Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations Concerning Long Haul COVID-19 October, November, December 2022

Prepared by Staff of the RACGWVI

RACGWVI: Long Haul COVID-19 — PubMed Citations for Oct, Nov, Dec 2022

The following is a selection of published research projects that focus on Long Haul COVID-19 for the months of October, November, December 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 …

post-acute sequelae sars-cov-2

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., Neuroinflammation and COVID-19, 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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Long Covid: where we stand and challenges ahead

Cell Death Differ. 2022 Oct;29(10):1891-1900. doi: 10.1038/s41418-022-01052-6. Epub 2022 Sep 7.

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Abstract

Post-acute sequelae of SARS-CoV-2 (PASC), also known as Post-Covid Syndrome, and colloquially as Long Covid, has been defined as a constellation of signs and symptoms which persist for weeks or months after the initial SARS-CoV-2 infection. PASC affects a wide range of diverse organs and systems, with manifestations involving lungs, brain, the cardiovascular system and other organs such as kidney and the neuromuscular system. The pathogenesis of PASC is complex and multifactorial. Evidence suggests that seeding and persistence of SARS-CoV-2 in different organs, reactivation, and response to unrelated viruses such as EBV, autoimmunity, and uncontrolled inflammation are major drivers of PASC. The relative importance of pathogenetic pathways may differ in different tissue and organ contexts. Evidence suggests that vaccination, in addition to protecting against disease, reduces PASC after breakthrough infection although its actual impact remains to be defined. PASC represents a formidable challenge for health care systems and dissecting pathogenetic mechanisms may pave the way to targeted preventive and therapeutic approaches.

Genome-wide transcriptional profiling of pulmonary functional sequelae in ARDS-secondary to SARS-CoV-2 infection

Biomed Pharmacother. 2022 Oct;154:113617. doi: 10.1016/j.biopha.2022.113617. Epub 2022 Aug 30.

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Abstract

Background: Up to 80% of patients surviving acute respiratory distress syndrome (ARDS) secondary to SARS-CoV-2 infection present persistent anomalies in pulmonary function after

hospital discharge. There is a limited understanding of the mechanistic pathways linked to post-acute pulmonary sequelae.

Aim: To identify the molecular underpinnings associated with severe lung diffusion involvement in survivors of SARS-CoV-2-induced ARDS.

Methods: Survivors attended to a complete pulmonary evaluation 3 months after hospital discharge. RNA sequencing (RNA-seq) was performed using Illumina technology in whole-blood samples from 50 patients with moderate to severe diffusion impairment (DLCO<60%) and age- and sex-matched individuals with mild-normal lung function (DLCO≥60%). A transcriptomic signature for optimal classification was constructed using random forest. Transcriptomic data were analyzed for biological pathway enrichment, cellular deconvolution, cell/tissue-specific gene expression and candidate drugs.

Results: RNA-seq identified 1357 differentially expressed transcripts. A model composed of 14 mRNAs allowed the optimal discrimination of survivors with severe diffusion impairment (AUC=0.979). Hallmarks of lung sequelae involved cell death signaling, cytoskeleton reorganization, cell growth and differentiation and the immune response. Resting natural killer (NK) cells were the most important immune cell subtype for the prediction of severe diffusion impairment. Components of the signature correlated with neutrophil, lymphocyte and monocyte counts. A variable expression profile of the transcripts was observed in lung cell subtypes and bodily tissues. One upregulated gene, TUBB4A, constitutes a target for FDA-approved drugs.

Conclusions: This work defines the transcriptional programme associated with post-acute pulmonary sequelae and provides novel insights for targeted interventions and biomarker development.

Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of autonomic dysfunction in patients with post-acute sequelae of SARS-CoV-2 infection (PASC)

PM R. 2022 Oct;14(10):1270-1291. doi: 10.1002/pmrj.12894. Epub 2022 Oct 8.

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No abstract available

Neuroinflammation and COVID-19

Curr Opin Neurobiol. 2022 Oct; 76:102608. doi: 10.1016/j.conb.2022.102608. Epub 2022 Jun 29.

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Abstract

Coronavirus disease 2019 (COVID-19) has caused a historic pandemic of respiratory disease. COVID-19 also causes acute and post-acute neurological symptoms, which range from mild, such as headaches, to severe, including hemorrhages. Current evidence suggests that there is no widespread infection of the central nervous system (CNS) by SARS-CoV-2, thus what is causing COVID-19 neurological disease? Here, we review potential immunological mechanisms driving neurological disease in COVID-19 patients. We begin by discussing the implications of imbalanced peripheral immunity on CNS function. Next, we examine the evidence for dysregulation of the blood-brain barrier during SARS-CoV-2 infection. Last, we discuss the role myeloid cells may play in promoting COVID-19 neurological disease. Combined, we highlight the role of innate immunity in COVID-19 neuroinflammation and suggest areas for future research.

Characterizing the COVID-19 Illness Experience to Inform the Study of Post-acute Sequelae and Recovery

Int J Behav Med. 2022 Oct;29(5):610-623. doi: 10.1007/s12529-021-10045-7. Epub 2021 Dec 16.

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Abstract

Background: There is an urgent need to fully understand the impact of variable COVID-19 experiences and the optimal management of post-acute sequelae of SARS-CoV-2 infection. We characterized the variability in the acute illness experience and ongoing recovery process from participants in a COVID-19 recovery cohort study in Northern California in 2020.

Method: We completed 24 semi-structured in-depth interviews with adults with confirmed positive SARV-CoV-2 nucleic acid amplification test result, had recovered or were recovering from acute infection, and underwent serial evaluations. We purposefully sampled English- and Spanish-speaking adults with asymptomatic, mild, and severe symptomatic infection, including those who were hospitalized and those with HIV co-infection. We used a thematic analysis to analyze interviews and identify salient themes.

Results: After integrating the thematic analysis with clinical data, we identified key themes: (1) across symptom profiles and severity, experiencing COVID-19 was associated with psychological distress; (2) symptomatic infection carried uncertainty in symptom presentation and ongoing recovery (e.g., long COVID); and (3) health information-seeking behavior was facilitated by access to medical care and uncertainty with the recovery process.

Conclusion: Our data informs the emerging field of "long COVID" research and shows a need to provide information and continuous support to persons with post-acute sequelae to ensure they feel secure along the path to recovery.

Long COVID in children and adolescents

Curr Opin Infect Dis. 2022 Oct 1;35(5):461-467. doi: 10.1097/QCO.0000000000000854. Epub 2022 Aug 3.

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Abstract

Purpose of review: Although acute COVID-19 has been milder in children and young people compared with adults, there is a concern that they may suffer persistent symptoms. There is a need to define the clinical phenotype, determine those most at risk, the natural course of the condition and evaluate preventive and therapeutic strategies for both mental health and physical symptoms.

Recent findings: More recent studies with control groups reported a lower prevalence of persistent symptoms in children and young people exposed to SARS-CoV-2. A systematic review and meta-analysis found that the frequency of the majority of reported persistent symptoms is similar in SARS-CoV-2 positive cases and controls. Children and young people infected with SARS-COV-2 had small but significant increases in persisting cognitive difficulties, headache and loss of smell. Factors associated with persisting, impairing symptoms include increased number of symptoms at the time of testing, female sex, older age, worse self-rated physical and mental health, and feelings of loneliness preinfection.

Summary: This review highlights the importance of a control group in studies following SARS-CoV-2 infection, the need for case definitions and research to understand the outcomes of long COVID in children and young people.

Use of Cardiopulmonary Exercise Testing to Evaluate Long COVID-19 Symptoms in Adults: A Systematic Review and Meta-analysis

JAMA Netw Open. 2022 Oct 3;5(10):e2236057. doi: 10.1001/jamanetworkopen.2022.36057.

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Abstract

Importance: Reduced exercise capacity is commonly reported among individuals with COVID-19 symptoms more than 3 months after SARS-CoV-2 infection (long COVID-19 [LC]). Cardiopulmonary exercise testing (CPET) is the criterion standard to measure exercise capacity and identify patterns of exertional intolerance.

Objectives: To estimate the difference in exercise capacity among individuals with and without LC symptoms and characterize physiological patterns of limitations to elucidate possible mechanisms of LC.

Data sources: A search of PubMed, EMBASE, Web of Science, preprint servers, conference abstracts, and cited references was performed on December 20, 2021, and again on May 24, 2022. A preprint search of medrxiv.org, biorxiv.org, and researchsquare.com was performed on June 9, 2022.

Study selection: Studies of adults with SARS-CoV-2 infection more than 3 months earlier that included CPET-measured peak oxygen consumption (V̇o2) were screened independently by 2 blinded reviewers; 72 (2%) were selected for full-text review, and 35 (1%) met the inclusion criteria. An additional 3 studies were identified from preprint servers.

Data extraction and synthesis: Data extraction was performed by 2 independent reviewers according to the PRISMA reporting guideline. Data were pooled using random-effects models.

Main outcomes and measures: Difference in peak V̇o2 (in mL/kg/min) among individuals with and without persistent COVID-19 symptoms more than 3 months after SARS-CoV-2 infection.

Results: A total of 38 studies were identified that performed CPET on 2160 individuals 3 to 18 months after SARS-CoV-2 infection, including 1228 with symptoms consistent with LC. Most studies were case series of individuals with LC or cross-sectional assessments within posthospitalization cohorts. Based on a meta-analysis of 9 studies including 464 individuals with LC symptoms and 359 without symptoms, the mean peak V̇o2 was -4.9 (95% CI, -6.4 to -3.4) mL/kg/min among those with symptoms with a low degree of certainty. Deconditioning and peripheral limitations (abnormal oxygen extraction) were common, but dysfunctional breathing and chronotropic incompetence were also described. The existing literature was limited by small sample sizes, selection bias, confounding, and varying symptom definitions and CPET interpretations, resulting in high risk of bias and heterogeneity.

Conclusions and relevance: The findings of this systematic review and meta-analysis study suggest that exercise capacity was reduced more than 3 months after SARS-CoV-2 infection

among individuals with symptoms consistent with LC compared with individuals without LC symptoms, with low confidence. Potential mechanisms for exertional intolerance other than deconditioning include altered autonomic function (eg, chronotropic incompetence, dysfunctional breathing), endothelial dysfunction, and muscular or mitochondrial pathology.

Post-acute sequelae of SARS-CoV-2 with clinical condition definitions and comparison in a matched cohort

Nat Commun. 2022 Oct 12;13(1):5822. doi: 10.1038/s41467-022-33573-6.

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Abstract

Disease characterization of Post-Acute Sequelae of SARS-CoV-2 (PASC) does not account for pre-existing conditions and time course of incidence. We utilized longitudinal data and matching to a COVID PCR-negative population to discriminate PASC conditions over time within our patient population during 2020. Clinical Classification Software was used to identify PASC condition groupings. Conditions were specified acute and persistent (occurring 0-30 days post COVID PCR and persisted 30-120 days post-test) or late (occurring initially 30-120 days post-test). We matched 3:1 COVID PCR-negative COVIDPCR-positive by age, sex, testing month and service area, controlling for pre-existing conditions up to four years prior; 28,118 PCR-positive to 70,293 PCR-negative patients resulted. We estimated PASC risk from the matched cohort. Risk of any PASC condition was 12% greater for PCR-positive patients in the late period with a significantly higher risk of anosmia, cardiac dysrhythmia, diabetes, genitourinary disorders, malaise, and nonspecific chest pain. Our findings contribute to a more refined PASC definition which can enhance clinical care.

Post-acute sequelae of covid-19 six to 12 months after infection: population based study

BMJ. 2022 Oct 13;379:e071050. doi: 10.1136/bmj-2022-071050.

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Abstract

Objectives: To describe symptoms and symptom clusters of post-covid syndrome six to 12 months after acute infection, describe risk factors, and examine the association of symptom clusters with general health and working capacity.

Design: Population based, cross sectional study SETTING: Adults aged 18-65 years with confirmed SARS-CoV-2 infection between October 2020 and March 2021 notified to health authorities in four geographically defined regions in southern Germany.

Participants: 50 457 patients were invited to participate in the study, of whom 12 053 (24%) responded and 11 710 (58.8% (n=6881) female; mean age 44.1 years; 3.6% (412/11 602) previously admitted with covid-19; mean follow-up time 8.5 months) could be included in the analyses.

Main outcome measures: Symptom frequencies (six to 12 months after versus before acute infection), symptom severity and clustering, risk factors, and associations with general health recovery and working capacity.

Results: The symptom clusters fatigue (37.2% (4213/11 312), 95% confidence interval 36.4% to 38.1%) and neurocognitive impairment (31.3% (3561/11 361), 30.5% to 32.2%) contributed most to reduced health recovery and working capacity, but chest symptoms, anxiety/depression, headache/dizziness, and pain syndromes were also prevalent and relevant for working capacity, with some differences according to sex and age. Considering new symptoms with at least moderate impairment of daily life and ≤80% recovered general health or working capacity, the overall estimate for post-covid syndrome was 28.5% (3289/11 536, 27.7% to 29.3%) among participants or at least 6.5% (3289/50 457) in the infected adult population (assuming that all non-responders had completely recovered). The true value is likely to be between these estimates.

Conclusions: Despite the limitation of a low response rate and possible selection and recall biases, this study suggests a considerable burden of self-reported post-acute symptom clusters and possible sequelae, notably fatigue and neurocognitive impairment, six to 12 months after acute SARS-CoV-2 infection, even among young and middle aged adults after mild infection, with a substantial impact on general health and working capacity.

Post-acute health care burden after SARS-CoV-2 infection: a retrospective cohort study

CMAJ. 2022 Oct 17;194(40):E1368-E1376. doi: 10.1503/cmaj.220728.

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Abstract

Background: The post-acute burden of health care use after SARS-CoV-2 infection is unknown. We sought to quantify the post-acute burden of health care use after SARS-CoV-2 infection among community-dwelling adults in Ontario by comparing those with positive and negative polymerase chain reaction (PCR) test results for SARS-CoV-2 infection.

Methods: We conducted a retrospective cohort study involving community-dwelling adults in Ontario who had a PCR test between Jan. 1, 2020, and Mar. 31, 2021. Follow-up began 56 days after PCR testing. We matched people 1:1 on a comprehensive propensity score. We compared per-person-year rates for health care encounters at the mean and 99th percentiles, and compared counts using negative binomial models, stratified by sex.

Results: Among 531 702 matched people, mean age was 44 (standard deviation [SD] 17) years and 51% were female. Females who tested positive for SARS-CoV-2 had a mean of 1.98 (95% CI 1.63 to 2.29) more health care encounters overall per-person-year than those who had a negative test result, with 0.31 (95% CI 0.05 to 0.56) more home care encounters to 0.81 (95% CI 0.69 to 0.93) more long-term care days. At the 99th percentile per-person-year, females who tested positive had 6.48 more days of hospital admission and 28.37 more home care encounters. Males who tested positive for SARS-CoV-2 had 0.66 (95% CI 0.34 to 0.99) more overall health care encounters per-person-year than those who tested negative, with 0.14 (95% CI 0.06 to 0.21) more outpatient encounters and 0.48 (95% CI 0.36 to 0.60) long-term care days, and 0.43 (95% CI -0.67 to -0.21) fewer home care encounters. At the 99th percentile, they had 8.69 more days in hospital per-person-year, with fewer home care (-27.31) and outpatient (-0.87) encounters.

Interpretation: We found significantly higher rates of health care use after a positive SARS-CoV-2 PCR test in an analysis that matched test-positive with test-negative people. Stakeholders can use these findings to prepare for health care demand associated with post-COVID-19 condition (long COVID).

Low perforin expression in CD8+ T lymphocytes during the acute phase of severe SARS-CoV-2 infection predicts long COVID

Front Immunol. 2022 Oct 20; 13:1029006. doi: 10.3389/fimmu.2022.1029006. eCollection 2022.

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Abstract

T cell cytotoxicity plays a major role in antiviral immunity. Anti-SARS-CoV-2 immunity may determine acute disease severity, but also the potential persistence of symptoms (long COVID). We therefore measured the expression of perforin, a cytotoxic mediator, in T cells of patients recently hospitalized for SARS-CoV-2 infection. We recruited 54 volunteers confirmed as being SARS-CoV-2-infected by RT-PCR and admitted to Intensive Care Units (ICUs) or non-ICU, and 29 age- and sex-matched healthy controls (HCs). Amounts of intracellular perforin and granzyme-B, as well as cell surface expression of the degranulation marker CD107A were determined by flow cytometry. The levels of 15 cytokines in plasma were measured by Luminex. The frequency of perforin-positive T4 cells and T8 cells was higher in patients than in HCs (9.9 ± 10.1% versus 4.6 ± 6.4%, p = 0.006 and 46.7 ± 20.6% vs 33.3 ± 18.8%, p = 0.004, respectively). Perforin expression was neither correlated with clinical and biological markers of disease severity nor predictive of death. By contrast, the percentage of perforin-positive T8 cells in the acute phase of the disease predicted the onset of long COVID one year later. A low T8 cytotoxicity in the first days of SARS-CoV-2 infection might favor virus replication and persistence, autoimmunity, and/or reactivation of other viruses such as Epstein-Barr virus or cytomegalovirus, paving the way for long COVID. Under this hypothesis, boosting T cell cytotoxicity during the acute phase of the infection could prevent delayed sequelae.

Saliva antibody-fingerprint of reactivated latent viruses after mild/asymptomatic COVID-19 is unique in patients with myalgic-encephalomyelitis/chronic fatigue syndrome

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Abstract

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic disease considered to be triggered by viral infections in a majority of cases. Symptoms overlap largely with those of post-acute sequelae of COVID-19/long-COVID implying common pathogenetic mechanisms. SARS-CoV-2 infection is risk factor for sustained latent virus reactivation that may account for the symptoms of post-viral fatigue syndromes. The aim of this study was first to investigate whether patients with ME/CFS and healthy donors (HDs) differed in their antibody response to mild/asymptomatic SARS-CoV-2 infection. Secondly, to analyze whether COVID-19 imposes latent virus reactivation in the cohorts.

Methods: Anti-SARS-CoV-2 antibodies were analyzed in plasma and saliva from non-vaccinated ME/CFS (n=95) and HDs (n=110) using soluble multiplex immunoassay. Reactivation of human herpesviruses 1-6 (HSV1, HSV2, VZV, EBV, CMV, HHV6), and human endogenous retrovirus K (HERV-K) was detected by anti-viral antibody fingerprints in saliva.

Results: At 3-6 months after mild/asymptomatic SARS-CoV-2 infection, virus-specific antibodies in saliva were substantially induced signifying a strong reactivation of latent viruses (EBV, HHV6 and HERV-K) in both cohorts. In patients with ME/CFS, antibody responses were significantly stronger, in particular EBV-encoded nuclear antigen-1 (EBNA1) IgG were elevated in patients with ME/CFS, but not in HDs. EBV-VCA IgG was also elevated at baseline prior to SARS-infection in patients compared to HDs.

Conclusion: Our results denote an altered and chronically aroused anti-viral profile against latent viruses in ME/CFS. SARS-CoV-2 infection even in its mild/asymptomatic form is a potent trigger for reactivation of latent herpesviruses (EBV, HHV6) and endogenous retroviruses (HERV-K), as detected by antibody fingerprints locally in the oral mucosa (saliva samples). This has not been shown before because the antibody elevation is not detected systemically in the circulation/plasma.

Infection with SARS-CoV-2 Variants Is Associated with Different Long COVID Phenotypes

Viruses. 2022 Oct 27;14(11):2367. doi: 10.3390/v14112367.

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Abstract

COVID-19 has been associated with a broad range of long-term sequelae, commonly referred to as "long-COVID" or "post-COVID-19" syndrome. Despite an increasing body of literature, long COVID remains poorly characterized. We retrospectively analysed data from electronic medical records of patients admitted to the post-COVID-19 outpatient service of the Infectious and Tropical Diseases Unit, Careggi University Hospital, Florence, Italy, between June 2020 and June 2021, 4-12 weeks after hospital discharge. A total of 428 patients, 41% women, median age 64 years, underwent a follow-up visit a median 53 days after hospital discharge. Overall, 76% patients reported at least one persistent symptom, including dyspnoea (37%), chronic fatigue (36%), insomnia (16%), visual disorders (13%) and brain fog (13%). Increasing oxygen support (OR 1.4, 95% CI 1.1-1.8), use of immunosuppressants (OR 6.4, 95% CI 1.5-28) and female sex (OR 1.8, 95% CI 1.1-2.9) were associated with a higher risk of long COVID symptoms. Comparison between symptomatic patients infected in the period March-December 2020 (prevalent circulation of wild-type SARS-CoV-2) with those infected in the period January-April 2021 (prevalent circulation of B.1.1.7 Alpha variant) showed a significant modification in the pattern of symptoms belonging to the neurological and cognitive/emotional categories. Our findings confirmed shortness of breath and chronic fatigue as the most frequent long COVID manifestations, while female sex and severe COVID-19 course were the main risk factors for developing lingering symptoms. SARS-CoV-2 variants may induce different long COVID phenotypes, possibly due to changes in cell tropism and differences in viral-host interaction.

Long-term neurological sequelae of SARS-CoV-2 infection

Nat Med. 2022 Nov;28(11):2269-2270. doi: 10.1038/s41591-022-02018-4.

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Abstract

We show that patients who survive the first 30 days of acute SARS-CoV-2 infection have an increased risk of various post-acute neurological disorders after 1 year compared with uninfected contemporaries. The burden of these sequelae (aspects of ‘long COVID’) has serious implications for patients as well as society.

Beyond COVID-19 and SARS-CoV-2, cardiovascular outcomes of "long covid" from a pathological perspective - a look back and road ahead

Pathol Res Pract. 2022 Nov;239:154144. doi: 10.1016/j.prp.2022.154144. Epub 2022 Sep 29.

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Abstract

With the decrease in severity of COVID-19 there is a sense of relief in the general population. However, there has been an increased incidence of cardiovascular and other organ complications post-infection, which have raised concerns about long COVID. The term "long COVID" was first used by Perego on social media to denote the persistence of symptoms weeks or months after initial SARS-CoV-2 infection and the term 'long haulers' was first described by Watson and by Yong to identify post-COVID conditions. There has been an increased incidence of sudden cardiac death and MI post-COVID-19 in healthy individuals, sports persons and prominent movie stars. Potential mechanisms contributing to the pathophysiology of post-acute COVID-19 may include 1) Damage to tissues and cells that are important for blood flow, so clotting of blood is increased. 2) Persistence of fragments of virus or its sub-particles/ protein material in a wide range of body sites and, 3) an immune system gone haywire. As the majority of countries across the globe are easing coronavirus precautionary measures, there is an urgent need by health care organizations and policymakers worldwide to generate awareness by educating the public at large, about the ill effects of long-COVID and varied types of post-acute sequelae of COVID-19.

Plasma proteomic signature predicts who will get persistent symptoms following SARS-CoV-2 infection

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Abstract

Background: The majority of those infected by ancestral Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) during the UK first wave (starting March 2020) did not require hospitalisation. Most had a short-lived mild or asymptomatic infection, while others had symptoms that persisted for weeks or months. We hypothesized that the plasma proteome at the time of first infection would reflect differences in the inflammatory response that linked to symptom severity and duration.

Methods: We performed a nested longitudinal case-control study and targeted analysis of the plasma proteome of 156 healthcare workers (HCW) with and without lab confirmed SARS-CoV-2 infection. Targeted proteomic multiple-reaction monitoring analysis of 91 pre-selected proteins was

undertaken in uninfected healthcare workers at baseline, and in infected healthcare workers serially, from 1 week prior to 6 weeks after their first confirmed SARS-CoV-2 infection. Symptom severity and antibody responses were also tracked. Questionnaires at 6 and 12 months collected data on persistent symptoms.

Findings: Within this cohort (median age 39 years, interquartile range 30-47 years), 54 healthcare workers (44% male) had PCR or antibody confirmed infection, with the remaining 102 (38% male) serving as uninfected controls. Following the first confirmed SARS-CoV-2 infection, perturbation of the plasma proteome persisted for up to 6 weeks, tracking symptom severity and antibody responses. Differentially abundant proteins were mostly coordinated around lipid, atherosclerosis and cholesterol metabolism pathways, complement and coagulation cascades, autophagy, and lysosomal function. The proteomic profile at the time of seroconversion associated with persistent symptoms out to 12 months. Data are available via ProteomeXchange with identifier PXD036590.

Interpretation: Our findings show that non-severe SARS-CoV-2 infection perturbs the plasma proteome for at least 6 weeks. The plasma proteomic signature at the time of seroconversion has the potential to identify which individuals are more likely to suffer from persistent symptoms related to SARS-CoV-2 infection.

Funding information: The COVIDsortium is supported by funding donated by individuals, charitable Trusts, and corporations including Goldman Sachs, Citadel and Citadel Securities, The Guy Foundation, GW Pharmaceuticals, Kusuma Trust, and Jagclif Charitable Trust, and enabled by Barts Charity with support from University College London Hospitals (UCLH) Charity. This work was additionally supported by the Translational Mass Spectrometry Research Group and the Biomedical Research Center (BRC) at Great Ormond Street Hospital.

A novel conceptual model of trauma-informed care for patients with post-acute sequelae of SARS-CoV-2 illness (PASC)

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Abstract

Aim: This paper proposes a novel, trauma-informed, conceptual model of care for Post-Acute Sequelae of COVID-19 illness (PASC).

Design: This paper describes essential elements, linkages and dimensions of the model that affect PASC patient experiences and the potential impact of trauma-informed care on outcomes.

Data sources: PASC is a consequence of the global pandemic, and a new disease of which little is known. Our model was derived from the limited available studies, expert clinical experience specific to PASC survivors and publicly available social media narratives authored by PASC survivors.

Implications for nursing: The model provides a critical and novel framework for the understanding and care of persons affected by PASC. This model is aimed at the provision of nursing care, with the intention of reducing the traumatic impacts of the uncertain course of this disease, a lack of defined treatment options and difficulties in seeking care. The use of a trauma-informed care approach to PASC patients can enhance nurses' ability to remediate and ameliorate both the traumatic burden of and the symptoms and experience of the illness.

Conclusion: Applying a trauma-informed perspective to care of PASC patients can help to reduce the overall burden of this complex condition. Owing to the fundamentally holistic perspective of the nursing profession, nurses are best positioned to implement care that addresses multiple facets of the PASC experience.

Impact: The proposed model specifically addresses the myriad ways in which PASC may affect physical as well as mental and psychosocial dimensions of health. The model particularly seeks to suggest means of supporting patients who have already experienced a life-threatening illness and are now coping with its long-term impact. Since the scope of this impact is not yet defined, trauma-informed care for PASC patients is likely to reduce the overall health and systems burdens of this complex condition.

Dysregulated naive B cells and de novo autoreactivity in severe COVID-19

Nature. 2022 Nov;611(7934):139-147. doi: 10.1038/s41586-022-05273-0. Epub 2022 Aug 31.

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Abstract

Severe SARS-CoV-2 infection1 has been associated with highly inflammatory immune activation since the earliest days of the COVID-19 pandemic2-5. More recently, these responses have been associated with the emergence of self-reactive antibodies with pathologic potential6-10, although their origins and resolution have remained unclear11. Previously, we and others have identified extrafollicular B cell activation, a pathway associated with the formation of new autoreactive antibodies in chronic autoimmunity12,13, as a dominant feature of severe and critical COVID-19 (refs. 14-18). Here, using single-cell B cell repertoire analysis of patients with mild and severe disease, we identify the expansion of a naive-derived, low-mutation IgG1 population of antibody-secreting cells (ASCs) reflecting features of low selective pressure. These features correlate with progressive, broad, clinically relevant autoreactivity, particularly directed against nuclear antigens and carbamylated proteins, emerging 10-15 days after the onset of symptoms. Detailed analysis of the low-selection compartment shows a high frequency of clonotypes specific for both SARS-CoV-2 and autoantigens, including pathogenic autoantibodies against the glomerular basement membrane. We further identify the contraction of this pathway on recovery, re-establishment of tolerance standards and concomitant loss of acute-derived ASCs irrespective of antigen specificity. However, serological autoreactivity persists in a subset of patients with postacute sequelae, raising important questions as to the contribution of emerging autoreactivity to continuing symptomology on recovery. In summary, this study demonstrates the origins, breadth and resolution of autoreactivity

in severe COVID-19, with implications for early intervention and the treatment of patients with post-COVID sequelae.

Does covid-19 impair endogenous neurogenesis?

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Abstract

Endogenous neural stem cells are thought to continue to generate new neurons throughout life in the human brain. Endogenous neurogenesis has been proposed to contribute to physiological roles in maintaining and regenerating olfaction, as well as promoting normal cognition, learning and memory. Specific impairments in these processes in COVID-19 - impaired olfaction and cognition - may implicate the SARS-CoV-2 virus in attenuating neurogenesis. Furthermore, neurogenesis has been linked with neuroregeneration; and impaired neuroregeneration has previously been linked with neurodegenerative diseases. Emerging evidence supports an association between COVID-19 infection and accelerated neurodegeneration. Also, structural changes indicating global reduction in brain size and specific reduction in the size of limbic structures - including orbitofrontal cortex, olfactory cortex and parahippocampal gyrus - as a result of SARS-CoV-2 infection have been demonstrated. This paper proposes the hypothesis that SARS-CoV-2 infection may impair endogenous neural stem cell activity. An attenuation of neurogenesis may contribute to reduction in brain size and/or neurodegenerative processes following SARS-CoV-2 infection. Furthermore, as neural stem cells are thought to be the cell of origin in glioma, better understanding of SARS-CoV-2 interaction with tumorigenic stem cells is indicated, with a view to informing therapeutic modulation. The subacute and chronic implications of attenuated endogenous neurogenesis are explored in the context of long COVID. Modulating endogenous neurogenesis may be a novel therapeutic strategy to address specific neurological manifestations of COVID-19 and potential applicability in tumour virotherapy.

The osteo-metabolic phenotype of COVID-19: an update

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Abstract

Context: In the multifaceted COVID-19 clinical scenario characterized by a multi-system disorder with negative implications not only on respiratory function but also on cardiac, hematological, neurological and endocrine-metabolic systems, a distinctive osteo-metabolic phenotype with an independent influence on disease severity and recovery of patients affected was early reported.

Aim: To summarize and update the main evidences regarding the distinct components of this phenotype in acute and Long COVID-19, reinforcing its clinical relevance and discussing the main pathophysiological and clinical-therapeutic implications of the most recent reported findings.

Results: This emerging phenotype is characterized by a widespread acute hypocalcemia and hypovitaminosis D with an impaired compensatory parathyroid hormone response, and a high prevalence of skeletal complications such as vertebral fractures. The clinical relevance of this osteo-metabolic phenotype on acute COVID-19 is well characterized, and novel seminal evidences are progressively highlighting its importance also in predicting patient's long-term outcomes and Long COVID-19 occurrence.

Conclusions: These findings reinforced the central role of a multidisciplinary team, including endocrinologists, in evaluating these patients for a proactive search of each aspect of the osteo-metabolic phenotype components since they may represent suitable therapeutic targets to prevent SARS-CoV-2 infection, poor COVID-19 outcomes, Long COVID-19 occurrence and even possibly better responses to COVID-19 vaccination.

Complexity and Challenges of the Clinical Diagnosis and Management of Long COVID

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Abstract

Importance: There is increasing recognition of the long-term health effects of SARS-CoV-2 infection (sometimes called long COVID). However, little is yet known about the clinical diagnosis and management of long COVID within health systems.

Objective: To describe dominant themes pertaining to the clinical diagnosis and management of long COVID in the electronic health records (EHRs) of patients with a diagnostic code for this condition (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10] code U09.9).

Design, setting, and participants: This qualitative analysis used data from EHRs of a national random sample of 200 patients receiving care in the Department of Veterans Affairs (VA) with documentation of a positive result on a polymerase chain reaction (PCR) test for SARS-CoV-2 between February 27, 2020, and December 31, 2021, and an ICD-10 diagnostic code for long

COVID between October 1, 2021, when the code was implemented, and March 1, 2022. Data were analyzed from February 5 to May 31, 2022.

Main outcomes and measures: A text word search and qualitative analysis of patients' VA-wide EHRs was performed to identify dominant themes pertaining to the clinical diagnosis and management of long COVID.

Results: In this qualitative analysis of documentation in the VA-wide EHR, the mean (SD) age of the 200 sampled patients at the time of their first positive PCR test result for SARS-CoV-2 in VA records was 60 (14.5) years. The sample included 173 (86.5%) men; 45 individuals (22.5%) were identified as Black and 136 individuals (68.0%) were identified as White. In qualitative analysis of documentation pertaining to long COVID in patients' EHRs 2 dominant themes were identified: (1) clinical uncertainty, in that it was often unclear whether particular symptoms could be attributed to long COVID, given the medical complexity and functional limitations of many patients and absence of specific markers for this condition, which could lead to ongoing monitoring, diagnostic testing, and specialist referral; and (2) care fragmentation, describing how post-COVID-19 care processes were often siloed from and poorly coordinated with other aspects of care and could be burdensome to patients.

Conclusions and relevance: This qualitative study of documentation in the VA EHR highlights the complexity of diagnosing long COVID in clinical settings and the challenges of caring for patients who have or are suspected of having this condition.

Cardiovascular symptom phenotypes of post-acute sequelae of SARS-CoV-2

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Abstract

Background: Acute COVID-19 infection has been shown to have significant effects on the cardiovascular system. Post-acute sequelae of SARS-CoV-2 (PASC) are being identified in patients; however, the cardiovascular effects are yet to be well-defined. The Post-COVID Cardiology Clinic at Washington University evaluates and treats patients with ongoing cardiovascular PASC.

Objectives: This investigation aims to describe the phenotypes of cardiovascular symptoms of PASC in patients presenting to the Post-COVID Cardiology Clinic, including their demographics, symptoms, and the clinical phenotypes observed.

Methods: This was a retrospective analysis of symptoms, clinical findings, and test results from the first 100 consecutive adult patients who presented to the Post-COVID Cardiology Clinic at Washington University in St. Louis, between September 2020 to May 2021 with cardiovascular symptoms following COVID-19 infection.

Results: The population (n = 100) had a mean age of 46.3 years and was 81% female. Most patients had mild acute illness, with only 23% of patients requiring hospitalization during acute COVID-19 infection. The most commonly reported PASC symptoms were chest pain (66%), palpitations (59%), and dyspnea on exertion (56%). Of those presenting with these symptoms, 74/98 patients (75.5%) were found to have a significant blood pressure elevation, considerable sinus tachycardia burden, reduced global longitudinal strain, increased indexed left-ventricular end-diastolic volume (LVEDVi) by echocardiogram, and/or cMRI findings consistent with possible active or healing myocarditis.

Conclusions: Our findings highlight clinical phenotypes of the cardiovascular manifestations of PASC. Further studies are needed to evaluate the pathophysiology, treatment options and long-term outcomes for these patients.

The neurobiology of long COVID

Neuron. 2022 Nov 2;110(21):3484-3496. doi: 10.1016/j.neuron.2022.10.006. Epub 2022 Oct 7.

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Abstract

Persistent neurological and neuropsychiatric symptoms affect a substantial fraction of people after COVID-19 and represent a major component of the post-acute COVID-19 syndrome, also known as long COVID. Here, we review what is understood about the pathobiology of post-acute COVID-19 impact on the CNS and discuss possible neurobiological underpinnings of the cognitive symptoms affecting COVID-19 survivors. We propose the chief mechanisms that may contribute to this emerging neurological health crisis.

Possible Application of Melatonin in Long COVID

Biomolecules. 2022 Nov 7;12(11):1646. doi: 10.3390/biom12111646.

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Abstract

Clinical sequelae and symptoms for a considerable number of COVID-19 patients can linger for months beyond the acute stage of SARS-CoV-2 infection, "long COVID". Among the long-term consequences of SARS-CoV-2 infection, cognitive issues (especially memory loss or "brain fog"), chronic fatigue, myalgia, and muscular weakness resembling myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are of importance. Melatonin may be particularly effective at reducing the signs and symptoms of SARS-CoV-2 infection due to its functions as an antioxidant, anti-inflammatory, and immuno-modulatory agent. Melatonin is also a chronobiotic medication effective in treating delirium and restoring the circadian imbalance seen in COVID patients in the intensive care unit. Additionally, as a cytoprotector, melatonin aids in the prevention of several COVID-19 comorbidities, including diabetes, metabolic syndrome, and ischemic and non-ischemic cardiovascular diseases. This narrative review discusses the application of melatonin as a neuroprotective agent to control cognitive deterioration ("brain fog") and pain in the ME/CFS syndrome-like documented in long COVID. Further studies on the therapeutic use of melatonin in the neurological sequelae of SARS-CoV-2 infection are warranted.

Rehabilitation of Post-COVID-19 Musculoskeletal Sequelae in Geriatric Patients: A Case Series Study

Int J Environ Res Public Health. 2022 Nov 21;19(22):15350. doi: 10.3390/ijerph192215350.

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Abstract

The musculoskeletal system is affected in over 40% of patients with Coronavirus disease 2019 (COVID-19). There is an increased need for post-acute rehabilitation after COVID-19, especially in elderly people with underlying health problems. The aim of this study was to evaluate the benefits of an early and goal-orientated rehabilitation program using combined approaches, robotic medical devices together with other rehabilitation techniques and therapies, in elderly people after acute COVID-19. Ninety-one patients (62.64 ± 14.21 years) previously diagnosed with severe SARS-CoV-2 infection were admitted to the Medical Rehabilitation Clinical Hospital Baile Felix, Romania, for medical rehabilitation, but only six patients (85.33 ± 3.07 years) met the inclusion criteria and participated in the study. The rehabilitation treatment was complex, performed over 4 weeks, and included combined approaches: exercise therapy, robotic gait training, occupational therapy, and massages. Activity and participation evaluation were performed using the Barthel Index and Functional Independence Measure for activities of daily living (ADLs). Assessments were performed at admission and discharge from the rehabilitation clinic. Lokomat patients' reports revealed that the patients had improved motor control (with one exception). The measurement of functional ability revealed an improvement in most cases. This study presents some of the first data on outcomes of COVID-19 patients' musculoskeletal rehabilitation in our country. Early complex medical rehabilitation improved functional independence and autonomy in ADLs in very old patients, post-COVID-19.

Post-acute sequelae of COVID-19 among hospitalized patients in Estonia: Nationwide matched cohort study

PLoS One. 2022 Nov 23;17(11):e0278057. doi: 10.1371/journal.pone.0278057. eCollection 2022.

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Abstract

Background: Post-acute COVID-19 sequelae refers to a variety of health complications involving different organ systems that have been described among individuals after acute phase of illness. Data from unselected population groups with long-time follow up is needed to comprehensively describe the full spectrum of post-acute COVID-19 complications.

Methods: In this retrospective nationwide cohort study, we used data obtained from electronic health record database. Our primary cohort were adults hospitalized with confirmed COVID-19 and matched (age, sex, Charlson Comorbidity Index) unaffected controls from general population. Individuals included from February 2020 until March 2021 were followed up for 12 months. We estimated risks of all-cause mortality, readmission and incidence of 16 clinical sequelae after acute COVID-19 phase. Using a frailty Cox model, we compared incidences of outcomes in two cohorts.

Results: The cohort comprised 3949 patients older than 18 years who were alive 30 days after COVID-19 hospital admission and 15511 controls. Among cases 40.3% developed at least one incident clinical sequelae after the acute phase of SARS-CoV-2 infection, which was two times higher than in general population group. We report substantially higher risk of all-cause mortality (adjusted hazard ratio (aHR) = 2.57 (95%CI 2.23-2.96) and hospital readmission aHR = 1.73 (95%CI 1.58-1.90) among hospitalized COVID-19 patients. We found that the risks for new clinical sequalae were significantly higher in COVID-19 patients than their controls, especially for dementia aHR = 4.50 (95% CI 2.35-8.64), chronic lower respiratory disease aHR = 4.39 (95% CI 3.09-6.22), liver disease aHR 4.20 (95% CI 2.01-8.77) and other (than ischemic) forms of heart diseases aHR = 3.39 (95%CI 2.58-4.44).

Conclusion: Our results provide evidence that the post-acute COVID-19 morbidity within the first year after COVID-19 hospitalization is substantial. Risks of all-cause mortality, hospitalisation and majority of clinical sequelae were significantly higher in hospitalized COVID-19 patients than in general population controls and warrant targeted prevention efforts.

Musculoskeletal Components of Post-Acute Sequelae of SARS-CoV-2 Infections

JBJS Rev. 2022 Nov 28;10(11). doi: 10.2106/JBJS.RVW.22.00088. eCollection 2022 Nov 1.

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Abstract

➢: Musculoskeletal (MSK) sequelae of severe acute respiratory syndrome coronavirus 2 infections seem to be common.

➢: Mechanisms of such effects are becoming clear.

➢: There is a complex interplay of biopsychosocial effects associated with MSK symptoms after acute coronavirus disease 2019.

➢: Additional research should focus on completely describing the breadth of these MSK sequelae and related psychosocial symptoms.

Pathophysiology and mechanism of long COVID: a comprehensive review

Ann Med. 2022 Dec;54(1):1473-1487. doi: 10.1080/07853890.2022.2076901.

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Abstract

Background: After almost 2 years of fighting against SARS-CoV-2 pandemic, the number of patients enduring persistent symptoms long after acute infection is a matter of concern. This set of symptoms was referred to as "long COVID", and it was defined more recently as "Post COVID-19 condition" by the World health Organization (WHO). Although studies have revealed that long COVID can manifest whatever the severity of inaugural illness, the underlying pathophysiology is still enigmatic.

Aim: To conduct a comprehensive review to address the putative pathophysiology underlying the persisting symptoms of long COVID.

Method: We searched 11 bibliographic databases (Cochrane Library, JBI EBP Database, Medline, Embase, PsycInfo, CINHAL, Ovid Nursing Database, Journals@Ovid, SciLit, EuropePMC, and CoronaCentral). We selected studies that put forward hypotheses on the pathophysiology, as well as those that encompassed long COVID patients in their research investigation.

Results: A total of 98 articles were included in the systematic review, 54 of which exclusively addressed hypotheses on pathophysiology, while 44 involved COVID patients. Studies that included patients displayed heterogeneity with respect to the severity of initial illness, timing of analysis, or presence of a control group. Although long COVID likely results from long-term organ damage due to acute-phase infection, specific mechanisms following the initial illness could contribute to the later symptoms possibly affecting many organs. As such, autonomic nervous system damage could account for many symptoms without clear evidence of organ damage. Immune dysregulation, auto-immunity, endothelial dysfunction, occult viral persistence, as well as coagulation activation are the main underlying pathophysiological mechanisms so far.

Conclusion: Evidence on why persistent symptoms occur is still limited, and available studies are heterogeneous. Apart from long-term organ damage, many hints suggest that specific mechanisms following acute illness could be involved in long COVID symptoms. KEY MESSAGES Long-COVID is a multisystem disease that develops regardless of the initial disease severity. Its clinical spectrum comprises a wide range of symptoms. The mechanisms underlying its pathophysiology are still unclear. Although organ damage from the acute infection phase likely accounts for symptoms, specific long-lasting inflammatory mechanisms have been proposed, as well. Existing studies involving Long-COVID patients are highly heterogeneous, as they include patients with various COVID-19 severity levels and different time frame analysis, as well.

Cardiac Manifestations of Post-Acute COVID-19 Infection

Curr Cardiol Rep. 2022 Dec;24(12):1775-1783. doi: 10.1007/s11886-022-01793-3. Epub 2022 Nov 2.

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Abstract

Purpose of review: There is emerging evidence that the post-acute and chronic phases of COVID-19 infection are associated with various significant cardiovascular sequelae.

Recent findings: Long COVID has been shown to be associated with multiple cardiovascular sequelae including direct myocardial injury, arrhythmias, and cardiomyopathies. Hypotheses on the mechanism of myocardial injury include direct viral infiltration and autoimmune dysregulation. Long COVID is associated with persistent cardiac ischemia in patients with no previous history of coronary disease, atrial and ventricular arrhythmias, and the development of new-onset heart failure in previously healthy patients. Onset of long COVID may be related to severity of the initial SARS-CoV2 infection. Cardiac MRI is a valuable tool in assessing myocarditis and the development of cardiomyopathies in the setting of long COVID. Both patients with and without pre-existing cardiovascular disease are at risk of developing myocardial injury in the setting of long COVID. Future studies will elucidate both cardiovascular mortality and cardiac rehabilitation in the post-acute and chronic phases of COVID-19.

Prevalence and clinical presentation of long COVID in children: a systematic review

Eur J Pediatr. 2022 Dec;181(12):3995-4009. doi: 10.1007/s00431-022-04600-x. Epub 2022 Sep 15.

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Abstract

A systematic literature review was conducted up to 15th February 2022 to summarize long COVID evidence and to assess prevalence and clinical presentation in children and adolescents. Articles reporting long COVID prevalence and symptoms based on original data in the paediatric population were included. Case series quality was assessed through the JBI Critical Appraisal Checklist. For observational studies, adherence to STROBE checklist was evaluated. Twenty-two articles were included: 19 observational studies (12 cohort/7 cross-sectional) and 3 case series. Nine studies provided a control group. We found a high variability in terms of prevalence (1.6-70%). The most frequently reported symptoms were fatigue (2-87%), headache (3.5-80%), arthro-myalgias (5.4-66%), chest tightness or pain (1.4-51%), and dyspnoea (2-57.1%). Five studies reported limitations in daily function due to long COVID. Alterations at brain imaging were described in one study, transient electrocardiographic abnormalities were described in a minority of children, while most authors did not evidence long-term pulmonary sequelae. Older age, female sex, and previous long-term pathological conditions were more frequently associated with persistent symptoms.

Conclusion: Long COVID evidence in children is limited, heterogeneous, and based on low-quality studies. The lockdown consequences are difficult to distinguish from long COVID symptoms. High-quality studies are required: WHO definition of long COVID should be used, controlled clinical studies should be encouraged, and the impact of new variants on long COVID prevalence should be investigated to ensure an objective analysis of long COVID characteristics in children and a proper allocation of healthcare system resources.

What is known: Children rarely develop a severe respiratory disease in the acute phase of COVID-19. A limited number of patients develop a multisystem inflammatory condition that can lead to multiorgan failure and shock.

What is new: Persistent symptoms after SARS-CoV-2 infection are reported in children and limitations in daily function due to long COVID symptoms affect school attendance. Functional complaints of post-acute COVID are difficult to be distinguished from those due to social restrictions.

Post-COVID-19 syndrome/condition or long COVID: Persistent illness after acute SARS CoV-2 infection

Aust J Gen Pract. 2022 Dec;51(12):952-957. doi: 10.31128/AJGP-05-22-6429.

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Abstract

Background: Approximately 10 million Australians have had confirmed SARS-CoV-2 infection. The waves of infection in the population have been succeeded by smaller waves of people affected by persistent illness following acute infection. Post-COVID-19 symptoms may extend for months following infection. There is a range of symptoms causing mild to debilitating impairment.

Objective: This article summarises what is currently understood about the pathophysiology, risk factors, symptoms and how to approach both the assessment and care of people with post-COVID-19 sequelae.

Discussion: Currently recommended is a person-centred approach from a multidisciplinary team, with general practitioners centrally coordinating care. As the understanding of post-acute COVID-19 is evolving, regularly updated or 'living guidelines' will be crucial for those affected to be provided with best care within the health system.

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

Emerg Microbes Infect. 2022 Dec;11(1):902-913. doi: 10.1080/22221751.2022.2049984.

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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.

SARS-CoV-2 infection and persistence in the human body and brain at autopsy

Nature. 2022 Dec;612(7941):758-763. doi: 10.1038/s41586-022-05542-y. Epub 2022 Dec 14.

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Abstract

Coronavirus disease 2019 (COVID-19) is known to cause multi-organ dysfunction1-3 during acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with some patients experiencing prolonged symptoms, termed post-acute sequelae of SARS-CoV-2 (refs. 4,5). However, the burden of infection outside the respiratory tract and time to viral clearance are not well characterized, particularly in the brain3,6-14. Here we carried out complete autopsies on 44 patients who died with COVID-19, with extensive sampling of the central nervous system in 11 of these patients, to map and quantify the distribution, replication and cell-type specificity of SARS-CoV-2 across the human body, including the brain, from acute infection to more than seven months following symptom onset. We show that SARS-CoV-2 is widely distributed, predominantly among patients who died with severe COVID-19, and that virus replication is present in multiple respiratory and non-respiratory tissues, including the brain, early in infection. Further, we detected persistent SARS-CoV-2 RNA in multiple anatomic sites, including throughout the brain, as late as 230 days following symptom onset in one case. Despite extensive distribution of SARS-CoV-2 RNA throughout the body, we observed little evidence of inflammation or direct viral cytopathology outside the respiratory tract. Our data indicate that in some patients SARS-CoV-2 can cause systemic infection and persist in the body for months.

Psychiatric and neurological complications of long COVID

J Psychiatr Res. 2022 Dec;156:349-360. doi: 10.1016/j.jpsychires.2022.10.045. Epub 2022 Oct 20.

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Abstract

COVID-19 was primarily considered a pulmonary disease with extrapulmonary manifestations. As the pandemic spread, there has been growing evidence that the disease affects various organs/systems, including the central and peripheral nervous systems. Accumulation of clinical data demonstrates that in a large population of survivors impairments in the function of one or more organs may persist for a long time, a phenomenon commonly known as post COVID or long COVID. Fatigue and cognitive dysfunction, such as concentration problems, short-term memory deficits, general memory loss, a specific decline in attention, language and praxis abilities, encoding and verbal fluency, impairment of executive functions, and psychomotor coordination, are amongst the most common and debilitating features of neuropsychatric symptoms of post COVID syndrome. Several patients also suffer from compromised sleep, depression, anxiety and post-traumatic stress disorder. Patients with long COVID may demonstrate brain hypometabolism, hypoperfusion of the cerebral cortex and changes in the brain structure and functional connectivity. Children and adolescents represent a minority of COVID-19 cases, so not surprisingly data on the long-term sequelae after SARS-CoV-2 infections in these age groups are scarce. Although the pathogenesis, clinical characteristics, epidemiology, and risk factors of the acute phase of COVID-19 have been largely explained, these areas are yet to be explored in long COVID. This review aims to provide an update on what is currently known about long COVID effects on mental health.

Post-acute sensory neurological sequelae in patients with severe acute respiratory syndrome coronavirus 2 infection: the COVID-PN observational cohort study

Pain. 2022 Dec 1;163(12):2398-2410. doi: 10.1097/j.pain.0000000000002639. Epub 2022 Mar 24.

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can cause neurological sequelae after the resolution of symptomatic COVID-19 illness, but the occurrence of peripheral neuropathy symptoms and cranial nerve dysfunction is unknown. This study aimed to characterize the occurrence and severity of pain and peripheral neuropathy symptoms in patients with SARS-CoV-2 infection. An observational cohort study included adults tested for a SARS-CoV-2 infection at an academic medical center (assigned as CV+ or control, based on test results). Thirty to 90 days after the index SARS-CoV-2 test, patients completed a web-based questionnaire assessing pain, peripheral neuropathy-related sensory symptoms, and symptoms in the distribution of cranial nerves (current symptoms, symptoms at testing and 2 weeks thereafter). Univariate analyses compared the outcomes between the groups. Multivariable analysis was used to determine the odds for neuropathy symptoms after adjusting for key baseline variables. A total of 1556 participants were included: 542 CV+ patients and 1014 control subjects. CV+ patients reported a higher occurrence of peripheral neuropathy symptoms in the extremities anytime within 90 days postinfection (28.8% vs 12.9%, odds ratio [OR] [95% confidence interval] = 2.72 [2.10-3.54]), as well as such symptoms persisting up to 90 days after infection (6.1% vs 1.9%, OR = 3.39 [1.91-6.03]). The occurrence of pain in the extremities was higher in the CV+ group (24.2% vs 9.8%, OR = 2.95 [2.21-3.91]). SARS-CoV-2 infection was also associated with higher occurrence of peripheral neuropathy symptoms, after adjusting for the history of chronic pain and neuropathy (OR = 3.19 [2.37-4.29]). The results suggest that SARS-CoV-2 infection was independently associated with an increased risk of pain and peripheral neuropathy symptoms.

SARS-CoV-2 Sequelae and Postdischarge Health Care Visits Over 5 Months Follow-up Among Children Hospitalized for COVID-19 or MIS-C

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Abstract

Although post-acute sequelae of COVID-19 among adult survivors has gained significant attention, data in children hospitalized for severe acute respiratory syndrome coronavirus 2 is limited. This study of commercially insured US children shows that those hospitalized with COVID-19 or multisystem inflammatory syndrome in children have a substantial burden of severe acute respiratory syndrome coronavirus 2 sequelae and associated health care visits postdischarge.

Oral GS-441524 derivatives: Next-generation inhibitors of SARS-CoV-2 RNA-dependent RNA polymerase

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Abstract

GS-441524, an RNA-dependent RNA polymerase (RdRp) inhibitor, is a 1'-CN-substituted adenine C-nucleoside analog with broad-spectrum antiviral activity. However, the low oral bioavailability of GS-441524 poses a challenge to its anti-SARS-CoV-2 efficacy. Remdesivir, the intravenously administered version (version 1.0) of GS-441524, is the first FDA-approved agent for SARS-CoV-2 treatment. However, clinical trials have presented conflicting evidence on the value of remdesivir in COVID-19. Therefore, oral GS-441524 derivatives (VV116, ATV006, and GS-621763; version 2.0, targeting highly conserved viral RdRp) could be considered as game-changers in treating COVID-19 because oral administration has the potential to maximize clinical benefits, including decreased duration of COVID-19 and reduced post-acute sequelae of SARS-CoV-2 infection, as well as limited side effects such as hepatic accumulation. This review summarizes the current research related to the oral derivatives of GS-441524, and provides important insights into the potential factors underlying the controversial observations regarding the clinical efficacy of remdesivir; overall, it offers an effective launching pad for developing an oral version of GS-441524.

Psychological and Mental Sequelae in Elite Athletes with Previous SARS-CoV-2 Infection: A Systematic Review

Int J Environ Res Public Health. 2022 Dec 7;19(24):16377. doi: 10.3390/ijerph192416377.

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Abstract

During the COVID-19 pandemic, many athletes from several sporting disciplines were infected with the SARS-CoV-2. The aim of this systematic review is to summarize the current scientific evidence on the psychological sequelae and mental health of elite athletes who have been infected by the virus. The review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement; three databases were searched: PubMed, ISI Web of Knowledge, and Scopus. The initial search resulted in 2420 studies; after duplicate removal and screening by title and abstract, 41 articles were screened by full-text. A total of four eligible articles were included in the review. All included articles measured depression and anxiety in athletes who had suffered from COVID-19, while in three papers levels of stress were measured. Overall, the only two questionnaires used in more than one study were the DASS-21 and the APSQ. In our systematic review, we highlighted that mental and psychological health in elite athletes has the same importance as physical health. This statement suggests that these examinations should be introduced and performed during the competitive sports' medical examinations conducted at the start of the sporting season, which currently consists only of the examination of physical parameters. Due to lack of studies on the topic, the results of our review show that mental health in athletes with a history of SARS-CoV-2 infection is an issue that requires more investigation, considering the evidence of clinical consequences. The importance of post-infection psychological sequelae is significant in assessing possible repercussions on the athletes' sporting performance.

COVID-19 and the heart

Br Med Bull. 2022 Dec 12;144(1):4-11. doi: 10.1093/bmb/ldac022.

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Abstract

Background: There is evidence for a bi-directional relationship between COVID-19 and the cardiovascular (CV) system.

Source of data: Published literature.

Areas of agreement: Pre-existing heart failure (HF) increases the risk of mortality with COVID-19. CV complications are recognized, including increased rates of acute coronary syndromes, HF, arrhythmia and myocarditis. Drugs targeting the angiotensin system are safe and may provide prognostic benefit.

Areas of controversy: Vaccination as a cause of myocarditis remains a key area of contention.

Growing points: As the pandemic progresses, we are gaining more data about the long-term effects of COVID-19 on the CV system: long COVID, and medium-to-long-term increases in CV risk.

Areas timely for developing research: Large-scale longitudinal studies will shed light on long-term CV outcomes with COVID-19. Furthermore, the differential effects of COVID-19 variants on the CV system must be investigated.

Post-COVID-19 syndrome: Cardiovascular manifestations

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No abstract available

Deep Dive into the Long Haul: Analysis of Symptom Clusters and Risk Factors for Post-Acute Sequelae of COVID-19 to Inform Clinical Care

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Abstract

Long COVID is a chronic condition characterized by symptoms such as fatigue, dyspnea, and cognitive impairment that persist or relapse months after an acute infection with the SARS-CoV-2 virus. Many distinct symptoms have been attributed to Long COVID; however, little is known about the potential clustering of these symptoms and risk factors that may predispose patients to certain clusters. In this study, an electronic survey was sent to patients in the UC San Diego Health (UCSDH) system who tested positive for COVID-19, querying if patients were experiencing symptoms consistent with Long COVID. Based on survey results, along with patient demographics reported in the electronic health record (EHR), linear and logistic regression models were used to examine putative risk factors, and exploratory factor analysis was performed to determine symptom clusters. Among 999 survey respondents, increased odds of Long COVID (n = 421; 42%) and greater Long COVID symptom burden were associated with female sex (OR = 1.73, 99% CI: 1.16-2.58; β = 0.48, 0.22-0.75), COVID-19 hospitalization (OR = 4.51, 2.50-8.43; β = 0.48, 0.17-0.78), and poorer pre-COVID self-rated health (OR = 0.75, 0.57-0.97; β = -0.19, -0.32--0.07). Over one-fifth of Long COVID patients screened positive for depression and/or anxiety, the latter of which was associated with younger age (OR = 0.96, 0.94-0.99). Factor analysis of 16 self-reported symptoms suggested five symptom clusters-gastrointestinal (GI), musculoskeletal (MSK), neurocognitive (NC), airway (AW), and cardiopulmonary (CP), with older age (β = 0.21, 0.11-0.30) and mixed race (β = 0.27, 0.04-0.51) being associated with greater MSK symptom burden. Greater NC symptom burden was associated with increased odds of depression (OR = 5.86, 2.71-13.8) and anxiety (OR = 2.83, 1.36-6.14). These results can inform clinicians in identifying patients at increased risk for Long COVID-related medical issues, particularly neurocognitive symptoms and symptom clusters, as well as informing health systems to manage operational expectations on a population-health level.