Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations Concerning Long Haul COVID-19 April, May, June 2023

Prepared by Staff of the RACGWVI.

RACGWVI: Long Haul COVID-19 — PubMed Citations for April, May, June 2023

The following is a list of published research projects that focus on Long Haul COVID-19 for the months of April, May and June 2023.

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

Insights for COVID-19 in 2023

Rev Esp Quimioter. 2023 Apr;36(2):114-124. doi: 10.37201/req/122.2022. Epub 2022 Dec 13.

F J Martín Sánchez, M Martínez-Sellés, J M Molero García, S Moreno Guillén, F J Rodríguez-Artalejo, J Ruiz-Galiana, R Cantón, P De Lucas Ramos, A García-Botella, A García-Lledó, T Hernández-Sampelayo, J Gómez-Pavón, J González Del Castillo, M C Martín-Delgado, E Bouza 1

Affiliation

1Servicio de Microbiología Clínica y Enfermedades Infecciosas del Hospital General Universitario Gregorio Marañón, Universidad Complutense. CIBERES. Ciber de Enfermedades Respiratorias. Madrid, Spain. emilio.bouza@gmail.com.

Abstract in English, Spanish

Predictions for a near end of the pandemic by the World Health Organization should be interpreted with caution. Current evidence indicates that the efficacy of a fourth dose of classical mRNA vaccines (BT162b2 or mRNA-1273) is low and short-lived in preventing SARS-CoV-2 infection in its predominant variant (Omicron). However, its efficacy is high against severe symptomatic infection, hospitalization and death. The new vaccines being introduced are bivalent and active against the Omicron variants. Potential new vaccines to be introduced in the coming year include a vaccine based on a recombinant protein that emulates the receptor binding domain of the Spike protein under development by the Spanish company Hipra, as well as vaccines for nasal or oral administration. Available information suggests that vaccines against COVID-19 can be administered in association with influenza vaccination without particular complications. New drugs against COVID-19, both antiviral and anti-inflammatory, are under investigation, but this does not seem to be the case with monoclonal antibodies. The indication to use masks in some circumstances will be maintained next year in view of the accumulation of scientific data on their efficacy. Finally, the long COVID or Post-COVID syndrome may continue to affect a very high proportion of patients who have had the disease, requiring combined diagnostic and therapeutic resources.

Long-COVID syndrome: physical-mental interplay in the spotlight

Inflammopharmacology. 2023 Apr;31(2):559-564. doi: 10.1007/s10787-023-01174-4. Epub 2023 Mar 9.

Carolin Thurner 1, Andreas Stengel 2 3

Affiliations

1Department of Psychosomatic Medicine and Psychotherapy, University Hospital Tübingen, Tübingen, Germany.

2Department of Psychosomatic Medicine and Psychotherapy, University Hospital Tübingen, Tübingen, Germany. andreas.stengel@med.uni-tuebingen.de.

3Charité Center for Internal Medicine and Dermatology, Medical Clinic for Psychosomatic Medicine, Charité Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität Zu Berlin and Berlin Institute of Health, Berlin, Germany. andreas.stengel@med.uni-tuebingen.de.

Abstract

Patients suffering from Long-COVID syndrome experience a variety of different symptoms on a physical, but also on a psychological and social level. Previous psychiatric conditions such as depression and anxiety have been identified as separate risk factors for developing Long-COVID syndrome. This suggests a complex interplay of different physical and mental factors rather than a simple cause-effect relationship of a specific biological pathogenic process. The biopsychosocial model provides a foundation for understanding these interactions and integrating them into a broader perspective of the patient suffering from the disease instead of the individual symptoms, pointing towards the need of treatment options on a psychological as well as social level besides biological targets. This leads to our conclusion, that the biopsychosocial model should be the underlying philosophy of understanding, diagnosing and treating patients suffering from Long-COVID syndrome, moving away from the strictly biomedical understanding suspected by many patients, treaters and the media while also reducing the stigma still associated with the suggestion of a physical-mental interplay.

In-depth characterization of long-term humoral and cellular immune responses to COVID-19m-RNA vaccination in multiple sclerosis patients treated with teriflunomide or alemtuzumab

Mult Scler Relat Disord. 2023 Apr;72:104616. doi: 10.1016/j.msard.2023.104616. Epub 2023 Mar 12.

Anat Achiron 1, Mathilda Mandel 2, Sapir Dreyer-Alster 2, David Magalashvili 2, Shay Menascu 3, Yehuda Warszawer 2, Mark Dolev 3, Maria Didikin 2, Gil Harari 4, Polina Sonis 2, Rina Falb 2, Michael Gurevich 3

Affiliations

1Multiple Sclerosis Center, Sheba Medical Center, Ramat-Gan, Israel; Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel.. Electronic address: Anat.achiron@sheba.health.gov.il.

2Multiple Sclerosis Center, Sheba Medical Center, Ramat-Gan, Israel.

3Multiple Sclerosis Center, Sheba Medical Center, Ramat-Gan, Israel; Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

4School of Public Health, University of Haifa, Israel.

Abstract

Background: The impact of disease-modifying therapies on the efficacy to mount appropriate immune responses to COVID-19 vaccination in patients with multiple sclerosis (MS) is currently under investigation.

Objective: To characterize long-term humoral and cellular immunity in mRNA-COVID-19 MS vaccinees treated with teriflunomide or alemtuzumab.

Methods: We prospectively measured SARS-COV-2 IgG, memory B-cells specific for SARS-CoV-2 RBD, and memory T-cells secreting IFN-γ and/or IL-2, in MS patients vaccinated with BNT162b2-COVID-19 vaccine before, 1, 3 and 6 months after the second vaccine dose, and 3-6 months following vaccine booster.

Results: Patients were either untreated (N = 31, 21 females), under treatment with teriflunomide (N = 30, 23 females, median treatment duration 3.7 years, range 1.5-7.0 years), or under treatment with alemtuzumab (N = 12, 9 females, median time from last dosing 15.9 months, range 1.8-28.7 months). None of the patients had clinical SARS-CoV-2 or immune evidence for prior infection. Spike IgG titers were similar between untreated, teriflunomide and alemtuzumab treated MS patients both at 1 month (median 1320.7, 25-75 IQR 850.9-3152.8 vs. median 901.7, 25-75 IQR 618.5-1495.8, vs. median 1291.9, 25-75 IQR 590.8-2950.9, BAU/ml, respectively), at 3 months (median 1388.8, 25-75 1064.6-2347.6 vs. median 1164.3 25-75 IQR 726.4-1399.6, vs. median 837.2, 25-75 IQR 739.4-1868.5 BAU/ml, respectively), and at 6 months (median 437.0, 25-75 206.1-1161.3 vs. median 494.3, 25-75 IQR 214.6-716.5, vs. median 176.3, 25-75 IQR 72.3-328.8 BAU/ml, respectively) after the second vaccine dose. Specific SARS-CoV-2 memory B cells were detected in 41.9%, 40.0% and 41.7% of subjects at 1 month, in 32.3%, 43.3% and 25% at 3 months, and in 32.3%, 40.0%, 33.3% at 6 months following vaccination in untreated, teriflunomide treated and alemtuzumab treated MS patients, respectively. Specific SARS-CoV-2 memory T cells were found in 48.4%, 46.7% and 41.7 at 1 month, in 41.9%, 56.7% and 41.7% at 3 months, and in 38.7%, 50.0%, and 41.7% at 6 months, of untreated, teriflunomide-treated and alemtuzumab - treated MS patients, respectively. Administration of a third vaccine booster significantly increased both humoral and cellular responses in all patients.

Conclusions: MS patients treated with teriflunomide or alemtuzumab achieved effective humoral and cellular immune responses up to 6 months following second COVID-19 vaccination. Immune responses were reinforced following the third vaccine booster.

What is really 'Long COVID'?

Inflammopharmacology. 2023 Apr;31(2):551-557. doi: 10.1007/s10787-023-01194-0. Epub 2023 Mar 25.

Sandor Szabo 1, Oksana Zayachkivska 2, Alamdar Hussain 2, Veronika Muller 2 3

Affiliations

1School of Medicine, American University of Health Sciences, 1600 East Hill St., Signal Hill/Long Beach, CA, 90755, USA. sszabo@auhs.edu.

2School of Medicine, American University of Health Sciences, 1600 East Hill St., Signal Hill/Long Beach, CA, 90755, USA.

3Department of Pulmonology, Semmelweis University, Budapest, Hungary.

Abstract

The previous acute respiratory diseases caused by viruses originating from China or the middle east (e.g., SARS, MERS) remained fast developing short diseases without major sequalae or any long-lasting complications. The new COVID-19, on the other hand, not only that it rapidly spread over the world, but some patients never fully recovered or even if they did, a few weeks later started to complain not only of shortness of breath, if any, but general weakness, muscle pains and 'brain fog', i.e., fuzzy memories. Thus, these signs and symptoms were eventually labelled 'long COVID', for which the most widely used definition is 'new signs and symptoms occurring 4-8 weeks after recovering from acute stage of COVID-19'. The other most frequent manifestations associated with long COVID include headache, loss of memory, smell and of hair, nausea, and vomiting. Thus, long COVID is not a simple disease, but complex disorder of several organ systems malfunctioning; hence, it is probably more appropriate to call this a syndrome. The pathogenesis of long COVID syndrome is poorly understood, but initial and persistent vascular endothelial injury that often triggers the formation of microthrombi that if dislodged as emboli, damage several organs, especially in the brain, heart and kidney, by creating microinfarcts. The other major contributory mechanistic factor is the persistent cytokine storm that may last longer in long COVID patients than in others, probably triggered by aggregates of SARS-Co-2 discovered recently in the adrenal cortex, kidney and brain. The prevalence of long COVID is relatively high, e.g., initially varied 3-30%, and recent data indicate that 2.5% of UK population suffers from this syndrome, while in the US 14.7% of acute COVID-19 patients continued to have symptoms longer than 2 months. Thus, the long COVID syndrome deserves to be further investigated, both from clinical and basic research perspectives.

Insufficient epitope-specific T cell clones are responsible for impaired cellular immunity to inactivated SARS-CoV-2 vaccine in older adults

Nat Aging. 2023 Apr;3(4):418-435. doi: 10.1038/s43587-023-00379-0. Epub 2023 Mar 13.

Chanchan Xiao # 1 2 3, Zhiyao Ren # 2 4 5 6 7, Bei Zhang # 4, Lipeng Mao # 2 4, Guodong Zhu # 2 5, Lijuan Gao 1 2, Jun Su 8, Jiezhou Ye 1 2, Ze Long 1 2, Yue Zhu 2 4, Pengfei Chen 1 2, Xiangmeng Su 1 2, Tong Zhou 1 2, Yanhao Huang 1 2, Xiongfei Chen 9, Chaojun Xie 9, Jun Yuan 9, Yutian Hu 10, Jingshan Zheng 11, Zhigang Wang 8, Jianrong Lou 12, Xiang Yang 12, Zhiqiang Kuang 8, Hongyi Zhang 1 2, Pengcheng Wang 13 14, Xiaofeng Liang 15, Oscar Junhong Luo 16 17, Guobing Chen 18 19 20 21

Affiliations

1Department of Microbiology and Immunology; Institute of Geriatric Immunology; School of Medicine, Jinan University, Guangzhou, China.

2Guangdong-Hong Kong-Macau Great Bay Area Geroscience Joint Laboratory, School of Medicine, Jinan University, Guangzhou, China.

3Guangzhou Laboratory, Guangzhou, China.

4Department of Systems Biomedical Sciences, School of Medicine, Jinan University, Guangzhou, China.

5Guangzhou Geriatric Hospital, Guangzhou, China.

6NHC Key Laboratory of Male Reproduction and Genetics, Guangzhou, China.

7Department of Central Laboratory, Guangdong Provincial Reproductive Science Institute (Guangdong Provincial Fertility Hospital), Guangzhou, China.

8Affiliated Huaqiao Hospital, Jinan University, Guangzhou, China.

9Guangzhou Center for Disease Control and Prevention, Guangzhou, China.

10Meng Yi Center Limited, Macau, China.

11Shenzhen Kangtai Biological Products Co. Ltd, Shenzhen, China.

12Leidebio Bioscience Co., Ltd., Guangzhou, China.

13Department of Microbiology and Immunology; Institute of Geriatric Immunology; School of Medicine, Jinan University, Guangzhou, China. twangpc@jnu.edu.cn.

14Guangdong-Hong Kong-Macau Great Bay Area Geroscience Joint Laboratory, School of Medicine, Jinan University, Guangzhou, China. twangpc@jnu.edu.cn.

15Department of Public Health and Preventive Medicine, School of Medicine, Jinan University, Guangzhou, China. liangxf@jnu.edu.cn.

16Guangdong-Hong Kong-Macau Great Bay Area Geroscience Joint Laboratory, School of Medicine, Jinan University, Guangzhou, China. luojh@jnu.edu.cn.

17Department of Systems Biomedical Sciences, School of Medicine, Jinan University, Guangzhou, China. luojh@jnu.edu.cn.

18Department of Microbiology and Immunology; Institute of Geriatric Immunology; School of Medicine, Jinan University, Guangzhou, China. guobingchen@jnu.edu.cn.

19Guangdong-Hong Kong-Macau Great Bay Area Geroscience Joint Laboratory, School of Medicine, Jinan University, Guangzhou, China. guobingchen@jnu.edu.cn.

20Guangzhou Laboratory, Guangzhou, China. guobingchen@jnu.edu.cn.

21Affiliated Huaqiao Hospital, Jinan University, Guangzhou, China. guobingchen@jnu.edu.cn.

Abstract

Aging is a critical risk factor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine efficacy. The immune responses to inactivated vaccine for older adults, and the underlying mechanisms of potential differences to young adults, are still unclear. Here we show that neutralizing antibody production by older adults took a longer time to reach similar levels in young adults after inactivated SARS-CoV-2 vaccination. We screened SARS-CoV-2 variant strains for epitopes that stimulate specific CD8 T cell response, and older adults exhibited weaker CD8 T-cell-

mediated responses to these epitopes. Comparison of lymphocyte transcriptomes from pre-vaccinated and post-vaccinated donors suggested that the older adults had impaired antigen processing and presentation capability. Single-cell sequencing revealed that older adults had less T cell clone expansion specific to SARS-CoV-2, likely due to inadequate immune receptor repertoire size and diversity. Our study provides mechanistic insights for weaker response to inactivated vaccine by older adults and suggests the need for further vaccination optimization for the old population.

Design and analysis of outcomes following SARS-CoV-2 infection in veterans

BMC Med Res Methodol. 2023 Apr 4;23(1):81. doi: 10.1186/s12874-023-01882-z.

Valerie A Smith 1 2 3, Theodore S Z Berkowitz 1, Paul Hebert 4 5, Edwin S Wong 4 5, Meike Niederhausen 6 7 8, John A Pura 1, Kristin Berry 4 9, Pamela Green 4, Anna Korpak 9, Alexandra Fox 9, Aaron Baraff 9, Alex Hickok 6, Troy A Shahoumian 10, Amy S B Bohnert 11 12, Denise M Hynes 6 13, Edward J Boyko 9, George N Ioannou 4 14, Theodore J Iwashyna 11 15 16, C Barrett Bowling 1 17 18, Ann M O'Hare 4 19, Matthew L Maciejewski 20 21 22

Affiliations

1Center of Innovation to Accelerate Discovery and Practice Transformation, Durham VA Medical Center, Durham, NC, USA.

2Department of Population Health Sciences, Duke University, Durham, NC, USA.

3Division of General Internal Medicine, Department of Medicine, Duke University, Durham, NC, USA.

4Health Services Research & Development Center of Innovation for Veteran-Centered and Value-Driven Care, and Gastroenterology section, Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA.

5Department of Health Systems and Population Health, University of Washington, Seattle, WA, USA.

6Center to Improve Veteran Involvement in Care, VA Portland Health Care System, Portland, OR, USA.

7Oregon Health & Science University (OHSU), Portland, OR, USA.

8Portland State University School of Public Health, Portland, OR, USA.

9Seattle Epidemiologic Research and Information Center, VA Puget Sound, Seattle, WA, USA.

10Population Health: Health Solutions, Veterans Health Administration, Washington, DC, USA.

11VA Center for Clinical Management Research, Ann Arbor, VA, MI, USA.

12Departments of Anesthesiology and Psychiatry, University of Michigan Medical School, Ann Arbor, MI, USA.

13College of Public Health and Human Sciences, Center for Quantitative Life Sciences, Oregon State University, Corvallis, OR, USA.

14Division of Gastroenterology, University of Washington, Seattle, WA, USA.

15National Clinical Scholars Program, University of Michigan Medical School, Ann Arbor, MI, USA.

16Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA.

17Geriatric Research Education and Clinical Center, Durham VA Medical Center, Durham, NC, USA.

18Department of Medicine, Duke University, Durham, NC, USA.

19Division of Nephrology, University of Washington, Seattle, WA, USA.

20Center of Innovation to Accelerate Discovery and Practice Transformation, Durham VA Medical Center, Durham, NC, USA. mlm34@duke.edu.

21Department of Population Health Sciences, Duke University, Durham, NC, USA. mlm34@duke.edu.

22Division of General Internal Medicine, Department of Medicine, Duke University, Durham, NC, USA. mlm34@duke.edu.

Abstract

Background: Understanding how SARS-CoV-2 infection impacts long-term patient outcomes requires identification of comparable persons with and without infection. We report the design and implementation of a matching strategy employed by the Department of Veterans Affairs' (VA) COVID-19 Observational Research Collaboratory (CORC) to develop comparable cohorts of SARS-CoV-2 infected and uninfected persons for the purpose of inferring potential causative long-term adverse effects of SARS-CoV-2 infection in the Veteran population.

Methods: In a retrospective cohort study, we identified VA health care system patients who were and were not infected with SARS-CoV-2 on a rolling monthly basis. We generated matched cohorts within each month utilizing a combination of exact and time-varying propensity score matching

based on electronic health record (EHR)-derived covariates that can be confounders or risk factors across a range of outcomes.

Results: From an initial pool of 126,689,864 person-months of observation, we generated final matched cohorts of 208,536 Veterans infected between March 2020-April 2021 and 3,014,091 uninfected Veterans. Matched cohorts were well-balanced on all 39 covariates used in matching after excluding patients for: no VA health care utilization; implausible age, weight, or height; living outside of the 50 states or Washington, D.C.; prior SARS-CoV-2 diagnosis per Medicare claims; or lack of a suitable match. Most Veterans in the matched cohort were male (88.3%), non-Hispanic (87.1%), white (67.2%), and living in urban areas (71.5%), with a mean age of 60.6, BMI of 31.3, Gagne comorbidity score of 1.4 and a mean of 2.3 CDC high-risk conditions. The most common diagnoses were hypertension (61.4%), diabetes (34.3%), major depression (32.2%), coronary heart disease (28.5%), PTSD (25.5%), anxiety (22.5%), and chronic kidney disease (22.5%).

Conclusion: This successful creation of matched SARS-CoV-2 infected and uninfected patient cohorts from the largest integrated health system in the United States will support cohort studies of outcomes derived from EHRs and sample selection for qualitative interviews and patient surveys. These studies will increase our understanding of the long-term outcomes of Veterans who were infected with SARS-CoV-2.

Use of either transcranial or whole-body photobiomodulation treatments improves COVID-19 brain fog

J Biophotonics. 2023 Apr 5;e202200391. doi: 10.1002/jbio.202200391. Online ahead of print.

Robert Bowen 1 2, Praveen R Arany 1 3

Affiliations

1Shepherd University, Shepherdstown, West Virginia, USA.

2West Virginia University, Martinsburg, West Virginia, USA.

3University at Buffalo, Buffalo, New York, USA.

Abstract

There is increasing recognition of post-COVID-19 sequelae involving chronic fatigue and brain fog, for which photobiomodulation (PBM) therapy has been utilized. This open-label, pilot, human clinical study examined the efficacy of two PBM devices, for example, a helmet (1070 nm) for transcranial (tPBM) and a light bed (660 and 850 nm) for whole body (wbPBM), over a 4-week period, with 12 treatments for two separate groups (n = 7 per group). Subjects were evaluated with a neuropsychological test battery, including the Montreal Cognitive Assessment (MoCA), the digit symbol substitution test (DSST), the trail-making tests A and B, the physical reaction time (PRT), and a quantitative electroencephalography system (WAVi), both pre- and post- the treatment series. Each device for PBM delivery was associated with significant improvements in cognitive tests ($p < 0.05$ and beyond). Changes in WAVi supported the findings. This study outlines the benefits of utilizing PBM therapy (transcranial or whole-body) to help treat long-COVID brain fog.

Exercise Pathophysiology in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Post-Acute Sequelae of SARS-CoV-2: More in Common Than Not?

Review Chest. 2023 Apr 11;S0012-3692(23)00502-0. doi: 10.1016/j.chest.2023.03.049. Online ahead of print.

Phillip Joseph 1, Inderjit Singh 1, Rudolf Oliveira 2, Christine A Capone 3, Mary P Mullen 4, Dane B Cook 5, Mary Catherine Stovall 6, Johanna Squires 6, Kristine Madsen 6, Aaron B Waxman 6, David M Systrom 7

Affiliations

1Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Yale-New, Haven Hospital, Yale University, New Haven, Connecticut, USA.

2Division of Respiratory Diseases; Department of Medicine; Federal University of Sao Paulo, (UNIFESP); Sao Paulo, Brazil.

3Division of Pediatric Cardiology; Department of Pediatrics; Cohen Children's Medical Center, Northwell Health, Donald and Barbara Zucker School of Medicine at Hofstra; Manhasset, NY, USA.

4Department of Cardiology; Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

5Research Service, William S. Middleton Memorial Veterans Hospital & Department of Kinesiology, University of Wisconsin-Madison, Madison, Wisconsin, USA.

6Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

7Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. Electronic address: dsystrom@bwh.harvard.edu.

Abstract

Topic importance: Post-Acute Sequelae of SARS-CoV-2 (PASC) is a long-term consequence of acute infection from coronavirus disease 2019 (COVID-19). Clinical overlap between PASC and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has been observed, with shared symptoms including intractable fatigue, postexertional malaise, and orthostatic intolerance. The mechanistic underpinnings of such symptoms are poorly understood.

Review findings: Early studies suggest deconditioning as the primary explanation for exertional intolerance in PASC. Cardiopulmonary exercise testing (CPET) reveals perturbations related to systemic blood flow and ventilatory control associated with acute exercise intolerance in PASC, which are not typical of simple detraining. Hemodynamic and gas exchange derangements in PASC have substantial overlap with those observed with ME/CFS, suggestive of shared mechanisms.

Summary: This review aims to illustrate exercise pathophysiologic commonalities between PASC and ME/CFS that will help guide future diagnostics and treatment.

Post-exertional malaise among people with long COVID compared to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Work. 2023;74(4):1179-1186. doi: 10.3233/WOR-220581.

Suzanne D Vernon 1, Megan Hartle 2, Karen Sullivan 1, Jennifer Bell 1, Saeed Abbaszadeh 1, Derya Unutmaz 3 4, Lucinda Bateman 1

Affiliations

1The Bateman Horne Center of Excellence, Salt Lake City, UT, USA.

2Drake University, Des Moines, IA, USA.

3Jackson Laboratory for Genomic Medicine, Farmington, CT, USA.

4University of Connecticut School of Medicine, Farmington, CT, USA.

Abstract

Background: Long COVID describes a condition with symptoms that linger for months to years following acute COVID-19. Many of these Long COVID symptoms are like those experienced by patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Objective: We wanted to determine if people with Long COVID experienced post-exertional malaise (PEM), the hallmark symptom of ME/CFS, and if so, how it compared to PEM experienced by patients with ME/CFS.

Methods: A questionnaire that asked about the domains of PEM including triggers, experience, recovery, and prevention was administered to 80 people seeking care for Long COVID at Bateman Horne Center. Their responses were compared to responses about PEM given by 151 patients with ME/CFS using chi-square tests of independence.

Results: All but one Long COVID respondent reported having PEM. There were many significant differences in the types of PEM triggers, symptoms experienced during PEM, and ways to recover and prevent PEM between Long COVID and ME/CFS. Similarities between Long COVID and ME/CFS included low and medium physical and cognitive exertion to trigger PEM, symptoms of fatigue, pain, immune reaction, neurologic, orthostatic intolerance, and gastrointestinal symptoms during PEM, rest to recover from PEM, and pacing to prevent PEM.

Conclusion: People with Long COVID experience PEM. There were significant differences in PEM experienced by people with Long COVID compared to patients with ME/CFS. This may be due to the newness of Long COVID, not knowing what exertional intolerance is or how to manage it.

COVID-19 and its long-term sequelae: what do we know in 2023?

Pol Arch Intern Med. 2023 Apr 19;133(4):16402. doi: 10.20452/pamw.16402. Epub 2023 Jan 9.

Giuseppe Lippi # 1, Fabian Sanchis-Gomar # 2, Brandon M Henry 3

Affiliations

1Section of Clinical Biochemistry and School of Medicine, University of Verona, Verona, Italy. giuseppe.lippi@univr.it

2Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, United States

3Clinical Laboratory, Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

#Contributed equally.

Abstract

Post-viral syndrome is a well-known medical condition characterized by different levels of physical, cognitive, and emotional impairment that may persist with fluctuating severity after recovering from an acute viral infection. Unsurprisingly, COVID-19 may also be accompanied by medium- and long-term clinical sequelae after recovering from a SARS-CoV-2 infection. Although many clinical definitions have been provided, "long-COVID" can be defined as a condition occurring in patients with a history of SARS-CoV-2 infection, developing 3 months from the symptoms onset, persisting for at least 2 months, and not explained by alternative diagnoses. According to recent global analyses, the cumulative prevalence of long-COVID seems to range between 9% and 63%, and is up to 6-fold higher than that of similar postviral infection conditions. Long-COVID primarily encompasses the presence of at least 1 symptom, such as fatigue, dyspnea, cognitive impairment / brain fog, postexertional malaise, memory issues, musculoskeletal pain / spasms, cough, sleep disturbances, tachycardia / palpitations, altered smell / taste perception, headache, chest pain, and depression. The most important demographic and clinical predictors to date are female sex, older age, cigarette smoking, pre-existing medical conditions, lack of COVID-19 vaccination, infection with pre-Omicron SARS-CoV-2 variants, number of acute phase symptoms, viral load, severe / critical COVID-19 illness, as well as invasive mechanical ventilation. Concerning the care for long-COVID patients, the greatest challenge is the fact that this syndrome cannot be considered a single clinical entity, and thus it needs an integrated multidisciplinary management, specifically tailored to the type and severity of symptoms.

Clinical assessment of children with long COVID syndrome

Pediatr Res. 2023 May;93(6):1616-1625. doi: 10.1038/s41390-022-02378-0. Epub 2022 Dec 7.

Réka Garai # 1 2 3, Péter Krivácsy # 4 5 6, Vivien Herczeg 1 2, Fanni Kovács 1 2, Bálint Tél 1 2, Judit Kelemen 1 2, Anna Máthé 1 2 3 7, Eszter Zsáry 1 2 7, Johanna Takács 8, Dániel Sándor Veres 9, Attila J Szabó 1 2 3 10

Affiliations

1st Department of Pediatrics, Semmelweis University, Budapest, Hungary.

2Semmelweis Pediatric Long COVID Research Group, Budapest, Hungary.

3Centre for Translational Medicine, Semmelweis University, Budapest, Hungary.

41st Department of Pediatrics, Semmelweis University, Budapest, Hungary. krivacsy.peter@med.semmelweis-univ.hu.

5Semmelweis Pediatric Long COVID Research Group, Budapest, Hungary. krivacsy.peter@med.semmelweis-univ.hu.

6Centre for Translational Medicine, Semmelweis University, Budapest, Hungary. krivacsy.peter@med.semmelweis-univ.hu.

7Faculty of Medicine, Semmelweis University, Budapest, Hungary.

8Department of Social Sciences, Faculty of Health Sciences, Semmelweis University, Budapest, Hungary.

9Department of Biophysics and Radiation Biology, Semmelweis University, Budapest, Hungary.

10ELKH-SE Pediatrics and Nephrology Research Group, Budapest, Hungary.

#Contributed equally.

Abstract

Background: There is a need for further understanding pediatric long COVID syndrome (LCS) to be able to create specific case definitions and guidelines for providing good clinical care.

Methods: Medical records of all LCS patients who presented at our designated LC clinic were collected. We carried out descriptive analyses summarizing the history, clinical presentation, and findings of children, while doing a diagnosis of exclusion with multi-disciplinary medical examinations (physical, laboratory, and radiological examinations, specialist consultations, etc.) without a control group.

Results: Most children reported at least minor impairment to their quality of life, of which 17 (23%) had moderate or severe difficulties. Findings that could be directly connected to the linked complaint category were observed in an average of 18%, respiratory symptoms with objective alterations being the most frequent (37%). Despite our detecting mostly non-specific conditions, in a smaller number we identified well-described causes such as autoimmune thyroiditis (7%).

Conclusions: The majority of children stated an impairment in their quality of life, while symptom-related conditions were detected only in a minority. Controlled studies are needed to separate the effect of the pandemic era from the infection itself. Evidence-based pediatric guidelines could aid to rationalize the list of recommended examinations.

Impact: Long COVID syndrome is a complex entity with a great impact on children's everyday lives. Still, there is no clear guidance for pediatric clinical management. Systematic, detailed studies with medical assessment findings could aid the process of creating evidence-based guidelines. We present validated systematic information collected during in-person medical assessments with detailed medical findings and quality of life changes. While making a diagnosis of exclusion, we could confirm symptom-related conditions only in a minority of children; however, the majority reported at least minor impairment to their quality of life.

Complement and COVID-19: Three years on, what we know, what we don't know, and what we ought to know

Immunobiology. 2023 May;228(3):152393. doi: 10.1016/j.imbio.2023.152393. Epub 2023 May 11.

Wioleta M Zelek 1, Richard A Harrison 2

Affiliations

1Dementia Research Institute and Division of Infection and Immunity, School of Medicine, Cardiff University, Cardiff, United Kingdom.

2School of Medicine, Cardiff University, Cardiff, United Kingdom. Electronic address: harrisonR4@cardiff.ac.uk.

Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus was identified in China in 2019 as the causative agent of COVID-19, and quickly spread throughout the world, causing over 7 million deaths, of which 2 million occurred prior to the introduction of the first vaccine. In the following discussion, while recognising that complement is just one of many players in COVID-19, we focus on the relationship between complement and COVID-19 disease, with limited digression into directly-related areas such as the relationship between complement, kinin release, and coagulation. Prior to the 2019 COVID-19 outbreak, an important role for complement in coronavirus diseases had been established. Subsequently, multiple investigations of patients with COVID-19 confirmed that complement dysregulation is likely to be a major driver of disease pathology, in some, if not all, patients. These data fuelled evaluation of many complement-directed therapeutic agents in small patient cohorts, with claims of significant beneficial effect. As yet, these early results have not been reflected in larger clinical trials, posing questions such as who to treat, appropriate time to treat, duration of treatment, and optimal target for treatment. While significant control of the pandemic has been achieved through a global scientific and medical effort to comprehend the etiology of the disease, through extensive SARS-CoV-2 testing and quarantine measures, through vaccine development, and through improved therapy, possibly aided by attenuation of the dominant strains, it is not yet over. In this review, we summarise complement-relevant literature, emphasise its main conclusions, and formulate a hypothesis for complement involvement in COVID-19. Based on this we make suggestions as to how any future outbreak might be better managed in order to minimise impact on patients.

Containment of COVID-19 outbreak at a veterans affairs community living center

J Infect Prev. 2023 May;24(3):132-136. doi: 10.1177/17571774231158205. Epub 2023 Feb 22.

Khalid M Dousa 1, Laura Hmiel 2, Brian Klonowski 3, Trina F Zabarsky 3, Kimberly Pyatt 4, Usha Stiefel 5 6, Curtis J Donskey 5 6 7, Robin Lp Jump 5 6 7 8

Affiliations

1Division of Infectious Diseases and HIV Medicine, University Hospitals of Cleveland, Cleveland, OH, USA.

2Department of Medicine, University Hospitals of Cleveland, Cleveland, OH, USA.

3Infection Prevention and Control, VA Northeast Ohio Healthcare System, Cleveland, OH, USA.

4Nursing Service, VA Northeast Ohio Healthcare System, Cleveland, OH, USA.

5Infectious Diseases Section, VA Northeast Ohio Healthcare System, Cleveland, OH, USA.

6Division of Infectious Diseases and HIV Medicine, Department of Medicine, Case Western Reserve University, Cleveland, OH, USA.

7Geriatric Research Education and Clinical Center, VA Northeast Ohio Healthcare System, Cleveland, OH, USA.

8Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH, USA.

Abstract

Asymptomatic and pre-symptomatic staff and residents likely contribute to widespread transmission of COVID-19 in long-term care settings. Here, we describe the successful containment of a COVID-19 outbreak on one floor of a 163-bed Veterans Affairs (VA) Community Living Center (CLC). Testing using nasopharyngeal swabs with a rapid turn-around-time identified 3 of 28 (11%) residents and 2 of 41 (5%) healthcare personnel (HCP) with COVID-19. Both HCP likely worked on the floor while pre-symptomatic. When one HCP reported a cough to the secondary (employee) screening clinic, she was erroneously advised to work. Protocols to limit the risk for HCP to import COVID-19 were reinforced with Community Living Center staff as well as with personnel in secondary screening. Further, the CLC implemented an expanded screening tool that assessed residents for typical and atypical symptoms of COVID-19. No further cases of COVID-19 were detected on the CLC floor in the subsequent 6 weeks. Swift recognition and response helped contain the outbreak and prevent further COVID-19 infections among other residents and staff.

Transcranial and Transcutaneous Stimulation for Pain: What Have We Learned From the COVID-19 Pandemic Shutdown?

Pain Physician. 2023 May;26(3):E223-E231.

Albert Leung 1, Samar Alhaqab 2, Alphonsa Kunne 2, Dillon Leung 3, Paul Krug 2, Shahrokh Golshan 4

Affiliations

1Veterans Medical Research Foundation, San Diego, CA; Veteran Affairs San Diego Healthcare System, San Diego, CA; University of California, San Diego, School of Medicine, Department of Anesthesiology, La Jolla, CA.

2Veteran Affairs San Diego Healthcare System, San Diego, CA.

3University of California, Berkeley, Berkeley, CA.

4Veterans Medical Research Foundation, San Diego, CA.

Abstract

Background: Transcranial magnetic stimulation (TMS) and transcutaneous magnetic stimulation (tMS) offer a novel noninvasive treatment option for chronic pain. While the recent COVID-19 pandemic caused by the SARS-CoV-2 virus resulted in a temporary interruption of the treatments for patients, it provided an excellent opportunity to assess the long-term sustainability of the treatment, and the feasibility of resuming the treatments after a brief period of interruption as no such data are available in current literature.

Methods: First, a list of patients whose pain/headache conditions have been stably controlled with either treatment for at least 6 months prior to the 3-month pandemic-related shutdown was generated. Those who returned for treatments after the shutdown were identified and their underlying pain diagnoses, pre- and posttreatment Mechanical Visual Analog Scale (M-VAS) pain scores, 3-item Pain, Enjoyment, and General Activity (PEG-3), and Patient Health Questionnaire-9 scores were assessed in 3 phases: Phase I (P1) consisted of a 6-month pre-COVID-19 period in which pain conditions were stably managed with either treatment modality; Phase II (P2) consisted of the first treatment visit period immediately after COVID-19 shutdown; and Phase III (P3) consisted of a 3-4 month post-COVID-19 shutdown period patients received up to 3 sessions of either treatment modality after the P2 treatment.

Results: For pre- and posttreatment M-VAS pain scores, mixed-effect analyses for both treatment groups demonstrated significant ($P < 0.01$) time interactions across all phases. For pretreatment M-VAS pain scores, TMS (n = 27) between-phase analyses indicated a significant ($F = 13.572$, $P = 0.002$) increase from 37.7 ± 27.6 at P1 to 49.6 ± 25.9 at P2, which then decreased significantly ($F = 12.752$, $P = 0.001$) back to an average score of 37.1 ± 24.7 at P3. Similarly, tMS (n = 25) between-phase analyses indicated the mean pretreatment pain score (mean ± standard deviation [SD]) increased significantly ($F = 13.383$, $P = 0.003$) from 34.9 ± 25.1 at P1 to 56.3 ± 27.0 at P2, which then decreased significantly ($F = 5.464$, $P = 0.027$) back to an average score of 41.9 ± 26.4 at P3. For posttreatment pain scores, the TMS group between-phase analysis indicated the mean posttreatment pain score (mean ± SD) increased significantly ($F = 14.206$, $P = 0.002$) from 25.6 ± 22.9 at P1 to 36.2 ± 23.4 at P2, which then significantly decreased ($F = 16.063$, $P < 0.001$) back to an average score of 23.2 ± 21.3 at P3. The tMS group between-phase analysis indicates a significant ($F = 8.324$, $P = 0.012$) interaction between P1 and P2 only with the mean posttreatment pain score (mean ± SD) increased from 24.9 ± 25.7 at P1 to 36.9 ± 26.7 at P2. The combined PEG-3 score between-phase analyses demonstrated similar significant ($P < 0.001$) changes across the phases in both treatment groups.

Conclusions: Both TMS and tMS treatment interruptions resulted in an increase of pain/headache severity and interference of quality of life and functions. However, the pain/headache symptoms, patients' quality of life, or function can quickly be improved once the maintenance treatments were restarted.

Effectiveness and safety of coronavirus disease 2019 vaccines

Curr Opin Pulm Med. 2023 May 1;29(3):138-142. doi: 10.1097/MCP.0000000000000948. Epub 2023 Feb 24.

Ting Shi 1, Chris Robertson 2 3, Aziz Sheikh 1

Affiliations

1Usher Institute, Edinburgh Medical School, University of Edinburgh, Edinburgh.

2Department of Mathematics and Statistics, University of Strathclyde, Glasgow.

3Public Health Scotland, Glasgow, Scotland, UK.

Abstract

Purpose of review: To review and summarise recent evidence on the effectiveness of coronavirus disease 2019 (COVID-19) vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19 hospitalisation and death in adults as well as in specific population groups, namely pregnant women, and children and adolescents. We also sought to summarise evidence on vaccine safety in relation to cardiovascular and neurological complications. In order to do so, we drew primarily on evidence from two our own data platforms and supplement these with insights from related large population-based studies and systematic reviews.

Recent findings: All studies showed high vaccine effectiveness against confirmed SARS-CoV-2 infection and in particular against COVID-19 hospitalisation and death. However, vaccine effectiveness against symptomatic COVID-19 infection waned over time. These studies also found that booster vaccines would be needed to maintain high vaccine effectiveness against severe COVID-19 outcomes. Rare cardiovascular and neurological complications have been reported in association with COVID-19 vaccines.

Summary: The findings from this paper support current recommendations that vaccination remains the safest way for adults, pregnant women, children and adolescents to be protected against COVID-19. There is a need to continue to monitor the effectiveness and safety of COVID-19 vaccines as these continue to be deployed in the evolving pandemic.

COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences

Pathol Res Pract. 2023 May 3;246:154497. doi: 10.1016/j.prp.2023.154497. Online ahead of print.

Felix Scholkmann 1, Christian-Albrecht May 2

Affiliations

1University Hospital Zurich, University of Zurich, 8091 Zurich, Switzerland. Electronic address: Felix.Scholkmann@usz.ch.

2Department of Anatomy, Faculty of Medicine Carl Gustav Carus, TU Dresden, 01307 Dresden, Germany.

Abstract

Worldwide there have been over 760 million confirmed coronavirus disease 2019 (COVID-19) cases, and over 13 billion COVID-19 vaccine doses have been administered as of April 2023, according to the World Health Organization. An infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can lead to an acute disease, i.e. COVID-19, but also to a post-acute COVID-19 syndrome (PACS, "long COVID"). Currently, the side effects of COVID-19 vaccines are increasingly being noted and studied. Here, we summarise the currently available indications and discuss our conclusions that (i) these side effects have specific similarities and differences to acute COVID-19 and PACS, that (ii) a new term should be used to refer to these side effects (post-COVID-19 vaccination syndrome, PCVS, colloquially "post-COVIDvac-syndrome"), and that (iii) there is a need to distinguish between acute COVID-19 vaccination syndrome (ACVS) and post-acute COVID-19 vaccination syndrome (PACVS) - in analogy to acute COVID-19 and PACS ("long COVID"). Moreover, we address mixed forms of disease caused by natural SARS-CoV-2 infection and COVID-19 vaccination. We explain why it is important for medical diagnosis, care and research to use the new terms (PCVS, ACVS and PACVS) in order to avoid confusion and misinterpretation of the underlying causes of disease and to enable optimal medical therapy. We do not recommend to use the term "Post-Vac-Syndrome" as it is imprecise. The article also serves to address the current problem of "medical gaslighting" in relation to PACS and PCVS by raising awareness among the medical professionals and supplying appropriate terminology for disease.

COVID-19 severity by vaccination status in the NCI COVID-19 and Cancer Patients Study (NCCAPS)

J Natl Cancer Inst. 2023 May 8;115(5):597-600. doi: 10.1093/jnci/djad015.

Ana F Best 1, Melissa Bowman 2, Jessica Li 1, Grace E Mishkin 3, Andrea Denicoff 3, Marwa Shekfeh 1, Larry Rubinstein 1, Jeremy L Warner 4, Brian Rini 4, Larissa A Korde 3

Affiliations

1Biometric Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, MD, USA.

2Emmes Corporation, Rockville, MD, USA.

3Clinical Investigations Branch, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, MD, USA.

4Vanderbilt Ingram Cancer Center, Nashville, TN, USA.

Abstract

We investigated the association of SARS CoV-2 vaccination with COVID-19 severity in a longitudinal study of adult cancer patients with COVID-19. A total of 1610 patients who were within 14 days of an initial positive SARS CoV-2 test and had received recent anticancer treatment or had a history of stem cell transplant or CAR-T cell therapy were enrolled between May 21, 2020, and February 1, 2022. Patients were considered fully vaccinated if they were 2 weeks past their second dose of mRNA vaccine (BNT162b2 or mRNA-1273) or a single dose of adenovirus vector vaccine (Ad26.COV2.S) at the time of positive SARS CoV-2 test. We defined severe COVID-19 disease as hospitalization for COVID-19 or death within 30 days. Vaccinated patients were significantly less likely to develop severe disease compared with those who were unvaccinated (odds ratio = 0.44, 95% confidence interval = 0.28 to 0.72, P < .001). These results support COVID-19 vaccination among cancer patients receiving active immunosuppressive treatment.

Thrombo-inflammation in Long COVID - the elusive key to post-infection sequelae?

J Thromb Haemost. 2023 May 11;S1538-7836(23)00400-2. doi: 10.1016/j.jtha.2023.04.039. Online ahead of print.

Leo Nicolai 1, Rainer Kaiser 2, Konstantin Stark 2

Affiliations

1Medizinische Klinik und Poliklinik I, University Hospital Ludwig-Maximilian University, Munich, Germany; DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Germany. Electronic address: leo.nicolai@med.uni-muenchen.de.

2Medizinische Klinik und Poliklinik I, University Hospital Ludwig-Maximilian University, Munich, Germany; DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Germany.

Abstract

Long COVID is a public health emergency affecting millions of people worldwide, characterized by heterogenous symptoms across multiple organs systems. Here, we discuss the current evidence linking thrombo-inflammation to Post-acute sequelae of COVID-19 (PASC). Studies have found persistence of vascular damage with increased circulating markers of endothelial dysfunction, coagulation abnormalities with increased thrombin generation capacity, and abnormalities in platelet counts in PASC. Neutrophil phenotype resembles acute COVID-19 with an increase in activation and NETosis. These insights are potentially linked by elevated platelet-neutrophil aggregate formation. This hypercoagulable state in turn can lead to microvascular thrombosis, evidenced by microclots and elevated D-Dimer in the circulation, as well as perfusion abnormalities in the lung and brain of Long COVID patients. Also, COVID-19 survivors suffer from an increased rate of arterial and venous thrombotic events. We discuss three important, potentially intertwined hypotheses, that might contribute to thromboinflammation in Long COVID: Lasting structural changes, most prominently endothelial damage, caused during initial infection, a persistent viral reservoir, and immunopathology driven by a misguided immune system. Lastly, we outline the necessity for large, well-characterized clinical cohorts and mechanistic studies to clarify the contribution of thromboinflammation to Long COVID.

Long COVID: clues about causes

Eur Respir J. 2023 May 11;61(5):2300409. doi: 10.1183/13993003.00409-2023. Print 2023 May.

Felicity Liew 1, Claudia Efstathiou 1, Peter J M Openshaw 2

Affiliations

1National Heart and Lung Institute, Imperial College London, London, UK.

2National Heart and Lung Institute, Imperial College London, London, UK p.openshaw@imperial.ac.uk.

Abstract

Many patients report persistent symptoms after resolution of acute COVID-19, regardless of SARS-CoV-2 variant and even if the initial illness is mild [1, 2]. A multitude of symptoms have been described under the umbrella term ‘Long COVID’, otherwise known as ‘post-COVID syndrome’ or ‘post-acute sequelae of SARS-CoV-2 (PASC)’; for simplicity we will use the term Long COVID. Symptoms are diverse but include breathlessness, fatigue and brain fog, reported to affect up to 69% of cases [3]. Long COVID can be debilitating, 45.2% of patients requiring a reduced work schedule [4]. The WHO estimates that 17 million people in Europe have experienced Long COVID during the first two years of the pandemic [5]. SARS-CoV-2 variants continue to circulate and the risk of post-acute complications remains; a recent study of 56 003 UK patients found that even after Omicron infection, 4.5% suffered persistent symptoms [6]. It is therefore likely that Long COVID will provide a substantial medical and economic burden for the foreseeable future. There is an urgent need to understand mechanisms of disease and develop effective treatments based on this understanding.

Impaired health-related quality of life in long-COVID syndrome after mild to moderate COVID-19

Sci Rep. 2023 May 12;13(1):7717. doi: 10.1038/s41598-023-34678-8.

Stefan Malesevic 1 2, Noriane A Sievi 3, Patrick Baumgartner 4 3, Katharina Roser 5, Grit Sommer 6 7, Dörthe Schmidt 8, Florence Vallelian 9, Ilijas Jelcic 10, Christian F Clarenbach 4 3, Malcolm Kohler 3

Affiliations

1Faculty of Medicine, University of Zurich, Zurich, Switzerland. stefan.malesevic@usz.ch.

2Department of Pulmonology, University Hospital Zurich, 8091, Zurich, Switzerland. stefan.malesevic@usz.ch.

3Department of Pulmonology, University Hospital Zurich, 8091, Zurich, Switzerland.

4Faculty of Medicine, University of Zurich, Zurich, Switzerland.

5Department of Health Sciences and Medicine, University of Lucerne, Lucerne, Switzerland.

6Division of Pediatric Endocrinology, Diabetology and Metabolism, Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland.

7Department of Biomedical Research, University of Bern, Bern, Switzerland.

8Department of Cardiology, University Hospital Zurich, Zurich, Switzerland.

9Department of Internal Medicine, University Hospital Zurich, Zurich, Switzerland.

10Department of Neurology, University Hospital Zurich, Zurich, Switzerland.

Abstract

A growing number of patients with SARS-CoV-2 infections experience long-lasting symptoms. Even patients who suffered from a mild acute infection show a variety of persisting and debilitating neurocognitive, respiratory, or cardiac symptoms (Long-Covid syndrome), consequently leading to limitations in everyday life. Because data on health-related quality of life (HRQoL) is scarce, we aimed to characterize the impact of Long-Covid symptoms after a mild or moderate acute infection on HRQoL. In this observational study, outpatients seeking counseling in the interdisciplinary Post-Covid consultation of the University Hospital Zurich with symptoms persisting for more than 4 weeks were included. Patients who received an alternative diagnosis or suffered from a severe acute Covid-19 infection were excluded. St. George's Respiratory Questionnaire (SGRQ), Euroquol-5D-5L (EQ-5D-5L), and the Short form 36 (SF-36) were distributed to assess HRQoL. 112 patients were included, 86 (76.8%) were female, median (IQR) age was 43 (32.0, 52.5) years with 126 (91, 180) days of symptoms. Patients suffered frequently from fatigue (81%), concentration difficulties (60%), and dyspnea (60%). Patients mostly stated impairment in performing usual activities and having pain/discomfort or anxiety out of the EQ-5D-5L. EQ index value and SGRQ activity score component were significantly lower in females. SF-36 scores showed remarkably lower scores in the physical health domain compared to the Swiss general population before and during the COVID-19 pandemic. Long-Covid syndrome has a substantial impact on HRQoL. Long-term surveillance of patients must provide clarity on the duration of impairments in physical and mental health.Trial registration: The study is registered on www.ClinicalTrials.gov , NCT04793269.

Inhibition of SARS-CoV-2-mediated thromboinflammation by CLEC2.Fc

EMBO Mol Med. 2023 May 22;e16351. doi: 10.15252/emmm.202216351. Online ahead of print.

Pei-Shan Sung 1, Cheng-Pu Sun 2, Mi-Hua Tao 2, Shie-Liang Hsieh 1 3 4 5

Affiliations

1Genomics Research Center, Academia Sinica, Taipei, Taiwan.

2Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan.

3Immunology Research Center, National Health Research Institutes, Zhunan, Taiwan.

4Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan.

5Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan.

Abstract

Thromboinflammation is the major cause of morbidity and mortality in COVID-19 patients, and post-mortem examination demonstrates the presence of platelet-rich thrombi and microangiopathy in visceral organs. Moreover, persistent microclots were detected in both acute COVID-19 and long COVID plasma samples. However, the molecular mechanism of SARS-CoV-2-induced thromboinflammation is still unclear. We found that the spleen tyrosine kinase (Syk)-coupled C-type lectin member 2 (CLEC2), which was highly expressed in platelets and alveolar macrophages, interacted with the receptor-binding domain (RBD) of SARS-CoV-2 spike protein (SARS-CoV-2 RBD) directly. Unlike the thread-like NETs, SARS-CoV-2-induced aggregated NET formation in the presence of wild-type (WT), but not CLEC2-deficient platelets. Furthermore, SARS-CoV-2 spike pseudotyped lentivirus was able to induce NET formation via CLEC2, indicating SARS-CoV-2 RBD engaged CLEC2 to activate platelets to enhance NET formation. Administration of CLEC2.Fc inhibited SARS-CoV-2-induced NET formation and thromboinflammation in AAV-ACE2-infected mice. Thus, CLEC2 is a novel pattern recognition receptor for SARS-CoV-2, and CLEC2.Fc and may become a promising therapeutic agent to inhibit SARS-CoV-2-induced thromboinflammation and reduced the risk of post-acute sequelae of COVID-19 (PASC) in the future.

Effectiveness of COVID-19 Treatment With Nirmatrelvir-Ritonavir or Molnupiravir Among U.S. Veterans: Target Trial Emulation Studies With One-Month and Six-Month Outcomes

Ann Intern Med. 2023 Jun;176(6):807-816. doi: 10.7326/M22-3565. Epub 2023 Jun 6.

Kristina L Bajema 1, Kristin Berry 2, Elani Streja 3, Nallakkandi Rajeevan 4, Yuli Li 3, Pradeep Mutalik 4, Lei Yan 5, Francesca Cunningham 6, Denise M Hynes 7, Mazhgan Rowneki 8, Amy Bohnert 9, Edward J Boyko 10, Theodore J Iwashyna 11, Matthew L Maciejewski 12, Thomas F Osborne 13, Elizabeth M Viglianti 14, Mihaela Aslan 15, Grant D Huang 16, George N Ioannou 17

Affiliations

1Veterans Affairs Portland Health Care System, and Division of Infectious Diseases, Department of Medicine, Oregon Health & Science University, Portland, Oregon (K.L.B.).

2Research and Development, Veterans Affairs Puget Sound Health Care System, Seattle, Washington (K.B.).

3Veterans Affairs Cooperative Studies Program Clinical Epidemiology Research Center (CSP-CERC), Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut (E.S., Y.L.).

4Veterans Affairs Cooperative Studies Program Clinical Epidemiology Research Center (CSP-CERC), Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut, and Yale Center for Medical Informatics, Yale School of Medicine, New Haven, Connecticut (N.R., P.M.).

5Veterans Affairs Cooperative Studies Program Clinical Epidemiology Research Center (CSP-CERC), Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut, and Department of Biostatistics, Yale School of Public Health, New Haven, Connecticut (L.Y.).

6Veterans Affairs Center for Medication Safety - Pharmacy Benefit Management (PBM) Services, Hines, Illinois (F.C.).

7Center of Innovation to Improve Veteran Involvement in Care (CIVIC), Veterans Affairs Portland Healthcare System, Portland, Oregon, and Health Management and Policy, School of Social and Behavioral Health Sciences, College of Public Health and Human Sciences, and Health Data and Informatics Program, Center for Quantitative Life Sciences, Oregon State University, Corvallis, Oregon (D.M.H.).

8Center of Innovation to Improve Veteran Involvement in Care (CIVIC), Veterans Affairs Portland Healthcare System, Portland, Oregon (M.R.).

9Center for Clinical Management Research, Veterans Affairs Ann Arbor Healthcare System, and Department of Anesthesiology, University of Michigan, Ann Arbor, Michigan (A.B.).

10Seattle Epidemiologic Research and Information Center, Veterans Affairs Puget Sound Health Care System, Seattle, Washington (E.J.B.).

11Center for Clinical Management Research, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan, and Schools of Medicine and Public Health, Johns Hopkins University, Baltimore, Maryland (T.J.I.).

12Center of Innovation to Accelerate Discovery and Practice Transformation, Durham Veterans Affairs Medical Center; Department of Population Health Sciences, Duke University School of Medicine; and Duke-Margolis Center for Health Policy, Duke University, Durham, North Carolina (M.L.M.).

13Veterans Affairs Palo Alto Health Care System, Palo Alto, California, and Department of Radiology, Stanford University School of Medicine, Stanford, California (T.F.O.).

14Center for Clinical Management Research, Veterans Affairs Ann Arbor Healthcare System, and Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan (E.M.V.).

15Veterans Affairs Cooperative Studies Program Clinical Epidemiology Research Center (CSP-CERC), Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut, and Department of Medicine, Yale School of Medicine, New Haven, Connecticut (M.A.).

16Office of Research and Development, Veterans Health Administration, Washington, DC (G.D.H.).

17Research and Development and Division of Gastroenterology, Veterans Affairs Puget Sound Health Care System, and Division of Gastroenterology, University of Washington, Seattle, Washington (G.N.I.).

Abstract

Background: Information about the effectiveness of oral antivirals in preventing short- and long-term COVID-19-related outcomes in the setting of Omicron variant transmission and COVID-19 vaccination is limited.

Objective: To measure the effectiveness of nirmatrelvir-ritonavir and molnupiravir for outpatient treatment of COVID-19.

Design: Three retrospective target trial emulation studies comparing matched cohorts of nirmatrelvir-ritonavir versus no treatment, molnupiravir versus no treatment, and nirmatrelvir-ritonavir versus molnupiravir.

Setting: Veterans Health Administration (VHA).

Participants: Nonhospitalized veterans in VHA care who were at risk for severe COVID-19 and tested positive for SARS-CoV-2 during January through July 2022.

Intervention: Nirmatrelvir-ritonavir or molnupiravir pharmacotherapy.

Measurements: Incidence of any hospitalization or all-cause mortality at 30 days and from 31 to 180 days.

Results: Eighty-seven percent of participants were male; the median age was 66 years, and 18% were unvaccinated. Compared with matched untreated control participants, those treated with nirmatrelvir-ritonavir (n = 9607) had lower 30-day risk for hospitalization (22.07 vs. 30.32 per 1000 participants; risk difference [RD], -8.25 [95% CI, -12.27 to -4.23] per 1000 participants) and death (1.25 vs. 5.47 per 1000 participants; RD, -4.22 [CI, -5.45 to -3.00] per 1000 participants). Among persons alive at day 31, reductions were seen in 31- to 180-day incidence of death (hazard ratio, 0.66 [CI, 0.49 to 0.89]) but not hospitalization (subhazard ratio, 0.90 [CI, 0.79 to 1.02]). Molnupiravir-treated participants (n = 3504) had lower 30-day and 31- to 180-day risks for death (3.14 vs. 13.56 per 1000 participants at 30 days; RD, -10.42 [CI, -13.49 to -7.35] per 1000 participants; hazard ratio at 31 to 180 days, 0.67 [CI, 0.48 to 0.95]) but not hospitalization. A difference in 30-day or 31- to 180-day risk for hospitalization or death was not observed between matched nirmatrelvir- or molnupiravir-treated participants.

Limitation: The date of COVID-19 symptom onset for most veterans was unknown.

Conclusion: Nirmatrelvir-ritonavir was effective in reducing 30-day hospitalization and death. Molnupiravir was associated with a benefit for 30-day mortality but not hospitalization. Further reductions in mortality from 31 to 180 days were observed with both antivirals.

Long-Term Safety Analysis of the ChAdOx1-nCoV-19 Corona Virus Vaccine: Results from a Prospective Observational Study in Priority Vaccinated Groups in North India

Drug Saf. 2023 Jun;46(6):553-563. doi: 10.1007/s40264-023-01301-8. Epub 2023 May 3.

Upinder Kaur 1, Zeba Fatima 2, Kalika Maheshwari 2, Vikas Sahni 2, Amol Dehade 1, Anju Kl 3, Ashish Kumar Yadav 4, Sangeeta Kansal 5, Vaibhav Jaisawal 6, Sankha Shubhra Chakrabarti 7

Affiliations

1Department of Pharmacology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India.

2Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India.

3Department of Kaumarbhritya-Balroga (Ayurvedic Paediatrics), Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India.

4Center for Biostatistics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India.

5Department of Community Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, 221005, India. sangeetakansalbhu@gmail.com.

6Department of Kaumarbhritya-Balroga (Ayurvedic Paediatrics), Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, 221005, India. drvaibhav29@gmail.com.

7Department of Geriatric Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, 221005, India. sankha.chakrabarti1@bhu.ac.in.

Abstract

Introduction: Various vaccines for protection against COVID-19 were provided emergency approval in late 2020 to early 2021. There is a scarcity of long-term safety data for many of these.

Objective: The main aim of this study is to provide the one-year safety results of the ChAdOx1-nCoV-19/AZD1222 vaccine and determine the risk factors of adverse events of special interest (AESIs) and persistent AESIs.

Methods: This was a prospective observational study conducted from February 2021 to April 2022 in a tertiary hospital in North India and its two associated centers. Health care workers, other frontline workers, and the elderly vaccinated with the ChAdOx1-nCoV-19 vaccine constituted the study population. Individuals were contacted telephonically at pre-decided intervals for one year and health issues of significant concern were recorded. Atypical adverse events developing after a booster dose of the COVID-19 vaccine were assessed. Regression analysis was conducted to determine risk factors of AESI occurrence and determinants of AESIs persisting for at least one month at the time of final telephonic contact.

Results: Of 1650 individuals enrolled, 1520 could be assessed at one-year post-vaccination. COVID-19 occurred in 44.1% of participants. Dengue occurred in 8% of participants. The majority of the AESIs belonged to the MedDRA® SOC of musculoskeletal disorders (3.7% of 1520). Arthropathy (knee joint involvement) was the most common individual AESI (1.7%). Endocrinal disorders such as thyroid abnormalities and metabolic disorders such as newly diagnosed diabetes developed in 0.4% and 0.3% of individuals, respectively. Regression analysis showed females, individuals with a pre-vaccination history of COVID-19, diabetes, hypothyroidism, and arthropathy had 1.78-, 1.55-, 1.82-, 2.47- and 3.9-times higher odds of AESI development. Females and individuals with hypothyroidism were at 1.66- and 2.23-times higher risk of persistent AESIs. Individuals receiving the vaccine after COVID-19 were at 2.85- and 1.94 times higher risk of persistent AESIs compared, respectively, to individuals with no history of COVID-19 and individuals developing COVID-19 after the vaccine. Among participants receiving a booster dose of the COVID-19 vaccine (n = 185), 9.7% developed atypical adverse events of which urticaria and new-onset arthropathy were common.

Conclusion: Nearly half of the ChAdOx1-nCoV-19 vaccine recipients developed COVID-19 over one year. Vigilance is warranted for AESIs such as musculoskeletal disorders. Females, individuals

with hypothyroidism, diabetes, and pre-vaccination history of COVID-19 are at higher risk of adverse events. Vaccines received after natural SARS-CoV-2 infection may increase the risk of persistence of adverse events. Sex and endocrinal differences and timing of the COVID-19 vaccine with respect to natural infection should be explored as determinants of AESIs in the future. Pathogenetic mechanisms of vaccine-related adverse events should be investigated along with comparisons with an unvaccinated arm to delineate the overall safety profile of COVID-19 vaccines.

Racial and ethnic disparities in excess mortality among U.S. veterans during the COVID-19 pandemic

Health Serv Res. 2023 Jun;58(3):642-653. doi: 10.1111/1475-6773.14112. Epub 2022 Dec 30.

Yevgeniy Feyman 1 2, Cecille Joan Avila 1 2, Samantha Auty 1, Martha Mulugeta 1, Kiersten Strombotne 1 2, Aaron Legler 2, Kevin Griffith 2 3

Affiliations

1Department of Health Law, Policy & Management, Boston University School of Public Health, Boston, Massachusetts, USA.

2Partnered Evidence-Based Policy Resource Center, VA Boston Healthcare System, Boston, Massachusetts, USA.

3Department of Health Policy, Vanderbilt University Medical Center, Nashville, Tennessee, USA.

Abstract

Objective: The COVID-19 pandemic disproportionately affected racial and ethnic minorities among the general population in the United States; however, little is known regarding its impact on U.S. military Veterans. In this study, our objectives were to identify the extent to which Veterans experienced increased all-cause mortality during the COVID-19 pandemic, stratified by race and ethnicity.

Data sources: Administrative data from the Veterans Health Administration's Corporate Data Warehouse.

Study design: We use pre-pandemic data to estimate mortality risk models using five-fold cross-validation and quasi-Poisson regression. Models were stratified by a combined race-ethnicity variable and included controls for major comorbidities, demographic characteristics, and county fixed effects.

Data collection: We queried data for all Veterans residing in the 50 states plus Washington D.C. during 2016-2020. Veterans were excluded from analyses if they were missing county of residence or race-ethnicity data. Data were then aggregated to the county-year level and stratified by race-ethnicity.

Principal findings: Overall, Veterans' mortality rates were 16% above normal during March-December 2020 which equates to 42,348 excess deaths. However, there was substantial variation by racial and ethnic group. Non-Hispanic White Veterans experienced the smallest relative increase in mortality (17%, 95% CI 11%-24%), while Native American Veterans had the highest increase (40%, 95% CI 17%-73%). Black Veterans (32%, 95% CI 27%-39%) and Hispanic Veterans (26%, 95% CI 17%-36%) had somewhat lower excess mortality, although these changes were significantly higher compared to White Veterans. Disparities were smaller than in the general population.

Conclusions: Minoritized Veterans experienced higher rates excess of mortality during the COVID-19 pandemic compared to White Veterans, though with smaller differences than the general population. This is likely due in part to the long-standing history of structural racism in the United States that has negatively affected the health of minoritized communities via several pathways including health care access, economic, and occupational inequities.

COVID-19: The disease, the vaccine and the heart

J Paediatr Child Health. 2023 Jun;59(6):786-793. doi: 10.1111/jpc.16407. Epub 2023 May 9.

Christian J Turner 1

Affiliation

1The Heart Centre for Children, The Sydney Children's Hospital Network, Sydney, New South Wales, Australia.

Abstract

Coronavirus SARS-CoV-2 has fundamentally affected the health, healthcare delivery and daily life in all populations and age groups in Australia. The aim of this report is to summarise how it has affected the paediatric population with an emphasis on, but not limited to, the cardiac manifestations. A literature review and appraisal of data relating to SARS-CoV-2 cardiac manifestations and vaccination in the paediatric population was undertaken.The majority of children with SARS-CoV-2 infection recover well. However, a very small proportion may develop severe acute disease. In the sub-acute phase, children may also develop a Kawasaki like illness, Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2. Whilst not directly cardiac in nature, SARS-CoV-2 also affected children in other profound ways. Public health measures with widespread lockdowns appeared to disproportionately affect the paediatric population causing physical deconditioning and psychological harm. Vaccination against SARS-CoV-2 has proven to be safe and effective, but the small rate of complications did disproportionately affect teenage children with risks of myocarditis and pericarditis. The long term outcomes following myocarditis related to SARS-Cov-2 vaccination are yet to be clarified. When treating children in the era of SARS-CoV-2, Paediatricians need to be well aware of the risks of infection in the acute and sub-acute phases, have a good understanding of the well-established recommendations for vaccination, and also be cognisant of psychological impacts.

Long COVID and especially headache syndromes

Review Curr Opin Neurol. 2023 Jun 1;36(3):168-174. doi: 10.1097/WCO.0000000000001153. Epub 2023 Apr 4.

Claudio Tana 1, Maria Adele Giamberardino 1 2, Paolo Martelletti 3

Affiliations

1Center of Excellence on Headache, Geriatrics and COVID-19 Clinic, SS Annunziata Hospital of Chieti, Chieti.

2Department of Medicine and Science of Aging and CAST, G. D'Annunzio University of Chieti.

3Internal Medicine and Emergency Medicine, Sant' Andrea Hospital, Sapienza University, Rome, Italy.

Abstract

Purpose of review: This is an expert overview on recent literature about the complex relationship between coronavirus disease 2019 (COVID-19) and headache.

Recent findings: Long COVID is a clinical syndrome characterized by the presence of persistent symptoms following the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Headache is one of the most common symptoms and is described most often as throbbing pain, associated with photo and phonofobia and worsening with physical exercise. In acute COVID-19, headache is usually described as moderate or severe, diffuse and oppressive although sometimes it has been described with a migraine-like phenotype, especially in patients with a previous history of migraine. Headache intensity during acute phase seems to be the most important predictor of duration of headache over time. Some COVID-19 cases can be associated with cerebrovascular complications, and red flags of secondary headaches (e.g. new worsening or unresponsive headache, or new onset of neurological focal signs) should be urgently investigated with imaging. Treatment goals are the reduction of number and intensity of headache crises, and the prevention of chronic forms.

Summary: This review can help clinicians to approach patients with headache and infection from SARS-CoV-2, with particular attention to persistent headache in long COVID.

The road to pandemic recovery: Tracking COVID-19's impact on cirrhosis care and outcomes among 111,558 Veterans

Hepatology. 2023 Jun 1;77(6):2016-2029. doi: 10.1097/HEP.0000000000000306. Epub 2023 Jan 30.

Adeyinka C Adejumo 1, Vera Yakovchenko 2, Timothy R Morgan 3, Patrick Spoutz 4, Linda Chia 5, Jasmohan S Bajaj 6 7, Michael F Chang 8, Jason A Dominitz 9 10, Shari S Rogal 1 2 11

Affiliations

1Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

2Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA.

3Gastroenterology Section, VA Long Beach Healthcare System, Long Beach, California, USA.

4Pharmacy Benefits Management, Veterans Integrated Service Network 20, Vancouver, Washington, USA.

5Pharmacy Benefits Management, Veterans Integrated Service Network 8, Bay Pines, Florida, USA.

6Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, Virginia, USA.

7VA Richmond Health Care System, Richmond, Virginia, USA.

8Gastroenterology and Hepatology, VA Portland Health Care System, Portland, Oregon, USA.

9VA Puget Sound Health Care System, Seattle, Washington, USA.

10Division of Gastroenterology, University of Washington School of Medicine, Seattle, Washington, USA.

11Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

Abstract

Background aims: This study aimed to evaluate quarterly trends in process and health outcomes among Veterans with cirrhosis and assess the factors associated with cirrhosis outcomes before and during the COVID-19 pandemic.

Approach results: US Veterans with cirrhosis were identified using the Veterans Health Administration Corporate Data Warehouse. Quarterly measures were evaluated from September 30, 2018, through March 31, 2022, including twice yearly screening for hepatocellular carcinoma (HCC-6), new HCC, surveillance for or treatment of esophageal varices, variceal bleeding, all-cause hospitalization, and mortality. Joinpoint analyses were used to assess the changes in trends over time. Logistic regression models were used to identify the demographic and medical factors associated with each outcome over time. Among 111,558 Veterans with cirrhosis with a mean Model for End-stage Liver Disease-Sodium of 11±5, rates of HCC-6 sharply declined from a prepandemic peak of 41%, to a nadir of 28%, and rebounded to 36% by March 2022. All-cause mortality did not significantly change over the pandemic, but new HCC diagnosis, EVST, variceal bleeding, and all-cause hospitalization significantly declined over follow-up. Quarterly HCC diagnosis declined from 0.49% to 0.38%, EVST from 50% to 41%, variceal bleeding from 0.15% to 0.11%, and hospitalization from 9% to 5%. Rurality became newly, significantly associated with nonscreening over the pandemic (aOR for HCC-6=0.80, 95% CI 0.74 to 0.86; aOR for EVST=0.95, 95% CI 0.90 to 0.997).

Conclusions: The pandemic continues to impact cirrhosis care. Identifying populations at the highest risk of care disruptions may help to address ongoing areas of need.

Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial

Lancet Infect Dis. 2023 Jun 8;S1473-3099(23)00299-2. doi: 10.1016/S1473-3099(23)00299-2. Online ahead of print.

Carolyn T Bramante 1, John B Buse 2, David M Liebovitz 3, Jacinda M Nicklas 4, Michael A Puskarich 5, Ken Cohen 6, Hrishikesh K Belani 7, Blake J Anderson 8, Jared D Huling 9, Christopher J Tignanelli 10, Jennifer L Thompson 11, Matthew Pullen 12, Esteban Lemus Wirtz 9, Lianne K Siegel 9, Jennifer L Proper 9, David J Odde 13, Nichole R Klatt 10, Nancy E Sherwood 14, Sarah M Lindberg 9, Amy B Karger 15, Kenneth B Beckman 16, Spencer M Erickson 17, Sarah L Fenno 17, Katrina M Hartman 17, Michael R Rose 18, Tanvi Mehta 9, Barkha Patel 17, Gwendolyn Griffiths 17, Neeta S Bhat 17, Thomas A Murray 9, David R Boulware 12

Affiliations

1Division of General Internal Medicine, University of Minnesota, Minneapolis, MN, USA. Electronic address: bramante@umn.edu.

2Endocrinology, University of North Carolina, Chapel Hill, NC, USA.

3General Internal Medicine, Northwestern University, Chicago, IL, USA.

4General Internal Medicine, University of Colorado, Denver, CO, USA.

5Emergency Medicine, Hennepin County Medical Center, Minneapolis, MN, USA.

6UnitedHealth Group, Optum Labs, Minnetonka, MN, USA.

7Department of Medicine, Olive View, University of California, Los Angeles, CA, USA.

8Atlanta Veterans Affairs Medical Center, Atlanta, GA, USA; Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA.

9Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN, USA.

10Department of Surgery, Medical School, University of Minnesota, Minneapolis, MN, USA.

11Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, TN, USA.

12Division of Infectious Diseases and International Medicine, Department of Medicine, Medical School, University of Minnesota, Minneapolis, MN, USA.

13Department of Biomedical Engineering, University of Minnesota, Minneapolis, MN, USA.

14Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA.

15Department of Laboratory Medicine and Pathology, Medical School, University of Minnesota, Minneapolis, MN, USA.

16Genomics Center, University of Minnesota, Minneapolis, MN, USA.

17Division of General Internal Medicine, University of Minnesota, Minneapolis, MN, USA.

18Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Abstract

Background: Post-COVID-19 condition (also known as long COVID) is an emerging chronic illness potentially affecting millions of people. We aimed to evaluate whether outpatient COVID-19 treatment with metformin, ivermectin, or fluvoxamine soon after SARS-CoV-2 infection could reduce the risk of long COVID.

Methods: We conducted a decentralised, randomised, quadruple-blind, parallel-group, phase 3 trial (COVID-OUT) at six sites in the USA. We included adults aged 30-85 years with overweight or obesity who had COVID-19 symptoms for fewer than 7 days and a documented SARS-CoV-2 positive PCR or antigen test within 3 days before enrolment. Participants were randomly assigned via 2 × 3 parallel factorial randomisation (1:1:1:1:1:1) to receive metformin plus ivermectin, metformin plus fluvoxamine, metformin plus placebo, ivermectin plus placebo, fluvoxamine plus

placebo, or placebo plus placebo. Participants, investigators, care providers, and outcomes assessors were masked to study group assignment. The primary outcome was severe COVID-19 by day 14, and those data have been published previously. Because the trial was delivered remotely nationwide, the a priori primary sample was a modified intention-to-treat sample, meaning that participants who did not receive any dose of study treatment were excluded. Long COVID diagnosis by a medical provider was a prespecified, long-term secondary outcome. This trial is complete and is registered with ClinicalTrials.gov, NCT04510194.

Findings: Between Dec 30, 2020, and Jan 28, 2022, 6602 people were assessed for eligibility and 1431 were enrolled and randomly assigned. Of 1323 participants who received a dose of study treatment and were included in the modified intention-to-treat population, 1126 consented for long-term follow-up and completed at least one survey after the assessment for long COVID at day 180 (564 received metformin and 562 received matched placebo; a subset of participants in the metformin vs placebo trial were also randomly assigned to receive ivermectin or fluvoxamine). 1074 (95%) of 1126 participants completed at least 9 months of follow-up. 632 (56·1%) of 1126 participants were female and 494 (43·9%) were male; 44 (7·0%) of 632 women were pregnant. The median age was 45 years (IQR 37-54) and median BMI was 29·8 kg/m2 (IQR 27·0-34·2). Overall, 93 (8·3%) of 1126 participants reported receipt of a long COVID diagnosis by day 300. The cumulative incidence of long COVID by day 300 was 6·3% (95% CI 4·2-8·2) in participants who received metformin and 10·4% (7·8-12·9) in those who received identical metformin placebo (hazard ratio [HR] 0·59, 95% CI 0·39-0·89; p=0·012). The metformin beneficial effect was consistent across prespecified subgroups. When metformin was started within 3 days of symptom onset, the HR was 0·37 (95% CI 0·15-0·95). There was no effect on cumulative incidence of long COVID with ivermectin (HR 0·99, 95% CI 0·59-1·64) or fluvoxamine (1·36, 0·78-2·34) compared with placebo.

Interpretation: Outpatient treatment with metformin reduced long COVID incidence by about 41%, with an absolute reduction of 4·1%, compared with placebo. Metformin has clinical benefits when used as outpatient treatment for COVID-19 and is globally available, low-cost, and safe.

Predictive value of ASCVD risk score for mortality and major adverse cardiovascular events in the year following a COVID-19 infection among US veterans

Int J Cardiol. 2023 Jun 15;131120. doi: 10.1016/j.ijcard.2023.131120. Online ahead of print.

Eric T Guardino 1, Laura Tarko 2, Peter W F Wilson 3, J Michael Gaziano 4, Kelly Cho 2, David R Gagnon 5, Ariela R Orkaby 6

Affiliations

1Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, 2 2 Avenue de Lafayette, Boston, MA 02111, USA; Division of Aging, Brigham & Women's Hospital, Harvard Medical School, 75 Francis St, Boston, MA 02115, USA. Electronic address: eguardino@une.edu.

2Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, 2 2 Avenue de Lafayette, Boston, MA 02111, USA.

3Atlanta VA Healthcare System, 1670 Clairmont Road, Decatur, GA 30033, USA; Emory Clinical Cardiology Research Institute, 1462 Clifton Rd NE, 5(th) Floor, Atlanta, GA 30322, USA.

4Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, 2 2 Avenue de Lafayette, Boston, MA 02111, USA; Division of Aging, Brigham & Women's Hospital, Harvard Medical School, 75 Francis St, Boston, MA 02115, USA.

5Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, 2 2 Avenue de Lafayette, Boston, MA 02111, USA; Boston University School of Public Health, Department of Biostatistics, Boston, MA 02118, USA.

6Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, 2 2 Avenue de Lafayette, Boston, MA 02111, USA; Division of Aging, Brigham & Women's Hospital, Harvard Medical School, 75 Francis St, Boston, MA 02115, USA; New England GRECC (Geriatric Research, Education, and Clinical Center) VA Boston Healthcare System, 150 S Huntington St, Boston, MA 02130, USA.

Abstract

Background: Morbidity and mortality following COVID-19 infection may be influenced by baseline atherosclerotic cardiovascular disease (ASCVD) risk, yet limited data are available to identify those at highest risk. We examined the association between baseline ASCVD risk with mortality and major adverse cardiovascular events (MACE) in the year following COVID-19 infection.

Methods: We evaluated a nationwide retrospective cohort of US Veterans free of ASCVD who were tested for COVID-19. The primary outcome was absolute risk of all-cause mortality in the year following a COVID-19 test among those hospitalized vs. not stratified by baseline VA-ASCVD risk scores. Secondarily, risk of MACE was examined.

Results: There were 393,683 Veterans tested for COVID-19 and 72,840 tested positive. Mean age was 57 years, 86% were male, and 68% were white. Within 30 days following infection, hospitalized Veterans with VA-ASCVD scores >20% had an absolute risk of death of 24.6% vs. 9.7% (P ≤0.0001) for those who tested positive and negative for COVID-19 respectively. In the year following infection, risk of mortality attenuated with no difference in risk after 60 days. The absolute risk of MACE was similar for Veterans who tested positive or negative for COVID-19.

Conclusions: Veterans without clinical ASCVD experienced an increased absolute risk of death within 30 days of a COVID-19 infection compared to Veterans with the same VA-ASCVD risk score who tested negative, but this risk attenuated after 60 days. Whether cardiovascular preventive medications can lower the risk of mortality and MACE in the acute period following COVID-19 infection should be evaluated.

Comparison of Medical and Mental Health Sequelae Following Hospitalization for COVID-19, Influenza, and Sepsis

JAMA Intern Med. 2023 Jun 20;e232228. doi: 10.1001/jamainternmed.2023.2228. Online ahead of print.

Kieran L Quinn 1 2 3 4 5, Thérèse A Stukel 2 3, Anjie Huang 2, Husam Abdel-Qadir 1 2 3 6 7, Azmina Altaf 2, Chaim M Bell 1 2 3 4, Angela M Cheung 1 2, Allan S Detsky 1 3 4, Susie Goulding 8, Margaret Herridge 1 2, Noah Ivers 6, Lauren Lapointe-Shaw 1 2 3 4, John Lapp 4, Candace D McNaughton 1 2 9, Afsaneh Raissi 10 11, Laura C Rosella 2 3, Nahrain Warda 4, Fahad Razak 1 3 10 11, Amol A Verma 1 3 10 11 12

Affiliations

1Department of Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada.

2ICES, Toronto and Ottawa, Ontario, Canada.

3Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada.

4Department of Medicine, Sinai Health and University Health Network, Toronto, Ontario, Canada.

5Temmy Latner Centre for Palliative Care, Toronto, Ontario, Canada.

6Women's College Hospital, University of Toronto, Toronto, Ontario, Canada.

7Peter Munk Cardiac Centre, University Health Network, Toronto, Ontario, Canada.

8COVID Long-Haulers Canada, Oakville, Ontario, Canada.

9Sunnybrook Research Institute, Toronto, Ontario, Canada.

10Li Ka Shing Knowledge Institute, Unity Health Toronto, Department of Medicine, Toronto, Ontario, Canada.

11Unity Health Toronto, Department of Medicine, St Michael's Hospital, Toronto, Ontario, Canada.

12Temerty Centre for AI Research and Education in Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada.

Abstract

Importance: People who survive hospitalization for COVID-19 are at risk for developing new cardiovascular, neurological, mental health, and inflammatory autoimmune conditions. It is unclear how posthospitalization risks for COVID-19 compare with those for other serious infectious illnesses.

Objective: To compare risks of incident cardiovascular, neurological, and mental health conditions and rheumatoid arthritis in 1 year following COVID-19 hospitalization against 3 comparator groups: prepandemic hospitalization for influenza and hospitalization for sepsis before and during the COVID-19 pandemic.

Design, setting, and participants: This population-based cohort study included all adults hospitalized for COVID-19 between April 1, 2020, and October 31, 2021, historical comparator groups of people hospitalized for influenza or sepsis, and a contemporary comparator group of people hospitalized for sepsis in Ontario, Canada.

Exposure: Hospitalization for COVID-19, influenza, or sepsis.

Main outcome and measures: New occurrence of 13 prespecified conditions, including cardiovascular, neurological, and mental health conditions and rheumatoid arthritis, within 1 year of hospitalization.

Results: Of 379 366 included adults (median [IQR] age, 75 [63-85] years; 54% female), there were 26 499 people who survived hospitalization for COVID-19, 299 989 historical controls (17 516 for influenza and 282 473 for sepsis), and 52 878 contemporary controls hospitalized for sepsis. Hospitalization for COVID-19 was associated with an increased 1-year risk of venous thromboembolic disease compared with influenza (adjusted hazard ratio, 1.77; 95% CI, 1.36-2.31) but with no increased risks of developing selected ischemic and nonischemic cerebrovascular and

cardiovascular disorders, neurological disorders, rheumatoid arthritis, or mental health conditions compared with influenza or sepsis cohorts.

Conclusions and relevance: In this cohort study, apart from an elevated risk of venous thromboembolism within 1 year, the burden of postacute medical and mental health conditions among those who survived hospitalization for COVID-19 was comparable with other acute infectious illnesses. This suggests that many of the postacute consequences of COVID-19 may be related to the severity of infectious illness necessitating hospitalization rather than being direct consequences of infection with SARS-CoV-2.