Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations Concerning Long Haul COVID-19 January, February, March 2024

Prepared by Staff of the RACGWVI.

RACGWVI: Long Haul COVID-19 — PubMed Citations for Jan, Feb, March 2024

The following is a selected list of published research projects that focus on Long Haul COVID-19 for the months of January, February and March 2024.

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.

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.

Table of Contents

A Survey of Sleep Quality From a Post-COVID Clinic

J Prim Care Community Health. 2024 Jan-Dec:15:21501319241233205. doi: 10.1177/21501319241233205.

Mantavya Punj 1 2, Michael Schwartz 1 3, Anjali Morris 4, Joseph Cheung 5, Bala Munipalli 5

Affiliations

1Mayo Clinic College of Medicine and Science, Jacksonville, FL, USA.

2Kadlec Regional Medical Center, Richland, WA, USA.

3University at Buffalo, Buffalo, NY, USA.

4University of Florida, Gainesville, FL, USA.

5Mayo Clinic, Jacksonville, FL, USA.

Abstract

Objectives: To assess the prevalence of sleep disturbance among patients evaluated at a clinic for patients afflicted with Post-acute sequelae of COVID-19 (PASC).

Methods: Sleep disturbance was assessed with the Patient-Reported Outcomes Measurement Information System-Sleep Disturbance (PROMIS-SD) framework among adult patients of the PASC clinic.

Results: Among 312 patients, the mean age was 46.2 years, and 70.2% were women. About 41.0% of patients had no sleep disturbance; sleep disturbance was mild to moderate in 51.3% and severe in 7.7%. PROMIS-SD score was negatively correlated with the time from the initial positive COVID-19 test to the initial consultation in the PASC clinic (Pearson r = -.094; r2 = .0088).

Conclusions: The PROMIS-Sleep Disturbance framework can serve as a tool to assess the burden of sleep disturbances in PASC patients.

Remission of severe forms of long COVID following monoclonal antibody (MCA) infusions: A report of signal index cases and call for targeted research

Am J Emerg Med. 2024 Jan:75:122-127. doi: 10.1016/j.ajem.2023.09.051. Epub 2023 Oct 4.

Kenneth A Scheppke 1, Paul E Pepe 2, Jonathan Jui 3, Remle P Crowe 4, Eric K Scheppke 5, Nancy G Klimas 6, Aileen M Marty 7

Affiliations

1Florida Department of Health, 4052 Bald Cypress Way, Tallahassee, FL 32399, USA; Palm Beach County Fire Rescue, 405 Pike Road, West Palm Beach, FL 33411, USA; Broward Sheriff's Office, 2601 West Broward Boulevard, Ft Lauderdale, FL 33312, USA.

2Palm Beach County Fire Rescue, 405 Pike Road, West Palm Beach, FL 33411, USA; Broward Sheriff's Office, 2601 West Broward Boulevard, Ft Lauderdale, FL 33312, USA; Broward Health Medical Center, 1600 S Andrews Ave, Fort Lauderdale, FL 33316, USA; Department of Management, Policy and Community Health, School of Public Health, University of Texas Health Sciences Center, 1200 Pressler St, Houston, TX 77030, USA; Dallas County EMS/Public Safety Agencies, Suite 500, 500 Elm St, Dallas, TX 75202, USA. Electronic address: Dr.PaulPepe@GMail.com.

3Department of Emergency Medicine, Oregon Health & Sciences University, CDW-EM, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA.

4ESO, 11500 Alterra Pkwy #100, Austin, TX 78758, USA.

5Edward Via College of Osteopathic Medicine-Auburn, 910 S Donahue Dr, Auburn, AL 36832, USA.

6Institute for Neuro-Immune Medicine, Nova Southeastern University, 7595 SW 33rd Street, Fourth Floor, Ft Lauderdale, FL 33314, USA; Miami Veterans Administration Medical Center, 1201 NW 16th St, Miami, FL 33125, USA.

7Department of Translational Medicine, Florida International University, 885 SW 109th Ave, PG-5, Suite 1313, Miami, FL, 33199, USA.

Abstract

Objective: Long COVID has afflicted tens of millions globally leaving many previously-healthy persons severely and indefinitely debilitated. The objective here was to report cases of complete, rapid remission of severe forms of long COVID following certain monoclonal antibody (MCA) infusions and review the corresponding pathophysiological implications.

Design: Case histories of the first three index events (among others) are presented. Unaware of others with similar remissions, each subject independently completed personal narratives and standardized surveys regarding demographics/occupation, past history, and the presence and respective severity grading of 33 signs/symptoms associated with long COVID, comparing the presence/severity of those symptoms during the pre-COVID, long-COVID, post-vaccination, and post-MCA phases.

Setting: Patient interviews, e-mails and telephone conversations.

Subjects: Three previously healthy, middle-aged, highly-functioning persons, two women and one man (ages 60, 43, and 63 years respectively) who, post-acute COVID-19 infection, developed chronic, unrelenting fatigue and cognitive impairment along with other severe, disabling symptoms. Each then independently reported incidental and unanticipated complete remissions within days of MCA treatment.

Interventions: The casirivimab/imdevimab cocktail.

Measurements and main results: Irrespective of sex, age, medical history, vaccination status, or illness duration (18, 8 and 5 months, respectively), each subject experienced the same complete remission of their persistent disabling disease within a week of MCA infusion. Each rapidly returned to normal health and previous lifestyles/occupations with normalized exercise tolerance, still sustained to date over two years later.

Conclusions: These index cases provide compelling clinical signals that MCA infusions may be capable of treating long COVID in certain cases, including those with severe debilitation. While the complete and sustained remissions observed here may only apply to long COVID resulting from pre-Delta variants and the specific MCA infused, the striking rapid and complete remissions observed in these cases also provide mechanistic implications for treating/managing other post-viral chronic conditions and long COVID from other variants.

'I'm still here, I'm alive and breathing': The experience of Black Americans with long COVID

J Clin Nurs. 2024 Jan;33(1):162-177. doi: 10.1111/jocn.16733. Epub 2023 May 4.

Rachel S Bergmans 1, Keiyana Chambers-Peeple 1, Christine Yu 1, Lillian Z Xiao 1, Riley Wegryn-Jones 1, Allie Martin 1, Samantha Dell'Imperio 1, Deena Aboul-Hassan 1, David A Williams 1, Daniel J Clauw 1, Melissa DeJonckheere 1

Affiliation

1Department of Anesthesiology, University of Michigan, Ann Arbor, Michigan, USA.

Abstract

Aims and objectives: In this study, we aimed to characterize the impact of long COVID on quality of life and approaches to symptom management among Black American adults.

Background: As a novel condition, qualitative evidence concerning long COVID symptoms and their impact on quality of life can inform the refinement of diagnostic criteria and care plans. However, the underrepresentation of Black Americans in long COVID research is a barrier to achieving equitable care for all long COVID patients.

Design: We employed an interpretive description study design.

Methods: We recruited a convenience sample of 15 Black American adults with long COVID. We analysed the anonymized transcripts from race-concordant, semi-structured interviews using an inductive, thematic analysis approach. We followed the SRQR reporting guidelines.

Results: We identified four themes: (1) The impact of long COVID symptoms on personal identity and pre-existing conditions; (2) Self-management strategies for long COVID symptoms; (3) Social determinants of health and symptom management; and (4) Effects on interpersonal relationships.

Conclusion: Findings demonstrate the comprehensive ramifications of long COVID on the lives of Black American adults. Results also articulate how pre-existing conditions, social risk factors, distrust due to systemic racism, and the nature of interpersonal relationships can complicate symptom management.

Relevance to clinical practice: Care approaches that support access to and implementation of integrative therapies may be best suited to meet the needs of long COVID patients. Clinicians should also prioritize eliminating patient exposure to discrimination, implicit bias, and microaggressions. This is of particular concern for long COVID patients who have symptoms that are difficult to objectively quantify, such as pain and fatigue.

No patient or public contribution: While patient perspectives and experiences were the focus of this study, patients were not involved with the design or conduct of the study, data analysis or interpretation, or writing the manuscript.

Long Covid

Prog Mol Biol Transl Sci. 2024:202:113-125. doi: 10.1016/bs.pmbts.2023.11.002. Epub 2024 Jan 3.

Asiya Kamber Zaidi 1, Puya Dehgani-Mobaraki 2

Affiliations

1ENT Surgeon and Research Fellow, Associazione Naso Sano, Italy. Electronic address: asiyazaidia@gmail.com.

2Founder and President, Associazione Naso Sano, Ringgold Institution ID 567754, San Mariano, Italy.

Abstract

Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), refers to a constellation of persistent symptoms and health issues that continue beyond the acute phase of COVID-19. This chapter provides an overview of the pathogenesis, risk factors, manifestations, major findings, and diagnosis and treatment strategies associated with Long COVID. Hypotheses regarding the pathogenesis of Long COVID are discussed, encompassing various factors such as persistent viral reservoirs, immune dysregulation with or without reactivation of herpesviruses (e.g., Epstein-Barr Virus and human herpesvirus), dysbiosis, autoimmunity triggered by infection, endothelial dysfunction, microvessel blood clotting, and dysfunctional brainstem and/or vagal signaling. The chapter also highlights the risk factors associated with Long COVID and its occurrence in children. The major findings of Long COVID, including immune dysregulation, vessel and tissue damage, neurological and cognitive pathology, eye symptoms, endocrinal issues, myalgic encephalomyelitis and chronic fatigue syndrome, reproductive system involvement, respiratory and gastrointestinal symptoms, and the chronology of symptoms, are thoroughly explored. Lastly, the chapter discusses the challenges and current approaches in the diagnosis and treatment of Long COVID, emphasizing the need for multidisciplinary care and individualized management strategies.

Intrinsic factors behind long COVID: III. Persistence of SARS-CoV-2 and its components

J Cell Biochem. 2024 Jan;125(1):22-44. doi: 10.1002/jcb.30514. Epub 2023 Dec 14.

Nawal Abd El-Baky 1, Amro A Amara 1, Vladimir N Uversky 2, Elrashdy M Redwan 3

Affiliations

1Protein Research Department, Genetic Engineering and Biotechnology Research Institute (GEBRI), City of Scientific Research and Technological Applications (SRTA-City), New Borg El-Arab City, Egypt.

2Department of Molecular Medicine, USF Health Byrd Alzheimer's Research Institute, Morsani College of Medicine, University of South Florida, Tampa, Florida, USA.

3Biological Sciences Department, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia.

Abstract

Considerable research has been done in investigating SARS-CoV-2 infection, its characteristics, and host immune response. However, debate is still ongoing over the emergence of post-acute sequelae of SARS-CoV-2 infection (PASC). A multitude of long-lasting symptoms have been reported several weeks after the primary acute SARS-CoV-2 infection that resemble several other viral infections. Thousands of research articles have described various post-COVID-19 conditions. Yet, the evidence around these ongoing health problems, the reasons behind them, and their molecular underpinnings are scarce. These persistent symptoms are also known as long COVID-19. The persistence of SARS-CoV-2 and/or its components in host tissues can lead to long COVID. For example, the presence of viral nucleocapsid protein and RNA was detected in the skin, appendix, and breast tissues of some long COVID patients. The persistence of viral RNA was reported in multiple anatomic sites, including non-respiratory tissues such as the adrenal gland, ocular tissue, small intestine, lymph nodes, myocardium, and sciatic nerve. Distinctive viral spike sequence variants were also found in non-respiratory tissues. Interestingly, prolonged detection of viral subgenomic RNA was observed across all tissues, sometimes in multiple tissues of the same patient, which likely reflects recent but defective viral replication. Moreover, the persistence of SARS-CoV-2 RNA was noticed throughout the brain at autopsy, as late as 230 days following symptom onset among unvaccinated patients who died of severe infection. Here, we review the persistence of SARS-CoV-2 and its components as an intrinsic factor behind long COVID. We also highlight the immunological consequences of this viral persistence.

The prevalence of obstructive sleep apnea syndrome after COVID-19 infection

J Med Virol. 2024 Jan;96(1):e29392. doi: 10.1002/jmv.29392.

Wen-Chun Lin 1 2, Meng-Che Wu 3 4 5, Yu-Hsun Wang 1 6, Che-Hsuan Lin 7 8, James Cheng-Chung Wei 1 9 10 11

Affiliations

1Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan.

2Division of Otolaryngology Head and Neck surgery, Taichung Veterans General Hospital, Taichung, Taiwan.

3Division of Pediatric Gastroenterology, Children's Medical Center, Taichung Veterans General Hospital, Taichung, Taiwan.

4Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan.

5School of Medicine, Chung Shan Medical University, Taichung, Taiwan.

6Department of Medical Research, Chung Shan Medical University Hospital, Taichung, Taiwan.

7Department of Otolaryngology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.

8Department of Otolaryngology, TMU Hospital, Taipei, Taiwan.

9Department of Allergy, Immunology and Rheumatology, Chung Shan Medical University Hospital, Taichung, Taiwan.

10Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan.

11Department of Nursing, Chung Shan Medical University, Taichung, Taiwan.

Abstract

Obstructive sleep apnea is a well-known risk factor regarding the severity of COVID-19 infection. However, to date, relatively little research performed on the prevalence of obstructive sleep apnea in COVID-19 survivors. The purpose of this study was to investigate the risk of obstructive sleep apnea after COVID-19 infection. This study was based on data collected from the US Collaborative Network in TriNetX. From January 1, 2020 to June 30, 2022, participants who underwent the SARS-CoV-2 test were included in the study. Based on their positive or negative results of the COVID-19 test results (the polymerase chain reaction [PCR] test), we divided the study population into two groups. The duration of follow-up began when the PCR test was administered and continued for 12 months. Hazard ratios (HRs) and 95% confidence intervals (CIs) for newly recorded COVID-19 positive subjects for obstructive sleep apnea were calculated using the Cox proportional hazards model and compared to those without COVID-19 infection. Subgroup analyses were performed for the age, sex, and race, groups. The COVID-19 group was associated with an increased risk of obstructive sleep apnea, at both 3 months of follow-up (HR: 1.51, 95% CI: 1.48-1.54), and 1 year of follow-up (HR: 1.57, 95% CI: 1.55-1.60). Kaplan-Meier curves regarding the risk of obstructive sleep apnea revealed a significant difference of probability between the two cohorts in the follow-up periods of 3 months and 1 year (Log-Rank test, $p < 0.001$). The risks of obstructive sleep apnea among COVID-19 patients were significant in the less than 65 year of age group (HR: 1.50, 95% CI: 1.47-1.52), as well as in the group older than or equal to 65 years (HR:1.69, 95% CI: 1.64-1.73). Furthermore, the risks of obstructive sleep apnea were evident in both the male and female COVID-19 groups. Compared to the control group, the risks of obstructive sleep apnea in the COVID-19 participants increased in the subgroups of White (HR: 1.62, 95% CI: 1.59-1.64), Blacks/African Americans (HR: 1.50, 95% CI: 1.45-1.55), Asian (HR: 1.46, 95% CI: 1.32-1.62) and American Indian/Alaska Native (HR: 1.36, 95% CI: 1.07-1.74). In conclusion, the incidence of new diagnosis obstructive sleep apnea could be substantially higher after COVID-19 infection than non-COVID-19 comparison group. Physicians should evaluate obstructive sleep apnea in patients after COVID-19 infection to help prevent future long-term adverse effects from occurring in the future, including cardiovascular and neurovascular disease.

Mitochondrial Dysfunction and Coenzyme Q10 Supplementation in Post-Viral Fatigue Syndrome: An Overview

Int J Mol Sci. 2024 Jan 1;25(1):574. doi: 10.3390/ijms25010574.

David Mantle 1, Iain Parry Hargreaves 2, Joan Carles Domingo 3, Jesus Castro-Marrero 4

Affiliations

1Pharma Nord (UK) Ltd., Morpeth, Northumberland NE61 2DB, UK.

2School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool L3 3AF, UK.

3Department of Biochemistry and Molecular Biomedicine, Faculty of Biology, University of Barcelona, 08028 Barcelona, Spain.

4Research Unit in ME/CFS and Long COVID, Rheumatology Division, Vall d'Hebron Research Institute, Universitat Autònoma de Barcelona, 08035 Barcelona, Spain.

Abstract

Post-viral fatigue syndrome (PVFS) encompasses a wide range of complex neuroimmune disorders of unknown causes characterised by disabling post-exertional fatigue, myalgia and joint pain, cognitive impairments, unrefreshing sleep, autonomic dysfunction, and neuropsychiatric symptoms. It includes myalgic encephalomyelitis, also known as chronic fatigue syndrome (ME/CFS); fibromyalgia (FM); and more recently post-COVID-19 condition (long COVID). To date, there are no definitive clinical case criteria and no FDA-approved pharmacological therapies for PVFS. Given the current lack of effective treatments, there is a need to develop novel therapeutic strategies for these disorders. Mitochondria, the cellular organelles responsible for tissue energy production, have recently garnered attention in research into PVFS due to their crucial role in cellular bioenergetic metabolism in these conditions. The accumulating literature has identified a link between mitochondrial dysfunction and low-grade systemic inflammation in ME/CFS, FM, and long COVID. To address this issue, this article aims to critically review the evidence relating to mitochondrial dysfunction in the pathogenesis of these disorders; in particular, it aims to evaluate the effectiveness of coenzyme Q10 supplementation on chronic fatigue and pain symptoms as a novel therapeutic strategy for the treatment of PVFS.

Increased von Willebrand and Factor VIII plasma levels in gynecologic patients with Post-Acute-COVID-Sequela (PASC)/Long COVID

Gynecol Oncol Rep. 2024 Jan 4:51:101324. doi: 10.1016/j.gore.2024.101324. eCollection 2024 Feb.

Stefania Bellone 1, Eric R Siegel 2, David E Scheim 3, Alessandro D Santin 1

Affiliations

1Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, CT 06520, USA.

2Department of Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA.

3US Public Health Service, Commissioned Corps, Inactive Reserve, Blacksburg, VA 24060-6367, USA.

Abstract

Up to 30 % of COVID-infected patients may develop post-acute sequelae of COVID-19 (PASC), also known as Long COVID (LC), a syndrome characterized by a variety of debilitating symptoms lasting for more than 3 months after the acute infection. While the pathophysiological mechanisms behind PASC/LC are not completely understood, growing evidence suggests that an important component of this syndrome may be related to persistent microvascular inflammation causing clumping/clotting of red blood cells and platelets and thrombotic complications. We retrospectively evaluated the plasma levels of von Willebrand factor (VWF), Factor VIII and D-dimer in 10 gynecologic patients (60 % with an endometrial or ovarian cancer diagnosis) affected by PASC/LC vs 5 control patients (60 % harboring endometrial or ovarian tumors). We found elevated VWF and Factor VIII levels in all 10 PASC/LC patients (means of 254 % and 229 %, respectively) vs none of the 5 randomly selected cancer control patients (means of 108 % and 95 %, respectively), $p = 0.0046$ and $p < 0.0001$, respectively. In contrast, no significant difference was noted in the levels of D-dimer in PASC/LC. Importantly, abnormally elevated VWF and Factor VIII levels were found to persist for at least 2 years in patients with Long COVID symptoms. VWF and Factor VIII but not D-dimer levels are significantly elevated in the plasma of PASC/LC cancer patients. Abnormally and persistently elevated VWF and Factor VIII levels may represent the results of persistent microvascular damage (i.e., spike-induced endotheliosis) and may be biomarkers of persistent inflammation in gynecologic patients with PASC/LC.

A survey on the role of artificial intelligence in managing Long COVID

Front Artif Intell. 2024 Jan 11:6:1292466. doi: 10.3389/frai.2023.1292466. eCollection 2023.

Ijaz Ahmad 1, Alessia Amelio 2, Arcangelo Merla 2, Francesca Scozzari 3

Affiliations

1Department of Human, Legal and Economic Sciences, Telematic University "Leonardo da Vinci", Chieti, Italy.

2Department of Engineering and Geology, University "G. d'Annunzio" Chieti-Pescara, Pescara, Italy.

3Laboratory of Computational Logic and Artificial Intelligence, Department of Economic Studies, University "G. d'Annunzio" Chieti-Pescara, Pescara, Italy.

Abstract

In the last years, several techniques of artificial intelligence have been applied to data from COVID-19. In addition to the symptoms related to COVID-19, many individuals with SARS-CoV-2 infection have described various long-lasting symptoms, now termed Long COVID. In this context, artificial intelligence techniques have been utilized to analyze data from Long COVID patients in order to assist doctors and alleviate the considerable strain on care and rehabilitation facilities. In this paper, we explore the impact of the machine learning methodologies that have been applied to analyze the many aspects of Long COVID syndrome, from clinical presentation through diagnosis. We also include the text mining techniques used to extract insights and trends from large amounts of text data related to Long COVID. Finally, we critically compare the various approaches and outline the work that has to be done to create a robust artificial intelligence approach for efficient diagnosis and treatment of Long COVID.

Nirmatrelvir/Ritonavir Utilization for the Treatment of Non-hospitalized Adults with COVID-19 in the National Veterans Affairs (VA) Healthcare System

Infect Dis Ther. 2024 Jan;13(1):155-172. doi: 10.1007/s40121-023-00910-1. Epub 2024 Jan 13.

Haley J Appaneal 1 2 3, Kerry L LaPlante 1 2 3, Vrishali V Lopes 1, Catherine Martin 4, Laura Puzniak 4, Timothy L Wiemken 4, Evan J Zasowski 4, John M McLaughlin 4, Aisling R Caffrey 5 6 7 8

Affiliations

1Infectious Diseases Research Program, Providence Veterans Affairs Medical Center, Providence, RI, USA.

2Center of Innovation in Long-Term Support Services, Providence Veterans Affairs Medical Center, Providence, RI, USA.

3College of Pharmacy, University of Rhode Island, 7 Greenhouse Rd, 265B, Kingston, RI, 02881, USA.

4Pfizer Inc., New York, NY, USA.

5Infectious Diseases Research Program, Providence Veterans Affairs Medical Center, Providence, RI, USA. Aisling_Caffrey@uri.edu.

6Center of Innovation in Long-Term Support Services, Providence Veterans Affairs Medical Center, Providence, RI, USA. Aisling_Caffrey@uri.edu.

7College of Pharmacy, University of Rhode Island, 7 Greenhouse Rd, 265B, Kingston, RI, 02881, USA. Aisling_Caffrey@uri.edu.

8School of Public Health, Brown University, Providence, RI, USA. Aisling_Caffrey@uri.edu.

Abstract

Introduction: Limited data exist regarding real-world utilization of nirmatrelvir/ritonavir. We identified predictors of nirmatrelvir/ritonavir use among Veterans Affairs (VA) outpatients nationally.

Methods: We conducted a retrospective cohort study among outpatients with coronavirus disease 2019 (COVID-19) who were eligible to receive nirmatrelvir/ritonavir between January and December of 2022, to identify factors associated with nirmatrelvir/ritonavir use (i.e., demographics, medical history, prior medication and healthcare exposures, frailty, and other clinical characteristics) using multivariable logistic regression.

Results: We included 309,755 outpatients with COVID-19 who were eligible for nirmatrelvir/ritonavir, of whom 12.2% received nirmatrelvir/ritonavir. Nirmatrelvir/ritonavir uptake increased from 1.1% to 23.2% over the study period. Factors associated with nirmatrelvir/ritonavir receipt included receiving a COVID-19 booster vs. none (adjusted odds ratio [aOR] 2.19 [95% confidence interval [CI] 2.12-2.26]), age ≥ 50 vs. 18-49 years (aORs > 1.5 for all age groups ≥ 50 years), having HIV (aOR 1.36 [1.22-1.51]), being non-frail vs. severely frail (aOR 1.22 [1.13-1.33]), and having rheumatoid arthritis (aOR 1.12 [1.04-1.21). Those with concomitant use of potentially interacting antiarrhythmics (aOR 0.35 [0.28-0.45]), anticoagulants/antiplatelets (aOR 0.42 [0.40-0.45]), and/or psychiatric/sedatives (aOR 0.84 [0.81-0.87]) were less likely to receive nirmatrelvir/ritonavir.

Conclusions: Despite increases over time, overall utilization of nirmatrelvir/ritonavir was low. Predictors of nirmatrelvir/ritonavir utilization were consistent with known risk factors for progression to severe COVID-19, including older age and underlying medical conditions. Unvaccinated and undervaccinated patients and those receiving potentially interacting medications for cardiovascular or mental health conditions (antiarrhythmic, alpha-1 antagonist, anticoagulant/antiplatelet, sedative/hypnotic/psychiatric) were less likely to receive nirmatrelvir/ritonavir. Further education of prescribers and patients about nirmatrelvir/ritonavir treatment guidelines is needed to improve overall uptake and utilization in certain high-risk subpopulations.

Risks of digestive diseases in long COVID: evidence from a population-based cohort study

BMC Med. 2024 Jan 10;22(1):14. doi: 10.1186/s12916-023-03236-4.

Yuying Ma # 1 2, Lijun Zhang # 1 3, Rui Wei 1, Weiyu Dai 1, Ruijie Zeng 1 4, Dongling Luo 5, Rui Jiang 1 3, Zewei Zhuo 1, Qi Yang 1, Jingwei Li 1 2, Felix W Leung 6 7, Chongyang Duan 8, Weihong Sha 9 10 11 12, Hao Chen 13 14 15 16

Affiliations

1Department of Gastroenterology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, 510080, China.

2The Second School of Clinical Medicine, Southern Medical University, Guangzhou, 510515, China.

3School of Medicine, South China University of Technology, Guangzhou, 510006, China.

4Shantou University Medical College, Shantou, 515000, Guangdong, China.

5Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Guangdong Cardiovascular Institute, Southern Medical University, Guangzhou, 510080, China.

6David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, 90024, USA. FelixLeung@socal.rr.com.

7Sepulveda Ambulatory Care Center, Veterans Affairs Greater Los Angeles Healthcare System, North Hills, CA, 91343, USA. FelixLeung@socal.rr.com.

8Department of Biostatistics, School of Public Health, Southern Medical University, Guangzhou, 510515, China. donyduang@126.com.

9Department of Gastroenterology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, 510080, China. shaweihong@gdph.org.cn.

10The Second School of Clinical Medicine, Southern Medical University, Guangzhou, 510515, China. shaweihong@gdph.org.cn.

11School of Medicine, South China University of Technology, Guangzhou, 510006, China. shaweihong@gdph.org.cn.

12Shantou University Medical College, Shantou, 515000, Guangdong, China. shaweihong@gdph.org.cn.

13Department of Gastroenterology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, 510080, China. chenhao@gdph.org.cn.

14The Second School of Clinical Medicine, Southern Medical University, Guangzhou, 510515, China. chenhao@gdph.org.cn.

15School of Medicine, South China University of Technology, Guangzhou, 510006, China. chenhao@gdph.org.cn.

16Shantou University Medical College, Shantou, 515000, Guangdong, China. chenhao@gdph.org.cn.

Abstract

Background: In the post-pandemic era, a wide range of COVID-19 sequelae is of growing health concern. However, the risks of digestive diseases in long COVID have not been comprehensively understood. To investigate the long-term risk of digestive diseases among COVID patients.

Methods: In this large-scale retrospective cohort study with up to 2.6 years follow-up (median follow-up: 0.7 years), the COVID-19 group (n = 112,311), the contemporary comparison group (n = 359,671) and the historical comparison group (n = 370,979) predated the COVID-19 outbreak were built using UK Biobank database. Each digestive outcome was defined as the diagnosis 30 days or more after the onset of COVID-19 infection or the index date. Hazard ratios (HRs) and corresponding 95% confidence intervals (CI) were computed utilizing the Cox regression models after inverse probability weighting.

Results: Compared with the contemporary comparison group, patients with previous COVID-19 infection had higher risks of digestive diseases, including gastrointestinal (GI) dysfunction (HR 1.38

(95% CI 1.26 to 1.51)); peptic ulcer disease (HR 1.23 (1.00 to 1.52)); gastroesophageal reflux disease (GERD) (HR 1.41 (1.30 to 1.53)); gallbladder disease (HR 1.21 (1.06 to 1.38)); severe liver disease (HR 1.35 (1.03 to 1.76)); non-alcoholic liver disease (HR 1.27 (1.09 to 1.47)); and pancreatic disease (HR 1.36 (1.11 to 1.66)). The risks of GERD were increased stepwise with the severity of the acute phase of COVID-19 infection. Even after 1-year follow-up, GERD (HR 1.64 (1.30 to 2.07)) and GI dysfunction (HR 1.35 (1.04 to 1.75)) continued to pose risks to COVID-19 patients. Compared to those with one SARS-CoV-2 infection, reinfected patients were at a higher risk of pancreatic diseases (HR 2.57 (1.23 to 5.38)). The results were consistent when the historical cohort was used as the comparison group.

Conclusions: Our study provides insights into the association between COVID-19 and the long-term risk of digestive system disorders. COVID-19 patients are at a higher risk of developing digestive diseases. The risks exhibited a stepwise escalation with the severity of COVID-19, were noted in cases of reinfection, and persisted even after 1-year follow-up. This highlights the need to understand the varying risks of digestive outcomes in COVID-19 patients over time, particularly those who experienced reinfection, and develop appropriate follow-up strategies.

Persistent complement dysregulation with signs of thromboinflammation in active Long Covid

Science. 2024 Jan 19;383(6680):eadg7942. doi: 10.1126/science.adg7942. Epub 2024 Jan 19.

Carlo Cervia-Hasler 1, Sarah C Brüningk 2 3, Tobias Hoch 1, Bowen Fan 2 3, Giulia Muzio 2 3, Ryan C Thompson 4 5 6, Laura Ceglarek 1, Roman Meledin 1, Patrick Westermann 7, Marc Emmenegger 8, Patrick Taeschler 1, Yves Zurbuchen 1, Michele Pons 1, Dominik Menges 9, Tala Ballouz 9, Sara Cervia-Hasler 1, Sarah Adamo 1, Miriam Merad 4, Alexander W Charney 4 5 6, Milo Puhan 9, Petter Brodin 10 11, Jakob Nilsson 1, Adriano Aguzzi 8, Miro E Raeber 1, Christoph B Messner 7, Noam D Beckmann 4 5 6 12, Karsten Borgwardt 2 3, Onur Boyman 1 13

Affiliations

1Department of Immunology, University Hospital Zurich, University of Zurich, 8091 Zurich, Switzerland.

2Department of Biosystems Science and Engineering, ETH Zurich, 4058 Basel, Switzerland.

3Swiss Institute of Bioinformatics, 1015 Lausanne, Switzerland.

4Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.

5Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.

6Mount Sinai Clinical Intelligence Center, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.

7Precision Proteomics Center, Swiss Institute of Allergy and Asthma Research, University of Zurich, 7265 Davos, Switzerland.

8Institute of Neuropathology, University Hospital Zurich, University of Zurich, 8091 Zurich, Switzerland.

9Epidemiology, Biostatistics and Prevention Institute, University of Zurich, 8001 Zurich, Switzerland.

10Unit for Clinical Pediatrics, Department of Women's and Children's Health, Karolinska Institute, 17165 Solna, Sweden.

11Department of Immunology and Inflammation, Imperial College London, London W12 0NN, UK.

12Division of Data Driven and Digital Medicine (D3M), Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.

13Faculty of Medicine and Faculty of Science, University of Zurich, 8006 Zurich, Switzerland.

Abstract

Long Covid is a debilitating condition of unknown etiology. We performed multimodal proteomics analyses of blood serum from COVID-19 patients followed up to 12 months after confirmed severe acute respiratory syndrome coronavirus 2 infection. Analysis of >6500 proteins in 268 longitudinal samples revealed dysregulated activation of the complement system, an innate immune protection and homeostasis mechanism, in individuals experiencing Long Covid. Thus, active Long Covid was characterized by terminal complement system dysregulation and ongoing activation of the alternative and classical complement pathways, the latter associated with increased antibody titers against several herpesviruses possibly stimulating this pathway. Moreover, markers of hemolysis, tissue injury, platelet activation, and monocyte-platelet aggregates were increased in Long Covid. Machine learning confirmed complement and thromboinflammatory proteins as top biomarkers, warranting diagnostic and therapeutic interrogation of these systems.

Reduction in Long COVID Symptoms and Symptom Severity in Vaccinated Compared to Unvaccinated Adults

Open Forum Infect Dis. 2024 Jan 23;11(2):ofae039. doi: 10.1093/ofid/ofae039. eCollection 2024 Feb.

Hannah E Maier 1, Theresa Kowalski-Dobson 1, Ashley Eckard 1, Carmen Gherasim 2, David Manthei 2, Alyssa Meyers 1, Dawson Davis 2, Kevin Bakker 1, Kathleen Lindsey 1, Zijin Chu 1, Lauren Warsinske 1, Matthew Arnold 1, Anna Buswinka 1, Emily Stoneman 3, Riccardo Valdez 2, Aubree Gordon 1

Affiliations

1Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA.

2Department of Pathology, Michigan Medicine, University of Michigan, Ann Arbor, Michigan, USA.

3Department of Internal Medicine, Michigan Medicine, University of Michigan, Ann Arbor, Michigan, USA.

Abstract

Background: The impact of vaccination prior to infection on postacute sequelae of coronavirus disease 2019 (COVID-19, PASC), also known as long COVID, remains unclear. Here we assess the protective effect of vaccination on long COVID in a community-based setting.

Methods: The Immunity Associated with SARS-CoV-2 (IASO) study is an ongoing prospective cohort of working adults that began in October 2020. Participants are actively followed for severe acute respiratory syndrome coronavirus 2 infection. We compared the prevalence of symptoms and symptom severity in vaccinated compared to unvaccinated cases. Our primary definition of long COVID was the presence of symptoms at 90 days postinfection; 30 days postinfection was also examined.

Results: Overall, by 90 days postinfection, 13% of cases had long COVID, with 27% of unvaccinated cases and 8% of vaccinated cases reporting long COVID (relative risk [RR], 0.31 [95% confidence interval {CI}, .22-.42]). Vaccination was also associated with significantly lower average severity scores at all timepoints (eg, relative severity at 90 days postinfection: -2.70 [95% CI, -1.68 to -3.73]). In the pre-Omicron era, 28% of unvaccinated cases and 18% of vaccinated cases reported long COVID (P = .07), and vaccinated cases reported less severe symptoms including less difficulty breathing (P = .01; 90-day RR, 0.07).

Conclusions: Vaccinated cases had lower prevalence of long COVID and reduced symptom severity.

Predictors of Acute Kidney Injury (AKI) among COVID-19 Patients at the US Department of Veterans Affairs: The Important Role of COVID-19 Vaccinations

Vaccines (Basel). 2024 Jan 30;12(2):146. doi: 10.3390/vaccines12020146.

Lilia R Lukowsky 1, Claudia Der-Martirosian 1, Heather Northcraft 1, Kamyar Kalantar-Zadeh 2 3, David S Goldfarb 4 5, Aram Dobalian 1 6

Affiliations

1Veterans Emergency Management Evaluation Center (VEMEC), US Department of Veterans Affairs, North Hills, CA 91343, USA.

2The Lundquist Institute for Biomedical Innovation, Harbor UCLA Medical Center, Torrance, CA 90502, USA.

3Tibor Rubin VA Medical Center, Long Beach VA Healthcare System, Long Beach, CA 90822, USA.

4New York Harbor VA Healthcare System (NYHHS), US Department of Veterans Affairs, New York, NY 10010, USA.

5NYU Langone Health, NYU Grossman School of Medicine, New York, NY 10016, USA.

6Division of Health Services Management and Policy in the College of Public Health, The Ohio State University, Columbus, OH 43210, USA.

Abstract

Background: There are knowledge gaps about factors associated with acute kidney injury (AKI) among COVID-19 patients. To examine AKI predictors among COVID-19 patients, a retrospective longitudinal cohort study was conducted between January 2020 and December 2022. Logistic regression models were used to examine predictors of AKI, and survival analysis was performed to examine mortality in COVID-19 patients.

Results: A total of 742,799 veterans diagnosed with COVID-19 were included and 95,573 were hospitalized within 60 days following COVID-19 diagnosis. A total of 45,754 developed AKI and 28,573 AKI patients were hospitalized. Use of vasopressors (OR = 14.73; 95% CL 13.96-15.53), history of AKI (OR = 2.22; CL 2.15-2.29), male gender (OR = 1.90; CL 1.75-2.05), Black race (OR = 1.62; CL 1.57-1.65), and age 65+ (OR = 1.57; CL 1.50-1.63) were associated with AKI. Patients who were vaccinated twice and boosted were least likely to develop AKI (OR = 0.51; CL 0.49-0.53) compared to unvaccinated COVID-19 patients. Patients receiving two doses (OR = 0.77; CL = 0.72-0.81), or a single dose (OR = 0.88; CL = 0.81-0.95) were also less likely to develop AKI compared to the unvaccinated. AKI patients exhibited four times higher mortality compared to those without AKI (HR = 4.35; CL 4.23-4.50). Vaccinated and boosted patients had the lowest mortality risk compared to the unvaccinated (HR = 0.30; CL 0.28-0.31).

Conclusion: Use of vasopressors, being unvaccinated, older age, male gender, and Black race were associated with post COVID-19 AKI. Whether COVID-19 vaccination, including boosters, decreases the risk of developing AKI warrants additional studies.

Traumatic Brain Injury in the Long-COVID Era

Neurotrauma Rep. 2024 Jan 30;5(1):81-94. doi: 10.1089/neur.2023.0067. eCollection 2024.

Denes V Agoston 1

Affiliation

1Department of Anatomy, Physiology, and Genetics, School of Medicine, Uniformed Services University, Bethesda, Maryland, USA.

Abstract

Major determinants of the biological background or reserve, such as age, biological sex, comorbidities (diabetes, hypertension, obesity, etc.), and medications (e.g., anticoagulants), are known to affect outcome after traumatic brain injury (TBI). With the unparalleled data richness of coronavirus disease 2019 (COVID-19; ~375,000 and counting!) as well as the chronic form, long-COVID, also called post-acute sequelae SARS-CoV-2 infection (PASC), publications (~30,000 and counting) covering virtually every aspect of the diseases, pathomechanisms, biomarkers, disease phases, symptomatology, etc., have provided a unique opportunity to better understand and appreciate the holistic nature of diseases, interconnectivity between organ systems, and importance of biological background in modifying disease trajectories and affecting outcomes. Such a holistic approach is badly needed to better understand TBI-induced conditions in their totality. Here, I briefly review what is known about long-COVID/PASC, its underlying-suspected-pathologies, the pathobiological changes induced by TBI, in other words, the TBI endophenotypes, discuss the intersection of long-COVID/PASC and TBI-induced pathobiologies, and how by considering some of the known factors affecting the person's biological background and the inclusion of mechanistic molecular biomarkers can help to improve the clinical management of TBI patients.

The lingering symptoms of post-COVID-19 condition (long-COVID): a prospective cohort study

Intern Med J. 2024 Feb;54(2):224-233. doi: 10.1111/imj.16251. Epub 2023 Nov 26.

Stuart Tan 1 2 3, Anna J G Pryor 4, Geoffrey W Melville 4 5, Olivia Fischer 4, Lyndel Hewitt 4 5, Kimberley J Davis 3 4

Affiliations

1Physician in Trauma and Rehabilitation Medicine, Illawarra Shoalhaven Local Health District, New South Wales, Australia.

2Senior Staff Specialist, Wollongong Hospital, Wollongong, New South Wales, Australia.

3Graduate School of Medicine, University of Wollongong, Wollongong, New South Wales, Australia.

4Research Central, Illawarra Shoalhaven Local Health District, Wollongong, New South Wales, Australia.

5Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, New South Wales, Australia.

Abstract

Background: Longer-term symptoms (long COVID) may be present in seemingly recovered patients for several months and can be debilitating.

Aim: To investigate the prevalence and type of symptoms in those with a prior COVID-19 diagnosis.

Methods: This prospective, longitudinal observational study commenced in July 2020 investigating the longer-term health impacts of COVID-19. Participants were recruited via public health units and media publicity. Surveys were completed upon enrolment, and at 1, 3, 6 and 12 months. Outcome measures included incidence of activity limitations and symptoms against health and vaccination status, age and gender.

Results: Overall, 339 participants were recruited. At 3 months after COVID-19, 66.8% reported symptoms, and 44.8% were still experiencing symptoms at 12 months. Fatigue was most common at every point (between 53.1% and 33.1%). Pain symptoms increased in relative prevalence over time, whereas respiratory/pulmonary-type symptoms decreased substantially after 3 months. Females and younger people were more likely to experience symptoms in the early stages of long COVID ($P < 0.01$) and those with more comorbidities in the latter stages ($P < 0.001$). Vaccination showed a statistically significant protective effect against symptoms ($P < 0.01$-0.001).

Conclusion: Long-term COVID-19 symptoms exist among recovered patients up to 12 months after contracting the virus. Fatigue is a primary contributor, while chronic pain became more problematic after 6 months. Vaccination was a factor in preventing long-term symptoms and aiding faster recovery from symptoms. Further work exploring additional contributors to symptom prevalence would assist in developing appropriate follow-up care.

Post-COVID dysautonomias: what we know and (mainly) what we don't know

Nat Rev Neurol. 2024 Feb;20(2):99-113. doi: 10.1038/s41582-023-00917-9. Epub 2024 Jan 11.

David S Goldstein 1

Affiliation

1Division of Intramural Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA. goldsteind@ninds.nih.gov.

Abstract

Following on from the COVID-19 pandemic is another worldwide public health challenge that is referred to variously as long COVID, post-COVID syndrome or post-acute sequelae of SARS-CoV-2 infection (PASC). PASC comes in many forms and affects all body organs. This heterogeneous presentation suggests involvement of the autonomic nervous system (ANS), which has numerous roles in the maintenance of homeostasis and coordination of responses to various stressors. Thus far, studies of ANS dysregulation in people with PASC have been largely observational and descriptive, based on symptom inventories or objective but indirect measures of cardiovascular function, and have paid little attention to the adrenomedullary, hormonal and enteric nervous components of the ANS. Such investigations do not consider the syndromic nature of autonomic dysfunction. This Review provides an update on the literature relating to ANS abnormalities in people with post-COVID syndrome and presents a theoretical perspective on how the ANS might participate in common features of PASC.

Association of vaccine status, reinfections, and risk factors with Long COVID syndrome

Sci Rep. 2024 Feb 2;14(1):2817. doi: 10.1038/s41598-024-52925-4.

Maria Elena Romero-Ibarguengoitia 1 2, Juan Francisco Rodríguez-Torres 3 4, Arnulfo Garza-Silva 5 3, Andrea Rivera-Cavazos 5, Devany Paola Morales-Rodriguez 5 3, Mauricio Hurtado-Cabrera 3, Ricardo Kalife-Assad 3, Diana Villarreal-Parra 3, Alejandro Loose-Esparza 3, Juan José Gutiérrez-Arias 3, Yaressi Guadalupe Mata-Porras 3, Daniela Abigail Ojeda-Salazar 3, Miguel Angel Sanz-Sánchez 5 3, Arnulfo González-Cantú 5 3, Elena Azzolini 6 7, Maria Rescigno 6 7

Affiliations

1Research Department, Hospital Clínica Nova de Monterrey, San Nicolás de los Garza, Nuevo León, México. MROMEROI@novaservicios.com.mx.

2Escuela de Medicina, Vicerrectoría de Ciencias de la Salud, Universidad de Monterrey, San Pedro Garza García, Nuevo León, México. MROMEROI@novaservicios.com.mx.

3Escuela de Medicina, Vicerrectoría de Ciencias de la Salud, Universidad de Monterrey, San Pedro Garza García, Nuevo León, México.

4Internal Medicine Department, Hospital Clínica Nova de Monterrey, San Nicolás de los Garza, Nuevo León, México.

5Research Department, Hospital Clínica Nova de Monterrey, San Nicolás de los Garza, Nuevo León, México.

6IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089, Rozzano, Milan, Italy.

7Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20072, Pieve Emanuele, Milan, Italy.

Abstract

The COVID-19 pandemic had a profound global impact, characterized by a high fatality rate and the emergence of enduring consequences known as Long COVID. Our study sought to determine the prevalence of Long COVID syndrome within a population of Northeastern Mexico, correlating it with patients' comorbidities, number of COVID-19 reinfection, and vaccination status. Employing an observational cross-sectional approach, we administered a comprehensive questionnaire covering medical history, demographics, vaccination status, COVID-related symptoms, and treatment. Our participant cohort included 807 patients, with an average age of 41.5 (SD 13.6) years, and women accounting 59.3% of the cohort. The follow-up was 488 (IQR 456) days. One hundred sixty-eight subjects (20.9%) met Long COVID criteria. Long COVID-19 was more prevalent when subjects had reinfections ($p = 0.02$) and less frequent when they had a complete vaccination scheme ($p = 0.05$). Through logistic regression, we found that male gender (OR 0.5, $p \leq 0.001$), blood types of AB- (OR 0.48, $p = 0.003$) and O- (OR 0.27, $p \leq 0.001$) in comparison with A+ and two doses of vaccines (OR 0.5, p = 006) to be protective factors against Long COVID; while higher BMI (OR 1.04, $p = 0.005$) was a risk factor. We saw that the prevalence of Long COVID was different within vaccinated patients and specific blood types, while being female and a higher BMI were associated with an increased risk of having long-COVID.

Association of Long COVID with mental health disorders: a retrospective cohort study using real-world data from the USA

BMJ Open. 2024 Feb 3;14(2):e079267. doi: 10.1136/bmjopen-2023-079267.

Yue Zhang 1, Vernon M Chinchilli 2, Paddy Ssentongo 2 3, Djibril M Ba 2

Affiliations

1Department of Public Health Sciences, The Pennsylvania State University College of Medicine, Hershey, Pennsylvania, USA ymz5503@psu.edu.

2Department of Public Health Sciences, The Pennsylvania State University College of Medicine, Hershey, Pennsylvania, USA.

3Department of Medicine, Penn State Health Medical Center, Hershey, PA, USA.

Abstract

Objectives: Mental health disorders (MHD) rank third for US adult hospitalisations. Given the substantial prevalence of 'Long COVID' in SARS-CoV-2 survivors, this study aims to assess its association with increased MHD risk using extensive real-world data.

Design: A retrospective cohort study with propensity score matching was conducted. We used the International Classification of Diseases, 10th Revision codes to identify individuals with Long COVID status and COVID-19 histories. Multivariable stratified Cox proportional hazards regression analysis was conducted to determine the association of Long COVID status with MHD.

Setting: Data were sourced from the TriNetX database, spanning records from 1 October 2021 to 16 April 2023.

Participants: Two distinct cohorts were established: one comprising individuals diagnosed with Long COVID and another comprising individuals with no history of Long COVID or COVID-19. At the start of the study, none of the participants had a recorded MHD.

Primary and secondary outcome measures: The main outcome of interest was a composite diagnosis of MHD. Secondary outcomes were individual mental health conditions.

Results: The study included 43 060 control participants without Long COVID and 4306 Long COVID participants, demonstrating well-balanced distribution across all covariates. After adjusting for 4 demographic factors and 10 comorbidities, Long COVID was associated with MHD (adjusted HR, aHR 2.60; 95% CI 2.37 to 2.85). In subgroup analysis, Long COVID was associated with major depression disorder (aHR 3.36; 95% CI 2.82 to 4.00) and generalised anxiety disorder (aHR 3.44; 95% CI 2.99 to 3.96).

Conclusions: In this retrospective large real-world cohort study, Long COVID was associated with an increased risk of incident MHD. The MHD impact is significant considering the vast number of patients with Long COVID. Enhanced MHD screening among COVID-19 survivors should be a priority.

Association of psychiatric disorders with clinical diagnosis of long COVID in US veterans

Psychol Med. 2024 Feb 5:1-9. doi: 10.1017/S0033291724000114. Online ahead of print.

Kristen Nishimi 1 2, Thomas C Neylan 1 2 3, Daniel Bertenthal 1, Karen H Seal 2 4 5, Aoife O'Donovan 1 2

Affiliations

1Mental Health Service, San Francisco Veterans Affairs Health Care System, San Francisco, CA, USA.

2Department of Psychiatry and Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA.

3Department of Neurology, University of California San Francisco, San Francisco, CA, USA.

4Integrative Health Service, San Francisco Veterans Affairs Health Care System, San Francisco, CA, USA.

5Department of Medicine, University of California San Francisco, San Francisco, CA, USA.

Abstract

Background: Psychiatric disorders may be a risk factor for long COVID, broadly defined as COVID-19 conditions continuing three months post-acute infection. In US Veterans with high psychiatric burden, we examined associations between psychiatric disorders and clinical diagnosis of long COVID.

Methods: We conducted a retrospective cohort study using health records from VA patients with a positive SARS-CoV-2 test from February 2020 to February 2023. Generalized linear models estimated associations between any psychiatric disorder and likelihood of subsequent diagnosis with long COVID (i.e. two or more long COVID clinical codes). Models were adjusted for socio-demographic, medical, and behavioral factors. Secondary models examined individual psychiatric disorders and age-stratified associations.

Results: Among 660 217 VA patients with positive SARS-CoV-2 tests, 56.3% had at least one psychiatric disorder diagnosis and 1.4% were diagnosed with long COVID. Individuals with any psychiatric disorder had higher risk for long COVID diagnosis in models adjusted for socio-demographic factors, vaccination status, smoking, and medical comorbidities (relative risk, RR = 1.28, 95% CI 1.21-1.35), with the strongest associations in younger individuals. Considering specific disorders, depressive, anxiety, and stress-related disorders were associated with increased risk for long COVID diagnoses (RRs = 1.36-1.48), but associations were in the opposite direction for substance use and psychotic disorders (RRs = 0.78-0.88).

Conclusions: Psychiatric disorder diagnoses were associated with increased long COVID diagnosis risk in VA patients, with the strongest associations observed in younger individuals. Improved surveillance, treatment, and prevention for COVID-19 and its long-term sequelae should be considered for individuals with psychiatric conditions.

Changes in Outpatient Health Care Use After COVID-19 Infection Among Veterans

JAMA Netw Open. 2024 Feb 5;7(2):e2355387. doi: 10.1001/jamanetworkopen.2023.55387.

Paul L Hebert 1 2, Kyle E Kumbier 3, Valerie A Smith 4 5 6, Denise M Hynes 7 8, Diana J Govier 7 9, Edwin Wong 1 2, Brystana G Kaufman 4 5 10, Megan Shepherd-Banigan 4 5 10, Mazhgan Rowneki 7, Amy S B Bohnert 3 11, George N Ioannou 1 12, Edward J Boyko 1 13 14, Theodore J Iwashyna 3 15 16 17, Ann M O'Hare 1 14, C Barrett Bowling 4 6 18, Elizabeth M Viglianti 3 15, Matthew L Maciejewski 4 5 6 9; VA COVID-19 Observational Research Collaboratory (CORC)

Collaborators

VA COVID-19 Observational Research Collaboratory (CORC): Andrew Admon, Kathleen Akgun, Livia Anderson, Stacy Anderson, Mihaela Aslan, David Au, Lisa Backus, Kristina Bajema, Aaron Baraff, Lisa Batten, Theodore Berkowitz, Taylor Bernstein, Kristin Berry Wyatt, Joseph Bogdan, Joleen Borgerding, Hayden Bosworth, Nathan Boucher, Nicholas Burwick, Kaitland Byrd, Aissa Cabrales, Jennifer Cano, Wen Chai, Jason Chen, Kei-Hoi Cheung, Kristina Crothers, Graham Cummin, Jeffrey Curtis, Marie Davis, Emily Del Monico, Paul Dennis, Aram Dobalian, Jacob Doll, Jason Dominitz, McKenna Eastment, Vincent Fan, Jacqueline Ferguson, Breana Floyd, Alexandra Fox, Matthew Goetz, Pamela Green, Susan Nicole Hastings, Katrina Hauschildt, Eric Hawkins, Mark Helfand, Alex Hickok, Dana Horowitz, Catherine Hough, Elaine Hu, Kevin Ikuta, Barbara Jones, Makoto Jones, Lee Kamphius, Sara Knight, Anna Korpak, Peggy Korpela, Kenneth Langa, Ryan Laundry, Stacy Lavin, Yuli Li, Jennifer Lindquist, Holly McCready, Cassie Meyer, Martha Michel, Amy Miles, Jessie Milne, Max Monahan, Daniel Morelli, Pradeep Mutalik, Jennifer Naylor, Meike Niederhausen, Summer Newell, Shannon Nugent, Michael Ong, Thomas Osborne, Matthew Peterson, Alexander Peterson, Hallie Prescott, John Pura, Nallakkandi Rajeevan, Ashok Reddy, Marylena Rouse, Somnath Saha, Sameer Saini, Sarah Seelye, Javeed Shah, Troy Shahoumian, Aasma Shaukat, Whitney Showalter, Christopher Slatore, Battista Smith, Nicholas Smith, Elani Streja, Pradeep Suri, Jeremy Sussman, Yumie Takata, Alan Teo, Eva Thomas, Laura Thomas, Anais Tuepker, Aaron Turner, Zachary Veigulis, Elizabeth Vig, Kelly Vranas, Xiao Qing Wang, Katrina Wicks, Kara Winchell, James Womer, Chris Woods, Katherine Wysham, Lei Yan, Donna Zulman

Affiliations

1Center for Veteran-Centered and Value-Driven Care, Veterans Affairs Puget Sound Health Care System, Seattle, Washington.

2Department of Health Systems and Population Health, University of Washington School of Medicine, Seattle.

3VA Health Services Research & Development, Center for Clinical Management and Research, VA Ann Arbor Healthcare System, Ann Arbor, Michigan.

4Center of Innovation to Accelerate Discovery and Practice Transformation (ADAPT), Durham Veterans Affairs Health Care System, Durham, North Carolina.

5Department of Population Health Sciences, Duke University, Durham, North Carolina.

6Department of Medicine, Duke University, Durham, North Carolina.

7Center of Innovation to Improve Veteran Involvement in Care, Veterans Affairs Portland Health Care System, Portland, Oregon.

8Health Management and Policy, Health Data and Informatics Program, Center for Quantitative Life Sciences, College of Health, Oregon State University, Corvallis.

9School of Nursing, Oregon Health & Science University, Portland.

10Duke-Margolis Center for Health Policy, Durham, North Carolina.

11Department of Anesthesiology, University of Michigan, Ann Arbor.

12Division of Gastroenterology, University of Washington, Seattle.

13Epidemiologic Research and Information Center, Veterans Affairs Puget Sound Health Care System, Seattle, Washington.

14Department of Epidemiology, University of Washington, Seattle.

15Department of Medicine, University of Michigan Medical School, Ann Arbor.

16School of Medicine, Johns Hopkins University, Baltimore, Maryland.

17School of Public Health, Johns Hopkins University, Baltimore, Maryland.

18Durham Veterans Affairs Geriatric Research Education and Clinical Center, Durham Veterans Affairs Medical Center, Durham, North Carolina.

Abstract

Importance: The association of COVID-19 infection with outpatient care utilization is unclear. Many studies reported population surveillance studies rather than comparing outpatient health care use between COVID-19-infected and uninfected cohorts.

Objective: To compare outpatient health care use across 6 categories of care (primary care, specialty care, surgery care, mental health, emergency care, and diagnostic and/or other care) between veterans with or without COVID-19 infection.

Design, setting, and participants: In a retrospective cohort study of Veterans Affairs primary care patients, veterans with COVID-19 infection were matched to a cohort of uninfected veterans. Data were obtained from the Veterans Affairs Corporate Data Warehouse and the Centers for Medicare & Medicaid Services Fee-for-Service Carrier/Physician Supplier file from January 2019 through December 2022. Data analysis was performed from September 2022 to April 2023.

Exposure: COVID-19 infection.

Main outcomes and measures: The primary outcome was the count of outpatient visits after COVID-19 infection. Negative binomial regression models compared outpatient use over a 1-year preinfection period, and peri-infection (0-30 days), intermediate (31-183 days), and long-term (184-365 days) postinfection periods.

Results: The infected (202 803 veterans; mean [SD] age, 60.5 [16.2] years; 178 624 men [88.1%]) and uninfected (202 803 veterans; mean [SD] age, 60.4 [16.5] years; 178 624 men [88.1%]) cohorts were well matched across all covariates. Outpatient use in all categories (except surgical care) was significantly elevated during the peri-infection period for veterans with COVID-19 infection compared with the uninfected cohort, with an increase in all visits of 5.12 visits per 30 days (95% CI, 5.09-5.16 visits per 30 days), predominantly owing to primary care visits (increase of 1.86 visits per 30 days; 95% CI, 1.85-1.87 visits per 30 days). Differences in outpatient use attenuated over time but remained statistically significantly higher at 184 to 365 days after infection (increase of 0.25 visit per 30 days; 95% CI, 0.23-0.27 visit per 30 days). One-half of the increased outpatient visits were delivered via telehealth. The utilization increase was greatest for veterans aged 85 years and older (6.1 visits, 95% CI, 5.9-6.3 visits) vs those aged 20 to 44 years (4.8 visits, 95% CI, 4.7-4.8 visits) and unvaccinated veterans (4.5 visits, 95% CI, 4.3-4.6 visits) vs vaccinated veterans (3.2 visits; 95% CI, 3.4-4.8 visits).

Conclusions and relevance: This study found that outpatient use increased significantly in the month after infection, then attenuated but remained greater than the uninfected cohorts' use through 12 months, which suggests that there are sustained impacts of COVID-19 infection.

Self-managing symptoms of Long COVID: an education and strategies research protocol

Front Public Health. 2024 Feb 7:12:1106578. doi: 10.3389/fpubh.2024.1106578. eCollection 2024.

Julia Rybkina 1, Nithin Jacob 1, Brenda Colella 2, David Gold 3, Donna E Stewart 4, Lesley A Ruttan 5, Liesel-Ann C Meusel 2, Mary P McAndrews 6, Susan Abbey 7, Robin Green 1 8

Affiliations

1KITE Research Institute, Toronto Rehabilitation Institute-University Health Network, Toronto, ON, Canada.

2Telerehab Centre for Acquired Brain Injury, Toronto Rehabilitation Institute-University Centre, University Health Network, Toronto, ON, Canada.

3Krembil Brain Institute, University of Toronto, Toronto Western Hospital, University Health Network, Toronto, ON, Canada.

4University of Toronto, Centre for Mental Health and Senior Scientist, University Health Network, Toronto, ON, Canada.

5University of Toronto Scarborough, Neuro-Rehab Program, Toronto Rehabilitation Institute-University Centre, University Health Network, Toronto, ON, Canada.

6Krembil Research Institute, University of Toronto, University Health Network, Toronto, ON, Canada.

7Medical Psychiatry and Psychiatry and Psychosocial Oncology, University Health Network, Toronto, ON, Canada.

8Department of Psychiatry, Division of Neurosciences and Clinical Translation, University of Toronto, Toronto, ON, Canada.

Abstract

Post-acute sequelae of SARS-COV-2 (PASC) is growing in prevalence, and involves symptoms originating from the central neurological, cardiovascular, respiratory, gastrointestinal, autonomic nervous, or immune systems. There are non-specific symptoms such as fatigue, headaches, and brain fog, which cannot be ascribed to a single system. PASC places a notable strain on our healthcare system, which is already laden with a large number of acute-COVID-19 patients. Furthermore, it impedes social, academic and vocational functioning, and impacts family life, relationships, and work/financial life. The treatment for PASC needs to target this non-specific etiology and wide-ranging sequelae. In conditions similar to PASC, such as "chemo brain," and prolonged symptoms of concussion, the non-specific symptoms have shown to be effectively managed through education and strategies for self-management and Mindfulness interventions. However, such interventions have yet to be empirically evaluated in PASC to our knowledge. In response to this gap, we have developed a virtual education intervention synthesized by psychiatrists and clinical psychologists for the current study. We will undertake a two-phase randomized controlled trial to determine the feasibility (Phase 1; N = 90) and efficacy (Phase 2; sample sized based on phase 1 results) of the novel 8 week Education and Self-Management Strategies group compared to a mindfulness skills program, both delivered virtually. Main outcomes include confidence/ability to self-manage symptoms, quality of life, and healthcare utilization. This study stands to mitigate the deleterious intrusiveness of symptoms on everyday life in patients with PASC, and may also help to reduce the impact of PASC on the healthcare system. Clinical trial registration:https://classic.clinicaltrials.gov/ct2/show/NCT05268523; identifier NCT05268523.

Association of Obstructive Sleep Apnea with Post-Acute Sequelae of SARS-CoV-2 Infection

Am J Med. 2024 Feb 22:S0002-9343(24)00109-8. doi: 10.1016/j.amjmed.2024.02.023. Online ahead of print.

Stuart F Quan 1, Matthew D Weaver 2, Mark É Czeisler 3, Laura K Barger 2, Lauren A Booker 4, Mark E Howard 5, Melinda L Jackson 6, Rashon I Lane 7, Christine F McDonald 8, Anna Ridgers 9, Rebecca Robbins 2, Prerna Varma 10, Joshua F Wiley 10, Shantha M W Rajaratnam 11, Charles A Czeisler 2

Affiliations

1Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, Mass; Division of Sleep Medicine. Electronic address: Stuart_Quan@hms.harvard.edu.

2Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, Mass; Division of Sleep Medicine.

3Francis Weld Peabody Society, Harvard Medical School, Boston, Mass; School of Psychological Sciences, Turner Institute for Brain and Mental Health, Monash University, Melbourne, Victoria, Australia; Institute for Breathing and Sleep, Austin Health, Heidelberg, Victoria, Australia.

4Institute for Breathing and Sleep, Austin Health, Heidelberg, Victoria, Australia; University Department of Rural Health, La Trobe Rural Health School, La Trobe University, Bendigo, Victoria, Australia.

5Institute for Breathing and Sleep, Austin Health, Heidelberg, Victoria, Australia; Turner Institute for Brain and Mental Health, Monash University, Clayton, Victoria, Australia; Department of Medicine, The University of Melbourne, Victoria, Australia.

6School of Psychological Sciences, Turner Institute for Brain and Mental Health, Monash University, Melbourne, Victoria, Australia; Institute for Breathing and Sleep, Austin Health, Heidelberg, Victoria, Australia.

7Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, Mass.

8Institute for Breathing and Sleep, Austin Health, Heidelberg, Victoria, Australia; Department of Medicine, The University of Melbourne, Victoria, Australia; Department of Respiratory and Sleep Medicine, Austin Health, Heidelberg, Victoria, Australia; Faculty of Medicine, Monash University, Melbourne, Victoria, Australia.

9Institute for Breathing and Sleep, Austin Health, Heidelberg, Victoria, Australia; Department of Medicine, The University of Melbourne, Victoria, Australia; Department of Respiratory and Sleep Medicine, Austin Health, Heidelberg, Victoria, Australia.

10School of Psychological Sciences, Turner Institute for Brain and Mental Health, Monash University, Melbourne, Victoria, Australia.

11Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, Mass; Division of Sleep Medicine; School of Psychological Sciences, Turner Institute for Brain and Mental Health, Monash University, Melbourne, Victoria, Australia; Institute for Breathing and Sleep, Austin Health, Heidelberg, Victoria, Australia.

Abstract

Background: Obstructive sleep apnea is associated with COVID-19 infection. Less clear is whether obstructive sleep apnea is a risk factor for the development of post-acute sequelae of SARS-CoV-2 infection (PASC).

Study design: Cross-sectional survey of a general population of 24,803 US adults to determine the association of obstructive sleep apnea with PASC.

Results: COVID-19 infection occurred in 10,324 (41.6%) participants. Prevalence of persistent (>3 months post infection) putative PASC-related physical and mental health symptoms ranged from 6.5% (peripheral edema) to 19.6% (nervous/anxious). In logistic regression models, obstructive sleep apnea was associated with all putative PASC-related symptoms with the highest adjusted odds ratios being fever (2.053) and nervous/anxious (1.939). In 4 logistic regression models of overall PASC derived from elastic net regression, obstructive sleep apnea was associated with PASC (range of adjusted odds ratios: 1.934-2.071); this association was mitigated in those with

treated obstructive sleep apnea. In the best fitting overall model requiring ≥3 symptoms, PASC prevalence was 21.9%.

Conclusion: In a general population sample, obstructive sleep apnea is associated with the development of PASC-related symptoms and a global definition of PASC. Treated obstructive sleep apnea mitigates the latter risk. The presence of 3 or more PASC symptoms may be useful in identifying cases and for future research.

COVID-19 and Influenza Vaccine Coadministration Among Older U.S. Adults

Am J Prev Med. 2024 Feb 23:S0749-3797(24)00067-9. doi: 10.1016/j.amepre.2024.02.013. Online ahead of print.

Daniel A Harris 1, Preeti Chachlani 2, Kaleen N Hayes 2, Ellen P McCarthy 3, Katherine J Wen 4, Yalin Deng 2, Andrew R Zullo 5, Djeneba Audrey Djibo 6, Cheryl N McMahill-Walraven 6, Renae L Smith-Ray 7, Stefan Gravenstein 8, Vincent Mor 9

Affiliations

1Center for Gerontology and Healthcare Research, Brown University School of Public Health, Providence, Rhode Island; Department of Health Services, Policy, and Practice, Brown University School of Public Health, Providence, Rhode Island. Electronic address: daniel_harris2@brown.edu.

2Center for Gerontology and Healthcare Research, Brown University School of Public Health, Providence, Rhode Island; Department of Health Services, Policy, and Practice, Brown University School of Public Health, Providence, Rhode Island.

3Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts; Division of Gerontology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.

4Department of Medicine, Health, and Society, Vanderbilt University, Nashville, Tennessee.

5Department of Epidemiology, Brown University School of Public Health, Providence, Rhode Island.

6CVS Health Clinical Trial Services, Bell, Pennsylvania.

7Walgreens Center for Health and Wellbeing Research, Walgreen Company, Deerfield, Illinios.

8Center for Gerontology and Healthcare Research, Brown University School of Public Health, Providence, Rhode Island; Department of Health Services, Policy, and Practice, Brown University School of Public Health, Providence, Rhode Island; Center of Innovation in Long-Term Services and Supports, Providence Veterans Affairs Medical Center, Providence, Rhode Island; Division of Geriatrics and Palliative Medicine, Alpert Medical School of Brown University, Providence, Rhode Island; Providence Medical Center Veterans Administration Research Service, Providence, Rhode Island.

9Center for Gerontology and Healthcare Research, Brown University School of Public Health, Providence, Rhode Island; Department of Health Services, Policy, and Practice, Brown University School of Public Health, Providence, Rhode Island; Center of Innovation in Long-Term Services and Supports, Providence Veterans Affairs Medical Center, Providence, Rhode Island; Providence Medical Center Veterans Administration Research Service, Providence, Rhode Island.

Abstract

Introduction: Coadministering COVID-19 and influenza vaccines is recommended by public health authorities and intended to improve uptake and convenience; however, the extent of vaccine coadministration is largely unknown. Investigations into COVID-19 and influenza vaccine coadministration are needed to describe compliance with newer recommendations and to identify potential gaps in the implementation of coadministration.

Methods: A descriptive, repeated cross-sectional study between September 1, 2021 to November 30, 2021 (Period 1) and September 1, 2022 to November 30, 2022 (Period 2) was conducted. This study included community-dwelling Medicare beneficiaries ≥ 66 years who received an mRNA COVID-19 booster vaccine in Periods 1 and 2. The outcome was an influenza vaccine administered on the same day as the COVID-19 vaccine. Adjusted ORs and 99% CIs were estimated using logistic regression to describe the association between beneficiaries' characteristics and vaccine coadministration. Statistical analysis was performed in 2023.

Results: Among beneficiaries who received a COVID-19 vaccine, 78.8% in Period 1 (N=6,292,777) and 89.1% in Period 2 (N=4,757,501), received an influenza vaccine at some point during the study period (i.e., before, after, or on the same day as their COVID-19 vaccine), though rates were lower in non-White and rural individuals. Vaccine coadministration increased from 11.1% to 36.5% between periods. Beneficiaries with dementia (aORPeriod 2=1.31; 99%CI=1.29-1.32) and in rural

counties (aORPeriod 2=1.19; 99%CI=1.17-1.20) were more likely to receive coadministered vaccines, while those with cancer (aORPeriod 2=0.90; 99%CI=0.89-0.91) were less likely.

Conclusions: Among Medicare beneficiaries vaccinated against COVID-19, influenza vaccination was high, but coadministration of the 2 vaccines was low. Future work should explore which factors explain variation in the decision to receive coadministered vaccines.

An open trial of biofeedback for long COVID

J Psychosom Res. 2024 Feb 23:179:111625. doi: 10.1016/j.jpsychores.2024.111625. Online ahead of print.

Natacha D Emerson 1, Helen Lavretsky 2, William Q Pittman 3, Nisha Viswanathan 3, Prabha Siddarth 2

Affiliations

1UCLA Psychiatry & Biobehavioral Sciences, David Geffen School of Medicine, United States. Electronic address: NDEmerson@mednet.ucla.edu.

2UCLA Psychiatry & Biobehavioral Sciences, David Geffen School of Medicine, United States.

3UCLA Department of Medicine, David Geffen School of Medicine, United States.

Abstract

Objective: Biofeedback is a therapeutic treatment model that teaches self-regulation of autonomic functions to alleviate stress-related symptoms. "Long COVID" refers to chronic physical and cognitive sequelae post-SARS-CoV-2 infection. This study examined the efficacy of a six-week intervention, consisting of weekly one-hour sessions combining heart rate variability and temperature biofeedback, for alleviating mood symptoms, somatic symptoms and sleep disturbance of patients diagnosed with long COVID.

Methods: Data were collected from 20 adult participants aged 22-63 (Mage = 44.1, SDage = 12.2) with varying long COVID symptoms. Within this single arm design, 16 of the 20 participants completed all six sessions of biofeedback; 14 completed an assessment at the three-month post-treatment time point.

Results: Participants self-reported significant improvements in somatic, anxiety, and depressive symptoms, sleep quality, quality of life, and number of "bad days" immediately after the intervention and three months later (Cohen's d effect size (ES) = 1.09-0.46). Reduced number of medical doctor visits (ES = 0.85) and prescription drug use over the last month (odds ratio = 0.33), as well as improved emotional wellbeing (ES = 0.97) were observed at the three-month time point only.

Conclusion: Results suggest that this short, readily scalable intervention can be potentially efficacious in alleviating symptoms of long COVID. Despite notable improvements, the major limitation of this study is its lack of control group. While a randomized trial merits study, biofeedback appears to be a brief, effective, non-invasive, and low-cost treatment option for patients with chronic somatic symptoms secondary to SARS-CoV-2 infection.

Long-term outcomes following hospital admission for COVID-19 versus seasonal influenza: a cohort study

Lancet Infect Dis. 2024 Mar;24(3):239-255. doi: 10.1016/S1473-3099(23)00684-9. Epub 2023 Dec 14.

Yan Xie 1, Taeyoung Choi 2, Ziyad Al-Aly 3

Affiliations

1Clinical Epidemiology Center, Research and Development Service, VA Saint Louis Health Care System, Saint Louis, MO, USA; Veterans Research and Education Foundation of Saint Louis, Saint Louis, MO, USA; Division of Pharmacoepidemiology, Clinical Epidemiology Center, Research and Development Service, VA Saint Louis Health Care System, Saint Louis, MO, USA.

2Clinical Epidemiology Center, Research and Development Service, VA Saint Louis Health Care System, Saint Louis, MO, USA; Veterans Research and Education Foundation of Saint Louis, Saint Louis, MO, USA.

3Clinical Epidemiology Center, Research and Development Service, VA Saint Louis Health Care System, Saint Louis, MO, USA; Veterans Research and Education Foundation of Saint Louis, Saint Louis, MO, USA; Department of Medicine, Washington University School of Medicine, Saint Louis, MO, USA; Nephrology Section, Medicine Service, VA Saint Louis Health Care System, Saint Louis, MO, USA; Institute for Public Health, Washington University in Saint Louis, Saint Louis, MO, USA. Electronic address: zalaly@gmail.com.

Abstract

Background: Previous comparative analyses of people admitted to hospital for COVID-19 versus influenza evaluated the risk of death, hospital readmission, and a narrow set of health outcomes up to 6 months following infection. We aimed to do a comparative evaluation of both acute and long-term risks and burdens of a comprehensive set of health outcomes following hospital admission for COVID-19 or seasonal influenza.

Methods: For this cohort study we used the health-care databases of the US Department of Veterans Affairs to analyse data from 81 280 participants admitted to hospital for COVID-19 between March 1, 2020, and June 30, 2022, and 10 985 participants admitted to hospital for seasonal influenza between Oct 1, 2015, and Feb 28, 2019. Participants were followed up for up to 18 months to comparatively evaluate risks and burdens of death, a prespecified set of 94 individual health outcomes, ten organ systems, overall burden across all organ systems, readmission, and admission to intensive care. Inverse probability weighting was used to balance the baseline characteristics. Cox and Poisson models were used to generate estimates of risk on both the relative scale and absolute scale as the event rate and disability-adjusted life-years (DALYs) per 100 persons.

Findings: Over 18 months of follow-up, compared to seasonal influenza, the COVID-19 group had an increased risk of death (hazard ratio [HR] 1·51 [95% CI 1·45-1·58]), corresponding to an excess death rate of 8·62 (95% CI 7·55-9·44) per 100 persons in the COVID-19 group versus the influenza group. Comparative analyses of 94 prespecified health outcomes showed that COVID-19 had an increased risk of 68·1% (64 of 94) pre-specified health outcomes; seasonal influenza was associated with an increased risk of 6·4% (six of 94) pre-specified health outcomes, including three out of four pre-specified pulmonary outcomes. Analyses of organ systems showed that COVID-19 had a higher risk across all organ systems except for the pulmonary system, the risk of which was higher in seasonal influenza. The cumulative rates of adverse health outcomes across all organ systems were 615·18 (95% CI 605·17-624·88) per 100 persons in COVID-19 and 536·90 (527·38-544·90) per 100 persons in seasonal influenza, corresponding to an excess rate of 78·72 (95% CI 66·15-91·24) per 100 persons in COVID-19. The total number of DALYs across all organ systems were 287·43 (95% CI 281·10-293·59) per 100 persons in the COVID-19 group and 242·66 (236·75, 247·67) per 100 persons in the seasonal influenza group, corresponding to 45·03 (95% CI 37·15-52·90) higher DALYs per 100 persons in COVID-19. Decomposition analyses showed that in both COVID-19 and seasonal influenza, there was a higher burden of health loss in the post-acute than

the acute phase; and comparatively, except for the pulmonary system, COVID-19 had a higher burden of health loss across all other organ systems than seasonal influenza in both the acute and post-acute phase. Compared to seasonal influenza, COVID-19 also had an increased risk of hospital readmission (excess rate 20·50 [95% CI 16·10-24·86] per 100 persons) and admission to intensive care (excess rate 9·23 [6·68-11·82] per 100 persons). The findings were consistent in analyses comparatively evaluating risks in seasonal influenza versus COVID-19 by individuals' respective vaccination status and in those admitted to hospital during the pre-delta, delta, and omicron eras.

Interpretation: Although rates of death and adverse health outcomes following hospital admission for either seasonal influenza or COVID-19 are high, this comparative analysis shows that hospital admission for COVID-19 was associated with higher long-term risks of death and adverse health outcomes in nearly every organ system (except for the pulmonary system) and significant cumulative excess DALYs than hospital admission for seasonal influenza. The substantial cumulative burden of health loss in both groups calls for greater prevention of hospital admission for these two viruses and for greater attention to the care needs of people with long-term health effects due to either seasonal influenza or SARS-CoV-2 infection.

Health-Related Quality of Life for Patients with Post-Acute COVID-19 Syndrome: Identification of Symptom Clusters and Predictors of Long-Term Outcomes

J Gen Intern Med. 2024 Feb 29. doi: 10.1007/s11606-024-08688-9. Online ahead of print.

Brittany Lapin 1 2, Yadi Li 3 4, Kristin Englund 5, Irene L Katzan 3

Affiliations

1Center for Outcomes Research and Evaluation, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA. LapinB@ccf.org.

2Department of Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA. LapinB@ccf.org.

3Center for Outcomes Research and Evaluation, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA.

4Department of Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA.

5Department of Infectious Disease, Respiratory Institute, Cleveland Clinic, Cleveland, OH, USA.

Abstract

Background: Following COVID-19 infection, as many as a third of patients have long-term symptoms, known as post-acute sequelae (PASC). The mechanisms contributing to PASC remain largely unknown and, due to the heterogeneity of symptoms, treating PASC provides unique challenges.

Objective: Our study sought to (1) identify clinical symptom profiles based on PROMIS Global Health (GH) items, (2) evaluate demographic and clinical differences across profiles, and (3) identify predictors of change in health-related quality of life (HRQL) over time.

Design: This was an observational cohort study of patients with PASC who completed PROMIS-GH between 2/11/21 and 12/3/21 as part of routine care, with data extracted from the electronic health record.

Participants: There were 1407 adult patients (mean age 49.6 ± 13.7, 73% female, 81% White race) with PASC seen in the recovery clinic between 2/11/21 and 12/3/21, with 1129 (80.2%) completing PROMIS-GH as routine care.

Main measures: HRQL was measured with PROMIS-GH at initial visit and after 12 months.

Key results: Latent profile analysis identified symptom classes based on five PROMIS-GH items (mental health, ability to carry out physical activities, pain, fatigue, and emotional problems). Four latent profiles were identified: (1) "Poor HRQL" (n = 346), (2) "Mixed HRQL: good mental/poor physical" (n = 232), (3) "Mixed HRQL: poor mental/good physical" (n = 324), and (4) "Good HRQL" (n = 227). Demographics and comorbidities varied significantly across profile with patients with more severe COVID-19 infection more likely to be in profiles 1 and 2. Overall, patients improved 2 T-score points on PROMIS-GH after 12 months, with differences by profile. Predictors of improved HRQL included profile, lower body mass index, and fewer COVID symptoms.

Conclusions: Patients with PASC have distinct HRQL symptom profiles which were able to differentiate across COVID-19 severity and symptoms. Improvement over 12 months differed by profile. These profiles may be used to better understand the mechanisms behind PASC. Future research should evaluate their ability to guide treatment decisions to improve HRQL.

Altered mitochondrial respiration in peripheral blood mononuclear cells of post-acute sequelae of SARS-CoV-2 infection

Mitochondrion. 2024 Mar:75:101849. doi: 10.1016/j.mito.2024.101849. Epub 2024 Feb 9.

Sahera Dirajlal-Fargo 1, David P Maison 2, Jared C Durieux 3, Anastasia Andrukhiv 4, Nicholas Funderburg 5, Kate Ailstock 6, Mariana Gerschenson 7, Grace A Mccomsey 8

Affiliations

1Case Western Reserve University, Cleveland, OH, USA; Ann and Robert Lurie Children's Hospital, Chicago, IL, USA. Electronic address: Sahera.dirajlal-fargo@uhhospitals.org.

2Department of Cell and Molecular Biology, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI, USA. Electronic address: davidm22@hawaii.edu.

3Case Western Reserve University, Cleveland, OH, USA. Electronic address: Jared.Durieux@UHhospitals.org.

4Department of Cell and Molecular Biology, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI, USA. Electronic address: andru78@hawaii.eduNicholas.

5Division of Medical Laboratory Science, School of Health and Rehabilitation Sciences, The Ohio State University, Columbus, OH, USA. Electronic address: Nicholas.Funderburg@osumc.edu.

6Division of Medical Laboratory Science, School of Health and Rehabilitation Sciences, The Ohio State University, Columbus, OH, USA. Electronic address: Kate.Ailstock@osumc.edu.

7Department of Cell and Molecular Biology, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI, USA. Electronic address: gerschen@hawaii.edu.

8Case Western Reserve University, Cleveland, OH, USA. Electronic address: grace.mccomsey@uhhospitals.org.

Abstract

Peripheral blood mononuclear cells (PBMC) mitochondrial respiration was measured ex vivo from participants without a history of COVID (n = 19), with a history of COVID and full recovery (n = 20), and with PASC (n = 20). Mean mitochondrial basal respiration, ATP-linked respiration, maximal respiration, spare respiration capacity, ATP-linked respiration, and non-mitochondrial respiration were highest in COVID + PASC+ ($p \leq 0.04$). Every unit increase in non-mitochondrial respiration, ATP-linked respiration, basal respiration, spare respiration capacity, and maximal respiration increased the predicted odds of PASC between 1 % and 6 %. Mitochondrial dysfunction in PBMCs may be contributing to the etiology of PASC.

Postacute Sequelae of SARS-CoV-2 in Children

Pediatrics. 2024 Mar 1;153(3):e2023062570. doi: 10.1542/peds.2023-062570.

Suchitra Rao 1, Rachel S Gross 2 3, Sindhu Mohandas 4 5, Cheryl R Stein 6, Abigail Case 7, Benard Dreyer 5, Nathan M Pajor 8, H Timothy Bunnell 9, David Warburton 5, Elizabeth Berg 10, Jonathan B Overdevest 10, Mark Gorelik 10, Joshua Milner 10, Sejal Saxena 10, Ravi Jhaveri 11, John C Wood 5, Kyung E Rhee 12, Rebecca Letts 3, Christine Maughan 3, Nick Guthe 3, Leah Castro-Baucom 3, Melissa S Stockwell 10 13

Affiliations

1Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, Colorado.

2Departments of Pediatrics.

3Population Health, NYU Grossman School of Medicine, New York, New York.

4Division of Infectious Diseases.

5Department of Pediatrics and Radiology, Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, California.

6Child and Adolescent Psychiatry, New York University Grossman School of Medicine, New York, New York.

7Department of Pediatrics and Rehabilitation Medicine, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

8Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio.

9Biomedical Research Informatics Center, Nemours Children's Health, Nemours Children's Hospital, Delaware, Wilmington, Delaware.

10Department of Pediatrics, Columbia University Vagelos College of Physicians and Surgeons, New York, New York.

11Division of Infectious Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois.

12Department of Pediatrics, University of California, San Diego, School of Medicine, San Diego, California.

13Department of Population and Family Health, Columbia University Mailman School of Public Health, New York, New York.

Abstract

The coronavirus disease 2019 (COVID-19) pandemic has caused significant medical, social, and economic impacts globally, both in the short and long term. Although most individuals recover within a few days or weeks from an acute infection, some experience longer lasting effects. Data regarding the postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection (PASC) in children, or long COVID, are only just emerging in the literature. These symptoms and conditions may reflect persistent symptoms from acute infection (eg, cough, headaches, fatigue, and loss of taste and smell), new symptoms like dizziness, or exacerbation of underlying conditions. Children may develop conditions de novo, including postural orthostatic tachycardia syndrome, myalgic encephalomyelitis/chronic fatigue syndrome, autoimmune conditions and multisystem inflammatory syndrome in children. This state-of-the-art narrative review provides a summary of our current knowledge about PASC in children, including prevalence, epidemiology, risk factors, clinical characteristics, underlying mechanisms, and functional outcomes, as well as a conceptual framework for PASC based on the current National Institutes of Health definition. We highlight the pediatric components of the National Institutes of Health-funded Researching COVID to Enhance Recovery Initiative, which seeks to characterize the natural history, mechanisms, and long-term health effects of PASC in children and young adults to inform future treatment and prevention efforts. These initiatives include electronic health record cohorts, which offer rapid assessments at scale with geographical and demographic diversity, as well as longitudinal prospective observational cohorts, to estimate disease burden, illness trajectory, pathobiology, and clinical manifestations and outcomes.

Self-Reported Everyday Functioning After COVID-19 Infection

JAMA Netw Open. 2024 Mar 4;7(3):e240869. doi: 10.1001/jamanetworkopen.2024.0869.

Theodore J Iwashyna 1 2 3 4, Valerie A Smith 5 6 7, Sarah Seelye 1, Amy S B Bohnert 1 8, Edward J Boyko 9 10, Denise M Hynes 11 12 13, George N Ioannou 10 14, Matthew L Maciejewski 5 6 13, Ann M O'Hare 10 14, Elizabeth M Viglianti 1 2, Theodore S Berkowitz 5, John Pura 5, James Womer 3, Lee A Kamphuis 1, Max L Monahan 1 3, C Barrett Bowling 5 15 6; VA HSR&D COVID-19 Observational Research Collaboratory (CORC)

Collaborators

VA HSR&D COVID-19 Observational Research Collaboratory (CORC): Andrew Admon, Kathleen Akgun, Stacy Anderson, Mihaela Aslan, David Au, Lisa Backus, Kristina Bajema, Aaron Baraff, Lisa Batten, Theodore Berkowitz, Taylor Bernstein, Kristin Berry Wyatt, Joseph Bogdan, Hayden Bosworth, Nathan Boucher, Nicholas Burwick, Aissa Cabrales, Jennifer Cano, Wen Chai, Jason Chen, Kei-Hoi Cheung, Kristina Crothers, Jeffrey Curtis, Marie Davis, Emily Del Monico, Aram Dobalian, Jacob Doll, Jason Dominitz, McKenna Eastment, Vincent Fan, Jacqueline Ferguson, Breanna Floyd, Alexandra Fox, Matthew Goetz, Diana Govier, Pamela Green, Susan Nicole Hastings, Katie Hauschildt, Eric Hawkins, Paul Hebert, Mark Helfand, Alex Hickok, Dana Horowitz, Catherine Hough, Elaine Hu, Kevin Ikuta, Barbara Jones, Makoto Jones, Lee Kamphuis, Brystana Kaufman, Sara Knight, Anna Korpak, Peggy Korpela, Kyle Kumbier, Kenneth Langa, Ryan Laundry, Stacy Lavin, Yuli Li, Jennifer Linquist, Holly McCready, Martha Michel, Amy Miles, Jessie Milne, Max Monahan, Daniel Morelli, Pradeep Mutalik, Jennifer Naylor, Meike Neiderhausen, Summer Newell, Shannon Nugent, Michael Ong, Thomas Osborne, Matthew Peterson, Alexander Peterson, Hallie Prescott, Nallakkandi Rajeevan, Ashok Reddy, Marylena Rouse, Mazhgan Rowneki, Som Saha, Sameer Saini, Javeed Shah, Troy Shahoumian, Aasma Shaukat, Megan Shepherd-Banigan, Whitney Showalter, Christopher Slatore, Nicholas Smith, Battista Smith, Pradeep Suri, Jeremy Sussman, Yumie Takata, Alan Teo, Eva Thomas, Laura Thomas, Anais Tuepker, Zachary Veigulis, Elizabeth Vig, Kelly Vranas, Xiao Qing Wang, Katrina Wicks, Kara Winchell, Edwin Wong, Chris Woods, Katherine Wysham, Lei Yan, Donna Zulman

Affiliations

1VA Center for Clinical Management Research, Ann Arbor VA, Ann Arbor, Michigan.

2Department of Medicine, University of Michigan Medical School, Ann Arbor.

3School of Medicine, Johns Hopkins University, Baltimore, Maryland.

4School of Public Health, Johns Hopkins University, Baltimore, Maryland.

5Center of Innovation to Accelerate Discovery and Practice Transformation, Durham VA Medical Center, Durham, North Carolina.

6Department of Medicine, Duke University, Durham, North Carolina.

7Department of Population Health Sciences, Duke University, Durham, North Carolina.

8Departments of Anesthesiology, Epidemiology, and Psychiatry, University of Michigan Medical School, Ann Arbor.

9Seattle Epidemiologic Research and Information Center, VA Puget Sound Health Care System, Seattle, Washington.

10University of Washington, Seattle.

11VA Portland Healthcare System, Center to Improve Veteran Involvement in Care, Portland, Oregon.

12College of Health, and Center for Quantitative Life Sciences, Oregon State University, Corvallis.

13School of Nursing, Oregon Health and Science University, Portland.

14VA Puget Sound Health Care System Hospital and Specialty Medicine Service and Seattle-Denver Center of Innovation for Veteran Centered and Value Driven Care, Seattle, Washington.

15Durham Veterans Affairs Geriatric Research Education and Clinical Center, Durham Veterans Affairs Medical Center, Durham, North Carolina.

Abstract

Importance: Changes in everyday functioning are crucial to assessing the long-term impact of COVID-19 infection.

Objective: To examine the impact of COVID-19 infection on everyday functioning 18 months after infection among veterans with and without histories of COVID-19 infection.

Design, setting, and participants: This cohort study used data from the US Veterans Affairs (VA) and included 186 veterans who had COVID-19 between October 2020 and April 2021 (ie, COVID-19 cohort) and 186 matched comparators who did not have documented COVID-19 infections (ie, control cohort). This match balanced the risk of COVID-19 based on 39 variables measured in the 24 months before infection or match, using principles of target trial emulation. Data were analyzed from December 2022 to December 2023.

Exposure: First documented COVID-19.

Main outcome and measures: The differences in self-reported everyday functioning 18 months after COVID-19 infection were estimated and compared with their matched comparators. Within-matched pair logistic and linear regressions assessed differences in outcomes and were weighted to account for sampling and nonresponse.

Results: Among the 186 matched pairs of participants, their weighted mean age was 60.4 (95% CI, 57.5 to 63.2) years among veterans in the COVID-19 cohort (weighted sample, 91 459 of 101 133 [90.4%] male; 30 611 [30.3%] Black or African American veterans; 65 196 [64.4%] White veterans) and 61.1 (95% CI, 57.8 to 64.4) years among their comparators in the control cohort (91 459 [90.4%] male; 24 576 [24.3%] Black or African American veterans; 70 157 [69.4%] White veterans). A high proportion of veterans in the COVID-19 cohort (weighted percentage, 44.9% [95% CI, 34.2% to 56.2%]) reported that they could do less than what they felt they could do at the beginning of 2020 compared with the control cohort (weighted percentage, 35.3%; [95% CI, 25.6% to 46.4%]; within-matched pair adjusted odds ratio [OR], 1.52 [95% CI, 0.79 to 2.91]). There was no association of documented COVID-19 infection with fatigue, substantial pain, limitations in either activities of daily living and instrumental activities of daily living, severely curtailed life-space mobility, employment, or mean health-related quality of life on a utility scale.

Conclusions and relevance: In this cohort study of veterans with and without documented COVID-19, many reported a substantial loss of everyday functioning during the pandemic regardless of whether or not they had a documented infection with COVID-19. Future work with larger samples is needed to validate the estimated associations.

The knowns and unknowns of long COVID-19: from mechanisms to therapeutical approaches

Front Immunol. 2024 Mar 4:15:1344086. doi: 10.3389/fimmu.2024.1344086. eCollection 2024.

Roxana Gheorghita 1 2, Iuliana Soldanescu 3, Andrei Lobiuc 2, Olga Adriana Caliman Sturdza 2 4, Roxana Filip 2 4, Adela Constantinescu-Bercu 2 5, Mihai Dimian 3 6, Serghei Mangul 7 8, Mihai Covasa 2 9

Affiliations

1Victor Babes University of Medicine and Pharmacy, Timisoara, Romania.

2Department of Biomedical Sciences, College of Medicine and Biological Science, University of Suceava, Suceava, Romania.

3Integrated Center for Research, Development and Innovation for Advanced Materials, Nanotechnologies, Manufacturing and Control Distributed Systems (MANSiD), University of Suceava, Suceava, Romania.

4Suceava Emergency Clinical County Hospital, Suceava, Romania.

5Institute of Cardiovascular Science, Hemostasis Research Unit, University College London (UCL), London, United Kingdom.

6Department of Computer, Electronics and Automation, University of Suceava, Suceava, Romania.

7Department of Clinical Pharmacy, USC Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences, University of Southern California, Los Angeles, CA, United States.

8Department of Quantitative and Computational Biology, USC Dornsife College of Letters, Arts and Sciences, University of Southern California (USC), Los Angeles, CA, United States.

9Department of Basic Medical Sciences, Western University of Health Sciences, College of Osteopathic Medicine, Pomona, CA, United States.

Abstract

The coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 has been defined as the greatest global health and socioeconomic crisis of modern times. While most people recover after being infected with the virus, a significant proportion of them continue to experience health issues weeks, months and even years after acute infection with SARS-CoV-2. This persistence of clinical symptoms in infected individuals for at least three months after the onset of the disease or the emergence of new symptoms lasting more than two months, without any other explanation and alternative diagnosis have been named long COVID, long-haul COVID, post-COVID-19 conditions, chronic COVID, or post-acute sequelae of SARS-CoV-2 (PASC). Long COVID has been characterized as a constellation of symptoms and disorders that vary widely in their manifestations. Further, the mechanisms underlying long COVID are not fully understood, which hamper efficient treatment options. This review describes predictors and the most common symptoms related to long COVID's effects on the central and peripheral nervous system and other organs and tissues. Furthermore, the transcriptional markers, molecular signaling pathways and risk factors for long COVID, such as sex, age, pre-existing condition, hospitalization during acute phase of COVID-19, vaccination, and lifestyle are presented. Finally, recommendations for patient rehabilitation and disease management, as well as alternative therapeutical approaches to long COVID sequelae are discussed. Understanding the complexity of this disease, its symptoms across multiple organ systems and overlapping pathologies and its possible mechanisms are paramount in developing diagnostic tools and treatments.

Approaches to long COVID care: the Veterans Health Administration experience in 2021

BMJ Mil Health. 2024 Mar 20;170(2):179-180. doi: 10.1136/military-2022-002185.

Allison M Gustavson 1 2, T L Eaton 3 4, R M Schapira 5 6, T J Iwashyna 7 8, M Adly 9 10, A Purnell 9

Affiliations

1VA Health Services Research and Development, Center for Care Delivery and Outcomes Research, Minneapolis, Minnesota, USA.

2Department of Medicine, Division of General Internal Medicine, University of Minnesota System, Minneapolis, Minnesota, USA.

3Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, Michigan, USA tameat@med.umich.edu.

4School of Nursing, University of Michigan, Ann Arbor, MI, USA.

5Research Service, New Orleans VA Medical Center, New Orleans, Louisiana, USA.

6Department of Internal Medicine, Tulane University School of Medicine, New Orleans, Louisiana, USA.

7Department of Medicine, Division of Pulmonary and Critical Care, University of Michigan Michigan Medicine, Ann Arbor, Michigan, USA.

8Veterans Affairs Center for Clinical Management Research, Ann Arbor, Michigan, USA.

9Central Office, US Department of Veterans Affairs, Washington, DC, USA.

10Office of the Chief Technology Officer, US Department of Veterans Affairs, Washington, DC, USA.

No abstract available

Precision nutrition to reset virus-induced human metabolic reprogramming and dysregulation (HMRD) in long-COVID

NPJ Sci Food. 2024 Mar 30;8(1):19. doi: 10.1038/s41538-024-00261-2.

A Satyanarayan Naidu 1 2, Chin-Kun Wang 3 4, Pingfan Rao 3 5, Fabrizio Mancini 3 6 7, Roger A Clemens 3 8, Aman Wirakartakusumah 9 10, Hui-Fang Chiu 11, Chi-Hua Yen 12, Sebastiano Porretta 3 13 14, Issac Mathai 3 15, Sreus A G Naidu 3 16

Affiliations

1Global Nutrition Healthcare Council (GNHC) Mission-COVID, Yorba Linda, CA, USA. asnaidu@nterminus.com.

2N-terminus Research Laboratory, 232659 Via del Rio, Yorba Linda, CA, 92887, USA. asnaidu@nterminus.com.

3Global Nutrition Healthcare Council (GNHC) Mission-COVID, Yorba Linda, CA, USA.

4School of Nutrition, Chung Shan Medical University, 110, Section 1, Jianguo North Road, Taichung, 40201, Taiwan.

5College of Food and Bioengineering, Fujian Polytechnic Normal University, No.1, Campus New Village, Longjiang Street, Fuqing City, Fujian, China.

6World Federation of Chiropractic, Toronto, ON, Canada.

7President-Emeritus, Parker University, 2540 Walnut Hill Lane, Dallas, TX, 75229, USA.

8University of Southern California, Alfred E. Mann School of Pharmacy/D. K. Kim International Center for Regulatory & Quality Sciences, 1540 Alcazar St., CHP 140, Los Angeles, CA, 90089, USA.

9International Union of Food Science and Technology (IUFoST), Guelph, ON, Canada.

10IPMI International Business School Jakarta; South East Asian Food and Agriculture Science and Technology, IPB University, Bogor, Indonesia.

11Department of Chinese Medicine, Taichung Hospital, Ministry of Health & Well-being, Taichung, Taiwan.

12Department of Family and Community Medicine, Chung Shan Medical University Hospital; School of Medicine, Chung Shan Medical University, Taichung, Taiwan.

13President, Italian Association of Food Technology (AITA), Milan, Italy.

14Experimental Station for the Food Preserving Industry, Department of Consumer Science, Viale Tanara 31/a, I-43121, Parma, Italy.

15Soukya International Holistic Health Center, Whitefield, Bengaluru, India.

16N-terminus Research Laboratory, 232659 Via del Rio, Yorba Linda, CA, 92887, USA.

Abstract

SARS-CoV-2, the etiological agent of COVID-19, is devoid of any metabolic capacity; therefore, it is critical for the viral pathogen to hijack host cellular metabolic machinery for its replication and propagation. This single-stranded RNA virus with a 29.9 kb genome encodes 14 open reading frames (ORFs) and initiates a plethora of virus-host protein-protein interactions in the human body. These extensive viral protein interactions with host-specific cellular targets could trigger severe human metabolic reprogramming/dysregulation (HMRD), a rewiring of sugar-, amino acid-, lipid-, and nucleotide-metabolism(s), as well as altered or impaired bioenergetics, immune dysfunction, and redox imbalance in the body. In the infectious process, the viral pathogen hijacks two major human receptors, angiotensin-converting enzyme (ACE)-2 and/or neuropilin (NRP)-1, for initial adhesion to cell surface; then utilizes two major host proteases, TMPRSS2 and/or furin, to gain cellular entry; and finally employs an endosomal enzyme, cathepsin L (CTSL) for fusogenic release of its viral genome. The virus-induced HMRD results in 5 possible infectious outcomes: asymptomatic, mild, moderate, severe to fatal episodes; while the symptomatic acute COVID-19 condition could manifest into 3 clinical phases: (i) hypoxia and hypoxemia (Warburg effect), (ii) hyperferritinemia ('cytokine storm'), and (iii) thrombocytosis (coagulopathy). The mean incubation period for COVID-19 onset was estimated to be 5.1 days, and most cases develop symptoms after

14 days. The mean viral clearance times were 24, 30, and 39 days for acute, severe, and ICU-admitted COVID-19 patients, respectively. However, about 25-70% of virus-free COVID-19 survivors continue to sustain virus-induced HMRD and exhibit a wide range of symptoms that are persistent, exacerbated, or new 'onset' clinical incidents, collectively termed as post-acute sequelae of COVID-19 (PASC) or long COVID. PASC patients experience several debilitating clinical condition(s) with >200 different and overlapping symptoms that may last for weeks to months. Chronic PASC is a cumulative outcome of at least 10 different HMRD-related pathophysiological mechanisms involving both virus-derived virulence factors and a multitude of innate host responses. Based on HMRD and virus-free clinical impairments of different human organs/systems, PASC patients can be categorized into 4 different clusters or sub-phenotypes: sub-phenotype-1 (33.8%) with cardiac and renal manifestations; sub-phenotype-2 (32.8%) with respiratory, sleep and anxiety disorders; sub-phenotype-3 (23.4%) with skeleto-muscular and nervous disorders; and sub-phenotype-4 (10.1%) with digestive and pulmonary dysfunctions. This narrative review elucidates the effects of viral hijack on host cellular machinery during SARS-CoV-2 infection, ensuing detrimental effect(s) of virus-induced HMRD on human metabolism, consequential symptomatic clinical implications, and damage to multiple organ systems; as well as chronic pathophysiological sequelae in virus-free PASC patients. We have also provided a few evidence-based, human randomized controlled trial (RCT)-tested, precision nutrients to reset HMRD for health recovery of PASC patients.