this study was to explore the presence of SPS 12 months after discharge in survivors hospitalised due to COVID-19 and compare it with survivors hospitalised due to other causes.

Methods: Prospective cohort study, the Andalusian Cohort of Hospitalised patients for COVID-19 (ANCOHVID study), conducted in 4 hospitals and 29 primary care centres in Andalusia, Spain. The sample was composed of 906 adult patients; 453 patients hospitalised due to COVID-19 (exposed) and 453 hospitalised due to other causes (non-exposed) from March 1 to April 15, 2020, and discharged alive. The main outcomes were (1) the prevalence of SPS at 12 months after discharge and (2) the incidence of SPS after discharge. Outcome data at 12 months were compared between the exposed and non-exposed cohorts. Risk ratios were calculated, and bivariate analyses were performed.

Results: A total of 163 (36.1%) and 160 (35.3%) patients of the exposed and non-exposed cohorts, respectively, showed at least one SPS at 12 months after discharge. The SPS with higher prevalence in the subgroup of patients hospitalised due to COVID-19 12 months after discharge were persistent pharyngeal symptoms ($p < 0.001$), neurological SPS ($p = 0.049$), confusion or memory loss ($p = 0.043$), thrombotic events ($p = 0.025$) and anxiety ($p = 0.046$). The incidence of SPS was higher for the exposed cohort regarding pharyngeal symptoms (risk ratio, 8.00; 95% CI, 1.85 to 36.12), confusion or memory loss (risk ratio, 3.50; 95% CI, 1.16 to 10.55) and anxiety symptoms (risk ratio, 2.36; 95% CI, 1.28 to 4.34).

Conclusions: There was a similar frequency of long-term SPS after discharge at 12 months, regardless of the cause of admission (COVID-19 or other causes). Nevertheless, some symptoms that were found to be more associated with COVID-19, such as memory loss or anxiety, merit further investigation. These results should guide future follow-up of COVID-19 patients after hospital discharge.

Dynamic Changes of the Blood Chemistry in Syrian Hamsters Post-Acute COVID-19

Microbiol Spectr. 2022 Feb 23;10(1): e0236221. doi: [10.1128/spectrum.02362-21](https://doi.org/10.1128/spectrum.02362-21). Epub 2022 Feb 23.

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that causes coronavirus disease 2019 (COVID-19). However, the long-term health consequences of COVID-19 are not fully understood. We aimed to determine the long-term lung pathology and blood chemistry changes in Syrian hamsters infected with SARS-CoV-2. Syrian hamsters (*Mesocricetus auratus*) were inoculated with 10⁵ PFU of SARS-CoV-2, and changes post-infection (pi) were observed for 20 days. On days 5 and 20 pi, the lungs were harvested and processed for pathology and viral load count. Multiple blood samples were collected every 3 to 5 days to observe dynamic changes in blood chemistry. Infected hamsters showed consistent weight loss until day 7 pi. At day 5 pi, histopathology of the lungs showed moderate to severe inflammation and the virus could be detected. These results indicate that SARS-CoV-2 has an acute onset and recovery course in the hamster infection model. During the acute onset, blood triglyceride levels increased significantly at day 3 pi. During the recovery course, uric acid and low-density lipoprotein levels increased significantly, but the total protein and albumin levels decreased. Together, our study suggests that SARS-CoV-2 infection in hamsters not only causes lung damage but also causes long-term changes in blood biochemistry during the recovery process. **IMPORTANCE** COVID-19 is now considered a multiorgan disease with a wide range of manifestations. There are increasing reports of persistent and long-term effects after acute COVID-19, but the long-term health consequences of COVID-19 are not fully understood. This study reported for the first time the use of blood samples collected continuously in a SARS-CoV-2-infected hamster model, which provides more information about the dynamic changes in blood biochemistry during the acute and recovery phases of SARS-CoV-2 infection. Our study suggests that SARS-CoV-2 infection in hamsters not only causes lung damage but also causes long-term changes in blood biochemistry during the recovery process. The study may be used by several researchers and clinicians, especially those who are studying potential treatments for patients with post-acute COVID-19 syndrome.

COVID-19 Post-Acute Sequela Rehabilitation: A look to the future through the lens of COPD and Pulmonary Rehabilitation

Arch Rehabil Res Clin Transl. 2022 Feb 24;100185. doi: 10.1016/j.arrct.2022.100185. Online ahead of print.

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Abstract

Post COVID-19 condition is characterized by a myriad of persistent symptoms experienced up to 60 days after the acute infection, not just in those hospitalized, but also in patients with mild to moderate acute symptoms. The overwhelming evidence on a multisystem involvement in post COVID-19 condition compounded with its notable prevalence brings to attention the need for integrated delivery models for addressing healthcare needs of this population. The World Health Organization recently highlighted critical gaps in current healthcare delivery models to adequately provide the level of integrative care required to address the multisystem needs of this population and recommended development of new innovative models of delivery. This paper presents a novel approach to addressing these gaps from a rehabilitation perspective.

Outpatient Pulmonary Rehabilitation in Patients with Long COVID Improves Exercise Capacity, Functional Status, Dyspnea, Fatigue, and Quality of Life

Respiration. 2022 Feb 24;1-9. doi: 10.1159/000522118. Online ahead of print.

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Abstract

Background: COVID-19 survivors face the risk of long-term sequelae including fatigue, breathlessness, and functional limitations. Pulmonary rehabilitation has been recommended, although formal studies quantifying the effect of rehabilitation in COVID-19 patients are lacking.

Methods: We conducted a prospective observational cohort study including consecutive patients admitted to an outpatient pulmonary rehabilitation center due to persistent symptoms after COVID-19. The primary endpoint was change in 6-min walk distance (6MWD) after undergoing a 6-week interdisciplinary individualized pulmonary rehabilitation program. Secondary endpoints included change in the post-COVID-19 functional status (PCFS) scale, Borg dyspnea scale, Fatigue Assessment Scale, and quality of life. Further, changes in pulmonary function tests were explored.

Results: Of 64 patients undergoing rehabilitation, 58 patients (mean age 47 years, 43% women, 38% severe/critical COVID-19) were included in the per-protocol-analysis. At baseline (i.e., in mean 4.4 months after infection onset), mean 6MWD was 584.1 m (± 95.0), and functional impairment was graded in median at 2 (IQR, 2-3) on the PCFS. On average, patients improved their 6MWD by 62.9 m (± 48.2 , $p < 0.001$) and reported an improvement of 1 grade on the PCFS scale. Accordingly, we observed significant improvements across secondary endpoints including presence of dyspnea ($p < 0.001$), fatigue ($p < 0.001$), and quality of life ($p < 0.001$). Also, pulmonary function parameters (forced expiratory volume in 1 s, lung diffusion capacity, inspiratory muscle pressure) significantly increased during rehabilitation.

Conclusion: In patients with long COVID, exercise capacity, functional status, dyspnea, fatigue, and quality of life improved after 6 weeks of personalized interdisciplinary pulmonary rehabilitation. Future studies are needed to establish the optimal protocol, duration, and long-term benefits as well as cost-effectiveness of rehabilitation.

Excess risk and clusters of symptoms after COVID-19 in a large Norwegian cohort

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Abstract

Physical, psychological and cognitive symptoms have been reported as post-acute sequelae for COVID-19 patients but are also common in the general uninfected population. We aimed to calculate the excess risk and identify patterns of 22 symptoms up to 12 months after COVID-19. We followed more than 70,000 adult participants in an ongoing cohort study, the Norwegian Mother, Father and Child Cohort Study (MoBa) during the COVID-19 pandemic. Infected and non-infected participants registered presence of 22 different symptoms in March 2021. One year after infection, 13 of 22 symptoms were associated with SARS-CoV-2 infection, based on relative risks between infected and uninfected subjects. For instance, 17.4% of SARS-CoV-2 infected cohort participants reported fatigue that persist 12 months after infection, compared to new occurrence of fatigue that had lasted less than 12 months in 3.8% of non-infected subjects (excess risk 13.6%). The adjusted relative risk for fatigue was 4.8 (95% CI 3.5-6.7). Two main underlying factors explained 50% of the variance in the 13 symptoms. Brain fog, poor memory, dizziness, heart palpitations, and fatigue had high loadings on the first factor, while shortness-of breath and cough had high loadings on the second factor. Lack of taste and smell showed low to moderate correlation to other symptoms. Anxiety, depression and mood swings were not strongly related to COVID-19. Our results suggest that there are clusters of symptoms after COVID-19 due to different mechanisms and question whether it is meaningful to describe long COVID as one syndrome.

Fatigue Symptoms Associated With COVID-19 in Convalescent or Recovered COVID-19 Patients; a Systematic Review and Meta-Analysis

Ann Behav Med. 2022 Mar 1;56(3):219-234. doi: 10.1093/abm/kaab081.

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Abstract

Background: The prevalence and prognosis of post-acute stage SARS-CoV-2 infection fatigue symptoms remain largely unknown.

Aims: We performed a systematic review to evaluate the prevalence of fatigue in post-recovery from SARS-CoV-2 infection.

Method: Medline, Embase, PsycINFO, CINAHL, Web of Science, Scopus, trial registries, Cochrane Central Register of Controlled Trials, and Google Scholar were searched for studies on fatigue in samples that recovered from polymerase chain reaction (PCR) diagnosed COVID-19. English, French, and Spanish studies were included. Meta-analyses were conducted separately for each recruitment setting.

Results: We identified 41 studies with 9,362 patients that recovered from COVID-19. Post-COVID-19 patients self-report of fatigue was higher compared to healthy controls (risk ratio (RR) = 3.688, 95%CI [2.502, 5.436], $p < .001$). Over 50% of patients discharged from inpatient care reported symptoms of fatigue during the first (event rate [ER] = 0.517, 95%CI [0.278, 0.749]) and second month following recovery (ER = 0.527, 95%CI [0.337, 0.709]). Ten percent of the community patients reported fatigue in the first-month post-recovery. Patient setting moderated the association between COVID-19 recovery and fatigue symptoms ($R^2 = 0.11$, $p < .001$). Female patients recovering from COVID-19 had a greater self-report of fatigue (odds ratio [OR] = 1.782, 95%CI [1.531, 2.870]). Patients recruited through social media had fatigue above 90% across multiple time points. Fatigue was highest in studies from Europe.

Conclusion: Fatigue is a symptom associated with functional challenges which could have economic and social impacts. Developing long-term planning for fatigue management amongst patients beyond the acute stages of SARS-CoV-2 infection is essential to optimizing patient care and public health outcomes. Further studies should examine the impact of sociodemographic, pandemic-related restrictions and pre-existing conditions on fatigue.

Long-Term Effects of COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is the third deadly coronavirus infection of the 21st century that has proven to be significantly more lethal than its predecessors, with the number of infected patients and deaths still increasing daily. From December 2019 to July 2021, this virus has infected nearly 200 million people and led to more than 4 million deaths. Our understanding of COVID-19 is constantly progressing, giving better insight into the heterogeneous nature of its acute and long-term effects. Recent literature on the long-term health consequences of COVID-19 discusses the need for a comprehensive understanding of the multisystemic pathophysiology, clinical predictors, and epidemiology to develop and inform an evidence-based, multidisciplinary management approach. A PubMed search was completed using variations on the term post-acute COVID-19. Only peer-reviewed studies in English published by July 17, 2021 were considered for inclusion. All studies discussed in this text are from adult populations unless specified (as with multisystem inflammatory syndrome in children). The preliminary evidence on the pulmonary, cardiovascular, neurological, hematological, multisystem inflammatory, renal, endocrine, gastrointestinal, and integumentary sequelae show that COVID-19 continues after acute infection. Interdisciplinary monitoring with holistic management that considers nutrition, physical therapy, psychological management, meditation, and mindfulness in addition to medication will allow for the early detection of post-acute COVID-19 sequelae symptoms and prevent long-term systemic damage. This review serves as a guideline for effective management based on current evidence, but clinicians should modify recommendations to reflect each patient's unique needs and the most up-to-date evidence. The presence of long-term effects presents another reason for vaccination against COVID-19.

The Female-Predominant Persistent Immune Dysregulation of the Post-COVID Syndrome

Mayo Clin Proc. 2022 Mar;97(3):454-464. doi: 10.1016/j.mayocp.2021.11.033. Epub 2022 Feb 5.

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Abstract

Objective: To describe the clinical data from the first 108 patients seen in the Mayo Clinic post-COVID-19 care clinic (PCOCC).

Methods: After Institutional Review Board approval, we reviewed the charts of the first 108 patients seen between January 19, 2021, and April 29, 2021, in the PCOCC and abstracted from the electronic medical record into a standardized database to facilitate analysis. Patients were grouped into phenotypes by expert review.

Results: Most of the patients seen in our clinic were female (75%; 81/108), and the median age at presentation was 46 years (interquartile range, 37 to 55 years). All had post-acute sequelae of SARS-CoV-2 infection, with 6 clinical phenotypes being identified: fatigue predominant (n=69), dyspnea predominant (n=23), myalgia predominant (n=6), orthostasis predominant (n=6), chest pain predominant (n=3), and headache predominant (n=1). The fatigue-predominant phenotype was more common in women, and the dyspnea-predominant phenotype was more common in men. Interleukin 6 (IL-6) was elevated in 61% of patients (69% of women; P=.0046), which was more common than elevation in C-reactive protein and erythrocyte sedimentation rate, identified in 17% and 20% of cases, respectively.

Conclusion: In our PCOCC, we observed several distinct clinical phenotypes. Fatigue predominance was the most common presentation and was associated with elevated IL-6 levels and female sex. Dyspnea predominance was more common in men and was not associated with elevated IL-6 levels. IL-6 levels were more likely than erythrocyte sedimentation rate and C-reactive protein to be elevated in patients with post-acute sequelae of SARS-CoV-2 infection.

The effectiveness of pulmonary rehabilitation for Post-COVID symptoms: A rapid review of the literature

Respir Med. 2022 Mar 2; 195:106782. doi: 10.1016/j.rmed.2022.106782. Online ahead of print.

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Abstract

Background: Multi-disciplinary rehabilitation is recommended for individuals with post-acute sequelae of COVID-19 infection (i.e., symptoms 3-4 weeks after acute infection). There are emerging reports of use of pulmonary rehabilitation (PR) in the post-acute stages of COVID-19, however the appropriateness of PR for managing post-COVID symptoms remains unclear. To offer practical guidance with regards to post-COVID PR, a greater understanding of the clinical effectiveness literature is required.

Methods: A rapid review of the published literature was completed. An electronic database search of the literature published between July 1, 2020 and June 1, 2021 was performed in MEDLINE, Pubmed, and EMBASE. Primary studies evaluating the clinical effectiveness of PR for individuals with post-COVID symptoms were included.

Results: Nine studies evaluating the effectiveness of PR were identified; most were small, experimental or quasi-experimental studies, including 1 RCT, and were primarily of low quality. After attending PR, all studies reported improvements in exercise capacity, pulmonary function, and/or quality of life for individuals with post-COVID symptoms who had been hospitalized for their acute COVID-19 infection. Few studies evaluated changes in post-COVID symptom severity or frequency and, of these, improvements in dyspnea, fatigue, anxiety and depression were observed following PR. Further, no studies evaluated non-hospitalized patients or long-term outcomes beyond 3 months after initiating PR.

Conclusions: With limited high-quality evidence, any recommendations or practical guidance for PR programmes for those with post-COVID symptoms should consider factors such as feasibility, current PR capacity, and resource constraints.

A 1-year longitudinal study on COVID-19 convalescents reveals persistence of anti-SARS-CoV-2 humoral and cellular immunity

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Abstract

The immune memory of over 400 million COVID-19 convalescents is not completely understood. In this integrated study, we recorded the post-acute sequelae symptoms and tested the immune memories, including circulating antibodies, memory B cell, and memory CD4 or CD8 T cell responses of a cohort of 65 COVID-19 patients over 1-year after infection. Our data show that 48% of them still have one or more sequelae symptoms and all of them maintain at least one of the immune components. The chances of having sequelae symptoms or having better immune memory are associated with peak disease severity. We did four-time points sampling per subject to precisely understand the kinetics of durability of SARS-CoV-2 circulating antibodies. We found that the RBD IgG levels likely reach a stable plateau at around 6 months, albeit it is waning at the first 6 months after infection. At 1-year after infection, more than 90% of the convalescents generated memory CD4 or CD8 T memory responses, preferably against the SARS-CoV-2 M peptide pool. The convalescents also have polyfunctional and central memory T cells that could provide rapid and efficient response to SARS-CoV-2 re-infection. Based on this information, we assessed the immune protection against the Omicron variant and concluded that convalescents should still induce effective T cell immunity against the Omicron. By studying the circulating antibodies and memory B or T cell responses to SARS-CoV-2 in an integrated manner, our study provides insight into the understanding of protective immunity against diseases caused by secondary SARS-CoV-2 infection.

Plasma Biomarkers of Neuropathogenesis in Hospitalized Patients With COVID-19 and Those With Postacute Sequelae of SARS-CoV-2 Infection

Neurol Neuroimmunol Neuroinflamm. 2022 Mar 7;9(3):e1151. doi:10.1212/NXI.0000000000001151. Print 2022 May.

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Abstract

Background and objectives: Although patients hospitalized with COVID-19 frequently present with encephalopathy, those with mild initial COVID-19 disease who never required hospitalization also often develop neurologic symptoms as part of postacute sequelae of severe acute respiratory coronavirus type 2 (SARS-CoV-2) infection (neuro-PASC). The pathogenic mechanisms of COVID-19 encephalopathy and neuro-PASC are unknown. We sought to establish biochemical evidence of CNS injury in those patients and their association with neuropsychiatric manifestations and SARS-CoV-2 antigenemia.

Methods: We recruited hospitalized, posthospitalized, and nonhospitalized patients with confirmed diagnosis of COVID-19 with neurologic symptoms in addition to healthy control (HC) subjects. Plasma neurofilament light chain (pNfL), plasma glial fibrillary acidic protein (pGFAP), and plasma SARS-CoV-2 Nucleocapsid antigen (pN Ag) were measured by HD-X Simoa analyzer (Quanterix) and compared with neuropsychiatric symptoms, patient-reported quality-of-life measures, and standardized cognitive assessments. Neuroglial scores (pGFAP/pNfL) were calculated to estimate the relative contribution of astroglial and neuronal involvement.

Results: We enrolled a total of 64 study participants, including 9 hospitalized patients with COVID-19 encephalopathy (CE), 9 posthospitalization neuro-PASC (PNP) patients, 38 nonhospitalized neuro-PASC (NNP) patients, and 8 HC subjects. Patients with CE were older, had higher pNfL and pGFAP concentrations, and more frequent pN Ag detection than all neuro-PASC groups. PNP and NNP patients exhibited similar PASC symptoms, decreased quality-of-life measures, and cognitive dysfunction, and 1 of the 38 (2.6%) NNP patients had pN Ag detectable 3 weeks postsymptoms onset. Patients with neuro-PASC presenting with anxiety/depression had higher neuroglial scores, which were correlated with increased anxiety on quality-of-life measures.

Discussion: pNfL, pGFAP, and pN Ag measurements indicate neuronal dysfunction and systemic involvement in hospitalized COVID-19 patients with encephalopathy. Detection of SARS-CoV-2 N Ag in blood 3 weeks after symptoms onset in a nonhospitalized patient suggests that prolonged antigenic stimulation, or possibly latent infection, may occur. Anxiety was associated with evidence of astroglial activation in patients with neuro-PASC. These data shed new light on SARS-Cov-2 neuropathogenesis and demonstrate the value of plasma biomarkers across the COVID-19 disease spectrum.

Nutritional Modulation of Gut Microbiota Alleviates Severe Gastrointestinal Symptoms in a Patient with Post-Acute COVID-19 Syndrome

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Abstract

With the increase in total coronavirus disease 2019 (COVID-19) infection cases, post-acute COVID-19 syndrome, defined as experiencing ongoing health problems 4 or more weeks after the first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has become a new arising public health concern. As part of post-acute COVID-19 syndrome, gastrointestinal symptoms might be associated with dysbiosis of the gut microbiota, which has the potential to become a target for intervention. In this study, a patient with post-acute COVID-19 syndrome with long-lasting severe gastrointestinal symptoms was provided 2-month expanded access to a high-fiber formula with investigational new drug (IND) status developed to alleviate COVID-19-related symptoms by modulating the gut microbiota. Symptoms including severe "loss of appetite," palpitation, and anxiety were significantly alleviated by the end of the intervention. The medication dosage for controlling nausea decreased during the intervention. The serum lipid profile, insulin level, and leptin level were improved compared to the baseline values. Significant structural changes of the patient's gut microbiota and reduced microbial fermentation activity in the small intestine were found during the intervention. Eighteen amplicon sequence variants (ASVs) of the V4 region of the 16S rRNA gene significantly responded to this nutritional intervention. Six out of the 18 ASVs were also found to be negatively correlated with symptom severity/medication dosage. Five of the six ASVs (ASV0AKS_*Oscillibacter*, ASV009F_*Anaerofustis*, ASV02YT_*Blautia*, ASV07LA_*Blautia*, and ASV0AM6_*Eubacterium hallii*) were potential short-chain fatty acid (SCFA)-producing bacteria, which might be associated with the alleviation of symptoms. Our study indicates the feasibility of alleviating gastrointestinal symptoms in patients with post-acute COVID-19 syndrome by way of nutritional modulation of their gut microbiota. **IMPORTANCE** It has become evident that the care of patients with COVID-19 does not end at the time of negative SARS-CoV-2 detection, as the number of patients with post-acute COVID-19 syndrome increases with an ever-increasing total infected patient population. This case report shows the possibility of alleviating the gastrointestinal symptoms of post-acute COVID-19 syndrome via microbiota-targeted nutritional intervention. As a promising strategy, it might not only improve the quality of life of patients but also reduce the burden to the public health system when the end of the COVID-19 pandemic is not in sight.

Early clues regarding the pathogenesis of long-COVID

Trends Immunol. 2022 Mar 7; S1471-4906(22)00047-3. doi: [10.1016/j.it.2022.02.008](https://doi.org/10.1016/j.it.2022.02.008). Online ahead of print.

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Abstract

Intense investigation into the predictors and determinants of post-acute sequelae of SARS-CoV-2 infection (PASC), including 'long COVID', is underway. Recent studies provide clues to the mechanisms that might drive this condition, with the goal of identifying host or virus factors that can be intervened upon to prevent or reverse PASC.

Long COVID and episodic disability: advancing the conceptualisation, measurement and knowledge of episodic disability among people living with Long COVID - protocol for a mixed-methods study

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Abstract

Introduction: As the prevalence of Long COVID increases, there is a critical need for a comprehensive assessment of disability. Our aims are to: (1) characterise disability experiences among people living with Long COVID in Canada, UK, USA and Ireland; and (2) develop a patient-reported outcome measure to assess the presence, severity and episodic nature of disability with Long COVID.

Methods and analysis: In phase 1, we will conduct semistructured interviews with adults living with Long COVID to explore experiences of disability (dimensions, uncertainty, trajectories, influencing contextual factors) and establish an episodic disability (ED) framework in the context of Long COVID (n~10 each country). Using the conceptual framework, we will establish the Long COVID Episodic Disability Questionnaire (EDQ). In phase 2, we will examine the validity (construct, structural) and reliability (internal consistency, test-retest) of the EDQ for use in Long COVID. We will electronically administer the EDQ and four health status criterion measures with adults living with Long COVID, and readminister the EDQ 1 week later (n~170 each country). We will use Rasch analysis to refine the EDQ, and confirm structural and cross-cultural validity. We will calculate Cronbach's alphas (internal consistency reliability), and intraclass correlation coefficients (test-retest reliability), and examine correlations for hypotheses theorising relationships between EDQ and criterion measure scores (construct validity). Using phase 2 data, we will characterise the profile of disability using structural equation modelling techniques to examine relationships between dimensions of disability and the influence of intrinsic and extrinsic contextual factors. This research involves an academic-clinical-community partnership building on foundational work in ED measurement, Long COVID and rehabilitation.

Post-acute COVID-19 syndrome

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Abstract

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease 2019 (COVID-19) pandemic that has resulted in millions of deaths and a major strain on health systems worldwide. Medical treatments for COVID-19 (anticoagulants, corticosteroids, anti-inflammatory drugs, oxygenation therapy and ventilation) and vaccination have improved patient outcomes. The majority of patients will recover spontaneously or after acute-phase management, but clinicians are now faced with long-term complications of COVID-19 including a large variety of symptoms, defined as "post-acute COVID-19 syndrome". Most studies have focused on patients hospitalised for severe COVID-19, but acute COVID-19 syndrome is not restricted to these patients and exists in outpatients. Given the diversity of symptoms and the high prevalence of persistent symptoms, the management of these patients requires a multidisciplinary team approach, which will result in the consumption of large amounts of health resources in the coming months. In this review, we discuss the presentation, prevalence, pathophysiology and evolution of respiratory complications and other organ-related injuries associated with post-acute COVID-19 syndrome.

Neurocognitive and psychiatric post-coronavirus disease 2019 conditions: pathogenic insights of brain dysfunction following severe acute respiratory syndrome coronavirus 2 infection

Curr Opin Neurol. 2022 Mar 11. doi: [10.1097/WCO.0000000000001046](https://doi.org/10.1097/WCO.0000000000001046). Online ahead of print.

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Abstract

Purpose of review: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19), can trigger a myriad of neuropsychiatric manifestations. As a 2-year-old disease (at the writing of this manuscript), its long-term cognitive and neuropsychiatric implications, known as post-COVID-19 conditions, are incompletely recognized and mechanistically obscure.

Recent findings: Fatigue, anxiety, depression, posttraumatic stress disorder, and cognitive dysfunction are reported more frequently in COVID-19 survivors than in matching, non-COVID-19 population. Risk factors are unclear, including comorbidities, age at COVID-19 onset, or disease severity; women, however, have been reported to be at increased risk than men. Although the frequency of these symptoms decreases over time, at least one in five will have persistent cognitive and neuropsychiatric manifestations one year after recovering from COVID-19.

Summary: Neurocognitive and psychiatric post-COVID-19 long-term conditions are frequent and complex multifactorial sequelae. Several acute and chronic factors such as hypoxemia, cerebral thrombotic and inflammatory endothelial damage, and disruption of the blood-brain barrier (leading to parenchymal translocation of pro-inflammatory molecules, cytokines, and cytotoxic T lymphocytes) are involved, leading to microglial activation and astrogliosis. As an evolving topic, evidence derived from prospective studies will expand our understanding of post-COVID-19 these long-term outcomes.

2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults: Myocarditis and Other Myocardial Involvement, Post-Acute Sequelae of SARS-CoV-2 Infection, and Return to Play: A Report of the American College of Cardiology Solution Set Oversight Committee

J Am Coll Cardiol. 2022 Mar 14; S0735-1097(22)00306-0. doi: [10.1016/j.jacc.2022.02.003](https://doi.org/10.1016/j.jacc.2022.02.003). Online ahead of print.

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No abstract available

Quantitative Chest CT Assessment of Small Airways Disease in Post-Acute SARS-CoV-2 Infection

Radiology. 2022 Mar 15; 212170. doi: [10.1148/radiol.212170](https://doi.org/10.1148/radiol.212170). Online ahead of print.

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Abstract

Background The long-term effects of SARS-CoV-2 infection on pulmonary structure and function remain incompletely characterized. **Purpose** To test whether SARS-CoV-2 infection leads to small airways disease in patients with persistent symptoms. **Materials and Methods** In this single center study at a university teaching hospital, adults with confirmed COVID-19 who remained symptomatic >30 days following diagnosis were prospectively enrolled between June and December 2020 and compared to healthy participants (controls) prospectively enrolled between March and August 2018. Participants with post-acute sequelae of COVID-19 (PASC) were classified as ambulatory, hospitalized, or requiring the intensive care unit (ICU) based on the highest level of care received during acute infection. Symptoms, pulmonary function tests, and chest CT images were collected, and quantitative CT analysis was performed using supervised machine-learning to measure regional ground glass opacities (GGO) and inspiratory and expiratory image-matching to measure regional air trapping. Univariable analyses and multivariable linear regression were used to compare groups. **Results** 100 participants with PASC (median age, 48 years; 66 women) were evaluated and compared with 106 matched healthy controls. Sixty-seven percent (67/100) of the participants with PASC were classified as ambulatory, 17% (17/100) were hospitalized and 16% (16/100) required care in the ICU. Among the hospitalized and ICU groups, the mean percent of total lung classified as GGO was 13.2% and 28.7%, respectively, and was higher than in the ambulatory group (3.7%, $p < .001$ for both comparisons). The mean percentage of total lung affected by air trapping was 25.4%, 34.6%, and 27.3% in the ambulatory, hospitalized, and ICU groups and 7.2% in healthy controls ($p < .001$). Air trapping correlated with the residual volume to total lung capacity ratio (RV/TLC; $r = 0.6$, $p < .001$). **Conclusions** In survivors of COVID-19, small airways disease occurred independently of initial infection severity. The long-term consequences are unknown. See also the editorial by Elicker.

COVID-19 atypical Parsonage-Turner syndrome: a case report

BMC Neurol. 2022 Mar 16;22(1):96. doi: 10.1186/s12883-022-02622-4.

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Abstract

Background: Neurological manifestations of Sars-CoV-2 infection have been described since March 2020 and include both central and peripheral nervous system manifestations. Neurological symptoms, such as headache or persistent loss of smell and taste, have also been documented in COVID-19 long-haulers. Moreover, long lasting fatigue, mild cognitive impairment and sleep disorders appear to be frequent long term neurological manifestations after hospitalization due to COVID-19. Less is known in relation to peripheral nerve injury related to Sars-CoV-2 infection.

Case presentation: We report the case of a 47-year-old female presenting with a unilateral chest pain radiating to the left arm lasting for more than two months after recovery from Sars-CoV-2 infection. After referral to our post-acute outpatient service for COVID-19 long haulers, she was diagnosed with a unilateral, atypical, pure sensory brachial plexus neuritis potentially related to COVID-19, which occurred during the acute phase of a mild Sars-CoV-2 infection and persisted for months after resolution of the infection.

Conclusions: We presented a case of atypical Parsonage-Turner syndrome potentially triggered by Sars-CoV-2 infection, with symptoms and repercussion lasting after viral clearance. A direct involvement of the virus remains uncertain, and the physiopathology is unclear. The treatment of COVID-19 and its long-term consequences represents a relatively new challenge for clinicians and

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health care providers. A multidisciplinary approach to following-up COVID-19 survivors is strongly advised.

Clinical, radiological, and pathological findings in patients with persistent lung disease following SARS-CoV-2 infection

Eur Respir J. 2022 Mar 17;2102411. doi: [10.1183/13993003.02411-2021](https://doi.org/10.1183/13993003.02411-2021). Online ahead of print.

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Abstract

Several patients experience pulmonary sequelae after Sars-Cov-2 infection, ranging from self-limited abnormalities to major lung diseases. Morphological analysis of lung tissue may help in understanding pathogenic mechanisms and provide consistent personalised management. Aim of the study was to ascertain morphologic and immuno-molecular features of lung tissue. Transbronchial lung cryobiopsy was carried out in patients with persistent symptoms and computed tomography suggestive of residual lung disease after recovery from Sars-CoV-2 infection. 164 patients were referred for suspected pulmonary sequelae after COVID-19; 10 patients with parenchymal lung disease extent >5% underwent lung biopsy. Histological pattern was not homogeneous, as three different case clusters could be evidenced, which were mirrored in clinical and radiological features: cluster one ("chronic fibrosing") characterised by post-infection progression of pre-existing interstitial pneumonias; cluster two ("acute/subacute injury") characterised by different types and grades of lung injury, ranging from organising pneumonia and fibrosing NSIP to diffuse alveolar damage; cluster three ("vascular changes") characterised by diffuse vascular increase, dilatation and distortion (capillaries and venules) within otherwise normal parenchyma. Clusters two and three were characterised by immunophenotypical changes similar to those observed in early/mild covid-19 pneumonias (abnormal expression of STAT3 in hyperplastic pneumocytes and PD-L1, IDO and STAT3 in endothelial cells). This is the first study correlating histological/immunohistochemical patterns with clinical and radiological pictures of patients with post-COVID lung disease. Different phenotypes with potential different underlying pathogenic mechanisms have been identified.

Long COVID syndrome and the lung-How long will it last?

QJM. 2022 Mar 22; hcac070. doi: [10.1093/qjmed/hcac070](https://doi.org/10.1093/qjmed/hcac070). Online ahead of print.

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Abstract

The prevalence and duration of the long term respiratory complications of COVID-19 infection remains to be elucidated. This short commentary reports on recently published studies in patients post acute COVID-19 infection in terms of symptom prevalence, physiological and radiological sequela and where only symptoms are present despite investigation. Pulmonary function testing, six minute walk tests, CT Chest and more advanced imaging modalities have been incorporated to reveal the underlying pathophysiology that cause such disabling symptoms in patient with post acute COVID-9 syndrome (PACS). PACS has a serious impact on people's ability to return to work, affecting the physical, mental, social sphere and with significant healthcare and general economic consequences for them, their families and society.

Post-COVID-19 Syndrome in Outpatients: a Cohort Study

J Gen Intern Med. 2022 Mar 22;1-10. doi: 10.1007/s11606-021-07242-1. Online ahead of print.

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Abstract

Background: After mild COVID-19, some outpatients experience persistent symptoms. However, data are scarce and prospective studies are urgently needed.

Objectives: To characterize the post-COVID-19 syndrome after mild COVID-19 and identify predictors.

Participants: Outpatients with symptoms suggestive of COVID-19 with (1) PCR-confirmed COVID-19 (COVID-positive) or (2) SARS-CoV-2 negative PCR (COVID-negative).

Design: Monocentric cohort study with prospective phone interview between more than 3 months to 10 months after initial visit to the emergency department and outpatient clinics.

Main measures: Data of the initial visits were extracted from the electronic medical file. Predefined persistent symptoms were assessed through a structured phone interview. Associations between long-term symptoms and PCR results, as well as predictors of persistent symptoms among COVID-positive, were evaluated by multivariate logistic regression adjusted for age, gender, smoking, comorbidities, and timing of the survey.

Key results: The study population consisted of 418 COVID-positive and 89 COVID-negative patients, mostly young adults (median age of 41 versus 36 years in COVID-positive and COVID-negative, respectively; $p = 0.020$) and healthcare workers (67% versus 82%; $p = 0.006$). Median time between the initial visit and the phone survey was 150 days in COVID-positive and 242 days in COVID-negative patients. Persistent symptoms were reported by 223 (53%) COVID-positive and 33 (37%) COVID-negative patients ($p = 0.006$) and proportions were stable among the periods of the phone interviews. Overall, 21% COVID-positive and 15% COVID-negative patients ($p = 0.182$) attended care for this purpose. Four surveyed symptoms were independently associated with COVID-19: fatigue (adjusted odds ratio 2.14, 95% CI 1.04-4.41), smell/taste disorder (26.5, 3.46-202), dyspnea (2.81, 1.10-7.16), and memory impairment (5.71, 1.53-21.3). Among COVID-

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positive, female gender (1.67, 1.09-2.56) and overweight/obesity (1.67, 1.10-2.56) were predictors of persistent symptoms.

Conclusions: More than half of COVID-positive outpatients report persistent symptoms up to 10 months after a mild disease. Only 4 of 14 symptoms were associated with COVID-19 status. The symptoms and predictors of the post-COVID-19 syndrome need further characterization as this condition places a significant burden on society.

Post-acute sequelae of COVID-19: A metabolic perspective

Elife. 2022 Mar 23;11:e78200. doi: [10.7554/eLife.78200](https://doi.org/10.7554/eLife.78200).

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Abstract

The SARS-CoV-2 pandemic continues to rage around the world. At the same time, despite strong public health measures and high vaccination rates in some countries, a post-COVID-19 syndrome has emerged which lacks a clear definition, prevalence, or etiology. However, fatigue, dyspnea, brain fog, and lack of smell and/or taste are often characteristic of patients with this syndrome. These are evident more than a month after infection, and are labeled as Post-Acute Sequelae of CoV-2 (PASC) or commonly referred to as long-COVID. Metabolic dysfunction (i.e., obesity, insulin resistance, and diabetes mellitus) is a predisposing risk factor for severe acute COVID-19, and there is emerging evidence that this factor plus a chronic inflammatory state may predispose to PASC. In this article, we explore the potential pathogenic metabolic mechanisms that could underly both severe acute COVID-19 and PASC, and then consider how these might be targeted for future therapeutic approaches.

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 Mar 24; 102823. doi: 10.1016/j.ctim.2022.102823. Online ahead of print.

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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 ($F(1,39) = 6.15, p = .020, \text{partial } \eta^2 = .198$). 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.

"Like before, but not exactly": the Qualy-REACT qualitative inquiry into the lived experience of long COVID

BMC Public Health. 2022 Mar 28;22(1):599. doi: 10.1186/s12889-022-13035-w.

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Abstract

Background: Post-acute sequelae of SARS-CoV-2 infection (PASC) affect millions of individuals worldwide. Rehabilitation interventions could support individuals during the recovery phase of COVID-19, but a comprehensive understanding of this new disease and its associated needs is crucial. This qualitative study investigated the experience of individuals who had been hospitalized for COVID-19, focusing on those needs and difficulties they perceived as most urgent.

Methods: This naturalistic qualitative study was part of a single-center mix-method cross-sectional study (REACT) conducted in Italy during the first peak of the SARS-CoV-2 pandemic. The qualitative data collection took place through a telephone interview conducted 3 months after hospital discharge. The experience of individuals discharged after hospitalization for COVID-19 was investigated through the main research question - "Tell me, how has it been going since you were discharged?". Two secondary questions investigated symptoms, activities, and participation. Data were recorded and transcribed verbatim within 48 h. An empirical phenomenological approach was used by the researchers, who independently analyzed the data and, through consensus, developed an interpretative model to answer the research question. Translation occurred after data was analyzed.

Results: During the first peak of the COVID-19 pandemic, 784 individuals with COVID-19 were discharged from the hospitals of the Local Health Authority of the Province of Reggio Emilia (Italy); 446 were excluded due to the presence of acute or chronic conditions causing disability other than COVID-19 (n. 339), inability to participate in the study procedures (n. 56), insufficient medical documentation to allow for screening (n. 21), discharge to residential facilities (n. 25), and pregnancy (n. 5). Overall, 150 individuals consented to participate in the REACT study, and 56 individuals (60.7% male, average age 62.8 years \pm 11.8) were interviewed in June-July 2020, up to data saturation. Persistent symptoms, feelings of isolation, fear and stigma, emotional distress, a fatalistic attitude, and return to (adapted) life course were the key themes that characterized the participants' experience after hospital discharge.

Conclusions: The experience as narrated by the participants in this study confirms the persistence of symptoms described in PASC and highlights the sense of isolation and psychological distress. These phenomena may trigger a vicious circle, but the participants also reported adaptation processes that allowed them to gradually return to their life course. Whether all individuals are able to rapidly activate these mechanisms and whether rehabilitation can help to break this vicious circle by improving residual symptoms remain to be seen.

Cardiovascular complications in the Post-Acute COVID-19 syndrome (PACS)

Int J Cardiol Heart Vasc. 2022 Mar 28; 40:101012. doi: 10.1016/j.ijcha.2022.101012. eCollection 2022 Jun.

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) or coronavirus disease 2019 (COVID-19) initially surfaced in December 2019 from Wuhan, China, sweeping the world with various strains, forcing the WHO to declare a pandemic epidemic in March 2020. Furthermore, COVID-19 manifests with a wide array of presentations from fever and fatigue to severe respiratory and cardiovascular complications. Post-COVID-19 syndrome is poorly understood affecting COVID-19 survivors at all levels of disease severity. The disease is most associated with post-discharge dyspnea and fatigue. However, other persistent symptoms as chest pains, palpitations, smell, and taste dysfunctions. Patients with high concentrations of CRP and creatinine in the acute phase of Covid-19 are more prone to cardiac sequelae. Therefore, high levels of cardiac-sensitive troponin and hypokalaemia can also be used for risk stratification. Furthermore, Cardiac damage can manifest as myocarditis, pericarditis, rhythm abnormalities. The use of different diagnostic modalities like electrocardiogram (ECG), echocardiogram, and cardiac magnetic resonance imaging (MRI)(CMR) to evaluate the myocardial damage were studied. However, Cardiovascular complications are a common manifestation of PASC, classification of severity of cardiac symptoms and the emergence of CMR as a diagnostic tool needs more evidence.

Keywords: ACE2, Angiotensin-converting enzyme 2; CAMKII, calmodulin-dependent protein kinase II; CMR, Cardiac magnetic resonance imaging; COVID-19; COVID-19, Coronavirus disease 2019; CVD, Cardiovascular disease; Cardiovascular diseases; DAMPs, damage-associated molecular patterns; IL, interleukin; Myocardial infarction; NOAC, novel oral anticoagulation; PACS, Post-Acute COVID-19 syndrome; Post covid sequelae; RAAS, Renin-Angiotensin Aldosterone System dysregulation; SARS-CoV 2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane protease serine 2; TNF-Alpha, Tumor necrosis factor-alpha; TTE, transthoracic echocardiogram; UFH, Unfractionated heparin; VTE, venous thromboembolism; WHO, World health organization.

Why obesity and psychological stress matter in recovery of post-acute sequelae of SARS-CoV-2

Obesity (Silver Spring). 2022 Mar 29. doi: [10.1002/oby.23442](https://doi.org/10.1002/oby.23442). Online ahead of print.

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Abstract

Numerous elements of the COVID-19 pandemic have proven challenging to overcome. We now recognize a perplexing characteristic of SARS-CoV-2 features mixed, unresolving symptoms that can last four weeks or longer after initial diagnosis, termed post-acute sequelae of SARS-CoV-2 (PASC). Full recovery can thus become a protracted ordeal as conservative estimates indicate 20% of SARS-CoV-2 cases will develop PASC with women at increased risk. Emerging evidence suggests latent virus reactivation including cytomegalovirus, Epstein-Barr virus, and / or varicella zoster virus may perpetuate the burden of PASC. This is problematic since immune dysfunction is linked to obesity and psychological stress both of which disproportionately affect socio-economically disadvantaged and racial / ethnic minorities. Applying a patient-centered approach where the principal factors guiding decision-making are based on the needs and abilities of the individual is essential. Still, the independent and combined influence of obesity and psychological stress on immune function necessitates due consideration in the context of PASC recovery.