Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations Concerning Long Haul COVID-19 July, August, September 2023

Prepared by Staff of the RACGWVI.

RACGWVI: Long Haul COVID-19 — PubMed Citations for July, Aug, Sept 2023

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

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Exacerbated PTSD symptoms among older U.S. military veterans during the COVID-19 pandemic: Results from the national health and resilience in veterans study

J Psychiatr Res. 2023 Jul;163:386-390. doi: 10.1016/j.jpsychires.2023.05.078. Epub 2023 May 30.

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Abstract

Research has demonstrated that the impact of the coronavirus 2019 (COVID-19) pandemic on the mental health of United States (U.S.) veterans was less negative than originally anticipated. However, U.S. veterans are susceptible to exacerbation of post-traumatic stress disorder (PTSD) symptomology in late life. The aims of this study were to examine the extent to which older U.S. veterans experienced an exacerbation of PTSD symptoms during the COVID-19 pandemic, and to identify pre- and peri-pandemic factors that conferred risk for symptom exacerbation. Participants were U.S. military veterans aged 60 and older who completed three waves of the 2019-2022 National Health and Resilience in Veterans Study (NHRVS) (n=1858). PTSD symptoms were measured at all waves using the PTSD Checklist for DSM-5, and a latent growth mixture model was conducted to compute latent slopes of change of PTSD symptoms over the 3-year period. 159 (8.3%) participants experienced a worsening of PTSD symptomology over the pandemic period. Factors related to PTSD exacerbation were incident trauma exposure between Waves 1 and 2, more medical conditions with onset prior to the pandemic, and peri-pandemic social restriction stress. Number of incident traumas moderated the relationship between both number of pre-pandemic medical conditions and pre-pandemic social connectedness, and exacerbated PTSD symptoms. These results suggest that the pandemic did not confer additional risk for PTSD exacerbation than would be expected over a 3-year period for older veterans. Those who experience incident trauma exposure should be monitored for symptom exacerbation.

Cardiovascular and haematological pathology in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): A role for viruses

Blood Rev. 2023 Jul;60:101075. doi: 10.1016/j.blre.2023.101075. Epub 2023 Mar 20.

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Abstract

ME/CFS is a debilitating chronic condition that often develops after viral or bacterial infection. Insight from the study of Long COVID/Post Acute Sequelae of COVID-19 (PASC), the post-viral syndrome associated with SARS-CoV-2 infection, might prove to be useful for understanding pathophysiological mechanisms of ME/CFS. Disease presentation is similar between the two conditions, and a subset of Long COVID patients meet the diagnostic criteria for ME/CFS. Since Long COVID is characterized by significant vascular pathology - including endothelial dysfunction, coagulopathy, and vascular dysregulation - the question of whether or not the same biological abnormalities are of significance in ME/CFS arises. Cardiac abnormalities have for a while now been documented in ME/CFS cohorts, with recent studies demonstrating major deficits in cerebral blood flow, and hence vascular dysregulation. A growing body of research is demonstrating that ME/CFS is accompanied by platelet hyperactivation, anomalous clotting, a procoagulant phenotype, and endothelial dysfunction. Endothelial damage and dysregulated clotting can impair substance exchange between blood and tissues, and result in hypoperfusion, which may contribute to the manifestation of certain ME/CFS symptoms. Here we review the ME/CFS literature to summarize cardiovascular and haematological findings documented in patients with the condition, and, in this context, briefly discuss the potential role of previously-implicated pathogens. Overall, cardiac and haematological abnormalities are present within ME/CFS cohorts. While atherosclerotic heart disease is not significantly associated with ME/CFS, suboptimal cardiovascular function defined by reduced cardiac output, impaired cerebral blood flow, and vascular dysregulation are, and these abnormalities do not appear to be influenced by deconditioning. Rather, these cardiac abnormalities may result from dysfunction in the (autonomic) nervous system. Plenty of recently published studies are demonstrating significant platelet hyperactivity and endothelial dysfunction in ME/CFS, as well as anomalous clotting processes. It is of particular importance to determine to what extent these cardiovascular and haematological abnormalities contribute to symptom severity, and if these two systems can be targeted for therapeutic purposes. Viral reservoirs of herpesviruses exist in ME/CFS, and most likely contribute to cardiovascular and haematological dysfunction directly or indirectly. This review highlights the potential of studying cardiac functioning, the vasculature, and coagulation system in ME/CFS.

Pain Trajectories among U.S. Veterans During COVID-19

J Pain. 2023 Jul 4;S1526-5900(23)00454-6. doi: 10.1016/j.jpain.2023.06.018. Online ahead of print.

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Abstract

Physical pain is highly prevalent among military veterans. As stress can impact pain, COVID-19-related stressors may have heightened pain among veterans. A prospective analysis of pain could advance understanding of how veterans fared during COVID-19 and lend knowledge of risk factors important beyond the pandemic. The present study employs growth mixture modeling with a sample of U.S. veterans high in pain (N = 1,230) followed from just before COVID-19 (February 2020) to 12 months later (February 2021; 81.7% retention). We explored heterogeneous pain trajectories as well as baseline and COVID-19-related predictors of pain. Results revealed 4 pain trajectory classes: 1) Chronic Pain (17.3% of the sample); 2) Decreasing Pain (57.2% of the sample); 3) Stable Mild Pain (19.8% of the sample); and 4) Increasing Pain (5.7% of the sample). Those with childhood trauma exposure were especially likely to report chronic pain. Female and racial/ethnic minority veterans were also relatively likely to fare poorly in pain. Loneliness was associated with subsequent pain among several classes. Most veterans in our sample fared better than expected in terms of pain. However, as those with childhood trauma and certain disadvantaged groups were less likely to fare well, we add to the important literature on disparities in pain. Clinicians should identify whether loneliness and other factors impacted pain during COVID-19 among their patients to inform ongoing, person-centered pain management approaches. PERSPECTIVE: This article presents pain trajectories and correlates of pain among a high-pain sample of U.S. veterans surveyed prior to and during COVID-19. Pain clinicians should screen for childhood trauma and remain vigilant in addressing health disparities.

Recapitulation of pathophysiological features of AD in SARS-CoV-2-infected subjects

Elife. 2023 Jul 7;12:e86333. doi: 10.7554/eLife.86333.

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Abstract

Infection with the etiological agent of COVID-19, SARS-CoV-2, appears capable of impacting cognition in some patients with post-acute sequelae of SARS-CoV-2 (PASC). To evaluate neuropathophysiological consequences of SARS-CoV-2 infection, we examine transcriptional and cellular signatures in the Brodmann area 9 (BA9) of the frontal cortex and the hippocampal formation (HF) in SARS-CoV-2, Alzheimer's disease (AD), and SARS-CoV-2-infected AD individuals compared to age- and gender-matched neurological cases. Here, we show similar alterations of neuroinflammation and blood-brain barrier integrity in SARS-CoV-2, AD, and SARS-CoV-2-infected AD individuals. Distribution of microglial changes reflected by the increase in Iba-1 reveals nodular morphological alterations in SARS-CoV-2-infected AD individuals. Similarly, HIF-1α is significantly upregulated in the context of SARS-CoV-2 infection in the same brain regions regardless of AD status. The finding may help in informing decision-making regarding therapeutic treatments in patients with neuro-PASC, especially those at increased risk of developing AD.

Amygdala and Insula Retraining (AIR) Significantly Reduces Fatigue and Increases Energy in People with Long COVID

Evid Based Complement Alternat Med. 2023 Jul 17;2023:7068326. doi: 10.1155/2023/7068326. eCollection 2023.

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Abstract

Long COVID affects approximately 10-30% of individuals after an acute COVID-19 infection (Ceban, Ling, et al. 2022; Ortona and Malorni, 2022). Numerous symptoms, including extreme fatigue, can persist for months, resulting in social and economic hardship for individuals and their families (Ortona and Malorni 2022). Therefore, approaches that offer some relief from Long COVID are urgently needed. Research suggests that Long COVID symptoms are akin to those of chronic conditions, such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and are likely caused by inflammation and immune dysfunction (Scordo et al., 2021). Amygdala and Insula Retraining (AIR), a neuroplasticity program, has successfully alleviated chronic conditions (Gupta 2010; Sanabria-Mazo et al. 2020; Toussaint et al. 2012). In this randomized controlled trial, AIR was tested against a structurally equivalent health and wellness intervention for its effectiveness in treating the symptom of fatigue among Long COVID sufferers. Results showed a significant decrease in participants' fatigue and a significant increase in their energy after the 3-month AIR intervention. Additionally, the AIR group experienced more significant outcomes than the active control group. The AIR group demonstrated a fatigue reduction effect size four times that of the active control group, and the absolute reduction in mean scores for the AIR group was more than double that of the control group. Furthermore, the AIR group showed an effect size in energy enhancement twice that of the active control group, and the absolute increase in energy mean scores for the AIR group was almost double that of the control group. These novel findings suggest AIR is a viable means of reducing fatigue and increasing energy among Long COVID patients. Limitations and future research are discussed.

The Health Status of the US Veterans: A Longitudinal Analysis of Surveillance Data Prior to and during the COVID-19 Pandemic

Healthcare (Basel). 2023 Jul 17;11(14):2049. doi: 10.3390/healthcare11142049.

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Abstract

Chronic diseases affect a disproportionate number of United States (US) veterans, causing significant long-term health issues and affecting entitlement spending. This longitudinal study examined the health status of US veterans as compared to non-veterans pre- and post-COVID-19, utilizing the annual Center for Disease Control and Prevention (CDC) behavioral risk factor surveillance system (BRFSS) survey data. Age-adjusted descriptive point estimates were generated independently for 2003 through 2021, while complex weighted panel data were generated from 2011 and onward. General linear modeling revealed that the average US veteran reports a higher prevalence of disease conditions except for mental health disorders when compared to a non-veteran. These findings were consistent with both pre- and post-COVID-19; however, both groups reported a higher prevalence of mental health issues during the pandemic years. The findings suggest that there have been no improvements in reducing veteran comorbidities to non-veteran levels and that COVID-19 adversely affected the mental health of both populations.

A Clinical Qualification Protocol Highlights Overlapping Genomic Influences and Neuro-Autonomic Mechanisms in Ehlers-Danlos and Long COVID-19 Syndromes

Curr Issues Mol Biol. 2023 Jul 17;45(7):6003-6023. doi: 10.3390/cimb45070379.

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Abstract

A substantial fraction of the 15% with double-jointedness or hypermobility have the traditionally ascertained joint-skeletal, cutaneous, and cardiovascular symptoms of connective tissue dysplasia and its particular manifestation as Ehlers-Danlos syndrome (EDS). The holistic ascertainment of 120 findings in 1261 EDS patients added neuro-autonomic symptoms like headaches, muscle weakness, brain fog, chronic fatigue, dyspnea, and bowel irregularity to those of arthralgia and skin laxity, 15 of these symptoms shared with those of post-infectious SARS-CoV-2 (long COVID-19). Underlying articulo-autonomic mechanisms guided a clinical qualification protocol that qualified DNA variants in 317 genes as having diagnostic utility for EDS, six of them identical (F2-LIFR-NLRP3-STAT1-T1CAM1-TNFRSF13B) and eighteen similar to those modifying COVID-19 severity/EDS, including ADAMTS13/ADAMTS2-C3/C1R-IKBKG/IKBKAP-PIK3C3/PIK3R1-POLD4/POLG-TMPRSS2/TMPRSS6-WNT3/WNT10A. Also, contributing to EDS and COVID-19 severity were forty and three genes, respectively, impacting mitochondrial functions as well as parts of an overlapping gene network, or entome, that are hypothesized to mediate the cognitive-behavioral, neuro-autonomic, and immune-inflammatory alterations of connective tissue in these conditions. The further characterization of long COVID-19 natural history and genetic predisposition will be necessary before these parallels to EDS can be carefully delineated and translated into therapies.

COVID, complement, and the brain

Front Immunol. 2023 Jul 18;14:1216457. doi: 10.3389/fimmu.2023.1216457. eCollection 2023.

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Abstract

The brains of COVID-19 patients are affected by the SARS-CoV-2 virus, and these effects may contribute to several COVID-19 sequelae, including cognitive dysfunction (termed "long COVID" by some researchers). Recent advances concerning the role of neuroinflammation and the consequences for brain function are reviewed in this manuscript. Studies have shown that respiratory SARS-CoV-2 infection in mice and humans is associated with selective microglial reactivity in the white matter, persistently impaired hippocampal neurogenesis, a decrease in the number of oligodendrocytes, and myelin loss. Brain MRI studies have revealed a greater reduction in grey matter thickness in the orbitofrontal cortex and parahippocampal gyrus, associated with a greater reduction in global brain size, in those with SARS-CoV-2 and a greater cognitive decline. COVID-19 can directly infect endothelial cells of the brain, potentially promoting clot formation and stroke; complement C3 seems to play a major role in this process. As compared to controls, the brain tissue of patients who died from COVID-19 have shown a significant increase in the extravasation of fibrinogen, indicating leakage in the blood-brain barrier; furthermore, recent studies have documented the presence of IgG, IgM, C1q, C4d, and C5b-9 deposits in the brain tissue of COVID-19 patients. These data suggest an activation of the classical complement pathway and an immune-mediated injury to the endothelial cells. These findings implicate both the classical and alternative complement pathways, and they indicate that C3b and the C5b-9 terminal complement complex (membrane attack complex, MAC) are acting in concert with neuroinflammatory and immune factors to contribute to the neurological sequelae seen in patients with COVID.

Clinical phenotypes and quality of life to define post-COVID-19 syndrome: a cluster analysis of the multinational, prospective ORCHESTRA cohort

EClinicalMedicine. 2023 Jul 21;62:102107. doi: 10.1016/j.eclinm.2023.102107. eCollection 2023 Aug.

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Abstract

Background: Lack of specific definitions of clinical characteristics, disease severity, and risk and preventive factors of post-COVID-19 syndrome (PCS) severely impacts research and discovery of new preventive and therapeutics drugs.

Methods: This prospective multicenter cohort study was conducted from February 2020 to June 2022 in 5 countries, enrolling SARS-CoV-2 out- and in-patients followed at 3-, 6-, and 12-month from diagnosis, with assessment of clinical and biochemical features, antibody (Ab) response, Variant of Concern (VoC), and physical and mental quality of life (QoL). Outcome of interest was identification of risk and protective factors of PCS by clinical phenotype, setting, severity of disease, treatment, and vaccination status. We used SF-36 questionnaire to assess evolution in QoL index during follow-up and unsupervised machine learning algorithms (principal component analysis, PCA) to explore symptom clusters. Severity of PCS was defined by clinical phenotype and QoL. We also used generalized linear models to analyse the impact of PCS on QoL and associated risk and preventive factors. CT registration number: NCT05097677.

Findings: Among 1796 patients enrolled, 1030 (57%) suffered from at least one symptom at 12-month. PCA identified 4 clinical phenotypes: chronic fatigue-like syndrome (CFs: fatigue, headache and memory loss, 757 patients, 42%), respiratory syndrome (REs: cough and dyspnoea, 502, 23%); chronic pain syndrome (CPs: arthralgia and myalgia, 399, 22%); and neurosensorial syndrome (NSs: alteration in taste and smell, 197, 11%). Determinants of clinical phenotypes were different (all comparisons $p < 0.05$): being female increased risk of CPs, NSs, and CFs; chronic pulmonary diseases of REs; neurological symptoms at SARS-CoV-2 diagnosis of REs, NSs, and CFs; oxygen therapy of CFs and REs; and gastrointestinal symptoms at SARS-CoV-2 diagnosis of CFs. Early treatment of SARS-CoV-2 infection with monoclonal Ab (all clinical phenotypes), corticosteroids therapy for mild/severe cases (NSs), and SARS-CoV-2 vaccination (CPs) were less likely to be associated to PCS (all comparisons $p < 0.05$). Highest reduction in QoL was detected in REs and CPs (43.57 and 43.86 vs 57.32 in PCS-negative controls, $p < 0.001$). Female sex ($p < 0.001$), gastrointestinal symptoms ($p = 0.034$) and renal complications ($p = 0.002$) during the acute infection were likely to increase risk of severe PCS (QoL <50). Vaccination and early treatment with monoclonal Ab reduced the risk of severe PCS ($p = 0.01$ and $p = 0.03$, respectively).

Interpretation: Our study provides new evidence suggesting that PCS can be classified by clinical phenotypes with different impact on QoL, underlying possible different pathogenic mechanisms. We identified factors associated to each clinical phenotype and to severe PCS. These results might

help in designing pathogenesis studies and in selecting high-risk patients for inclusion in therapeutic and management clinical trials.

Persistent endothelial dysfunction in post-COVID-19 syndrome and its associations with symptom severity and chronic inflammation

Angiogenesis. 2023 Jul 28. doi: 10.1007/s10456-023-09885-6. Online ahead of print.

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Erratum in

Correction: Persistent endothelial dysfunction in post-COVID-19 syndrome and its associations with symptom severity and chronic inflammation.

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Abstract

Background: Post-COVID-19 syndrome (PCS) is a lingering disease with ongoing symptoms such as fatigue and cognitive impairment resulting in a high impact on the daily life of patients. Understanding the pathophysiology of PCS is a public health priority, as it still poses a diagnostic and treatment challenge for physicians.

Methods: In this prospective observational cohort study, we analyzed the retinal microcirculation using Retinal Vessel Analysis (RVA) in a cohort of patients with PCS and compared it to an age- and gender-matched healthy cohort (n = 41, matched out of n = 204).

Measurements and main results: PCS patients exhibit persistent endothelial dysfunction (ED), as indicated by significantly lower venular flicker-induced dilation (vFID; 3.42% ± 1.77% vs. 4.64% ± 2.59%; p = 0.02), narrower central retinal artery equivalent (CRAE; 178.1 [167.5-190.2] vs. 189.1 [179.4-197.2], p = 0.01) and lower arteriolar-venular ratio (AVR; (0.84 [0.8-0.9] vs. 0.88 [0.8-0.9], p = 0.007). When combining AVR and vFID, predicted scores reached good ability to discriminate

groups (area under the curve: 0.75). Higher PCS severity scores correlated with lower AVR (R = -0.37 p = 0.017). The association of microvascular changes with PCS severity were amplified in PCS patients exhibiting higher levels of inflammatory parameters.

Conclusion: Our results demonstrate that prolonged endothelial dysfunction is a hallmark of PCS, and impairments of the microcirculation seem to explain ongoing symptoms in patients. As potential therapies for PCS emerge, RVA parameters may become relevant as clinical biomarkers for diagnosis and therapy management.

Trial registration: This study was previously registered at ClinicalTrials ("All Eyes on PCS-Analysis of the Retinal Microvasculature in Patients with Post-COVID-19 Syndrome". NCT05635552. https://clinicaltrials.gov/ct2/show/NCT05635552). Persistent endothelial dysfunction in post-COVID-19 syndrome. Acute SARS-CoV-2 infection indirectly or directly causes endotheliitis in patients. N = 41 PCS patients were recruited and retinal vessel analysis was performed to assess microvascular endothelial function. Images of SVA and DVA are illustrative for RVA data analysis. For each PCS patient and healthy cohort, venular vessel diameter of the three measurement cycles was calculated and plotted on a diameter-time curve. Patients exhibited reduced flicker-induced dilation in veins (vFID) measured by dynamic vessel analysis (DVA) and lower central retinal arteriolar equivalent (CRAE) and arteriolar-venular ratio (AVR) and a tendency towards higher central retinal venular equivalent (CRVE) when compared to SARS-CoV-2 infection naïve participants. Created with BioRender.com.

COVID-19-related media consumption and posttraumatic stress symptoms in U.S. military veterans: A nationally representative, longitudinal study

Psychiatry Res. 2023 Aug;326:115354. doi: 10.1016/j.psychres.2023.115354. Epub 2023 Jul 18.

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Abstract

Purpose: To examine the association between COVID-19 media consumption and pandemic-related posttraumatic stress symptoms (PTSS) in U.S. veterans.

Methods: A population-based sample of 3,074 U.S. veterans was surveyed prior to the pandemic (fall 2019) and a year later during the height of the pandemic (fall 2020).

Results: Greater COVID-19 media consumption was associated with pandemic-related PTSS, particularly in veterans with pre-existing posttraumatic stress disorder (PTSD) who were 79% more likely to report pandemic-related PTSS relative to veterans with PTSD who consumed less COVID-19 media.

Conclusion: COVID-19 media consumption is independently linked to a greater likelihood of pandemic-related PTSS in U.S. veterans.

Mitigating neurological, cognitive, and psychiatric sequelae of COVID-19-related critical illness

Lancet Respir Med. 2023 Aug;11(8):726-738. doi: 10.1016/S2213-2600(23)00238-2. Epub 2023 Jul 17.

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Abstract

Despite advances in the treatment and mitigation of critical illness caused by infection with SARS-CoV-2, millions of survivors have a devastating, post-acute infection syndrome known as long COVID. A large proportion of patients with long COVID have nervous system dysfunction, which is also seen in the distinct but overlapping condition of post-intensive care syndrome (PICS), putting survivors of COVID-19-related critical illness at high risk of long-lasting morbidity affecting multiple organ systems and, as a result, engendering measurable deficits in quality of life and productivity. In this Series paper, we discuss neurological, cognitive, and psychiatric sequelae in patients who have survived critical illness due to COVID-19. We review current knowledge of the epidemiology and pathophysiology of persistent neuropsychological impairments, and outline potential preventive strategies based on safe, evidence-based approaches to the management of pain, agitation, delirium, anticoagulation, and ventilator weaning during critical illness. We highlight priorities for current and future research, including possible therapeutic approaches, and offer considerations for health services to address the escalating health burden of long COVID.

The Department of Veterans' Affairs Depleted Uranium Cohort in the Time of COVID-19: Translating a Traditional Surveillance Protocol to a Telehealth Platform

J Occup Environ Med. 2023 Aug 1;65(8):670-676. doi: 10.1097/JOM.0000000000002875. Epub 2023 May 12.

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Abstract

Objective: In 2021, 37 members of a cohort of depleted uranium-exposed Gulf War I veterans were evaluated using a protocol tailored to accommodate COVID-19 safety practices on a telehealth platform.

Methods: Individual elements of the legacy protocol were reviewed for urgency and feasibility of inclusion in a modified, telehealth platform.

Results: The redesigned protocol included a participant readiness for telehealth assessment, nurse and physician telehealth visits, collection of usual health questionnaires, and urine collections for exposure monitoring for uranium and other fragment-related metal measures.

Conclusions: Despite some limitations in scope, the telehealth platform permitted a visual "visit" with surveillance participants who expressed a high comfort level with the format. The telehealth platform has apparent utility for occupational surveillance and should be explored as a standard approach for surveillance outside of public health emergencies.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and COVID-19: is there a connection?

Curr Med Res Opin. 2023 Aug;39(8):1119-1126. doi: 10.1080/03007995.2023.2242244. Epub 2023 Aug 4.

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Abstract

Objectives: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic systemic disease that leads to neurological, immunological, autonomic, and energy metabolism dysfunction. COVID-19 has been reported to cause similar symptoms to ME/CFS. The study aims to investigate the prevalence of myalgic encephalomyelitis in patients post-COVID-19 infection by assessing acute and long-term COVID-19 symptoms.

Methods: A cross-sectional questionnaire was developed based on the ME/CFS diagnostic criteria, as specified by the IOM clinical diagnostic criteria, and administered to participants with confirmed COVID-19 who are more than 18 years old and have BMI below 40 Kg/m2. Data from 437 participants were completed.

Results: The current study results revealed that 8.1% of the study participants met the ME/CFS diagnostic criteria. Interestingly, 2.8 of the study participants were classified to have COVID-19 related to ME/CFS. While 4.6% of participants were determined to have disease-related fatigue, 0.7% of participants showed ME/CFS that was not related to COVID-19, and 3.7% of participants were considered to have long COVID-19. Almost one-fourth of the study participants had a family history of ME/CFS. The current study demonstrated that the prevalence of ME/CFS is similar to slightly higher than reported in the literature.

Conclusion: The presence of a relationship between ME/CFS and COVID-19 has been supported by the results of our study. Follow-up of COVID-19 patients is strongly recommended to ensure proper management of ME/CFS symptoms.

Health outcomes before and during the COVID-19 pandemic in caregivers of service members and veterans with traumatic brain injury

Qual Life Res. 2023 Aug 12. doi: 10.1007/s11136-023-03491-1. Online ahead of print.

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Abstract

Purpose: To examine change in health-related quality of life (HRQOL) during the COVID-19 pandemic in caregivers of service members/veterans (SMVs) with traumatic brain injury (TBI), by comparing HRQOL during the first year of the pandemic to HRQOL 12 months pre-pandemic.

Methods: Caregivers (N = 246) were classified into three COVID-19 Pandemic Impact groups based on impact ratings of the pandemic on HRQOL: No Impact (n = 50), Mild Impact (n = 117), and Moderate-Severe Impact (n = 79). Caregivers completed 19 measures across physical, social, caregiving, and economic HRQOL domains, and a measure of SMV Adjustment. T-scores were used to determine individual symptom trajectories for each measure as follows: Asymptomatic (pre + during < 60 T); Developed (pre < 60 + during ≥ 60 T); Improved (pre ≥ 60 T + during < 60 T); and Persistent (pre + during ≥ 60 T).

Results: Using ANOVA, during the pandemic, the Moderate-Severe Impact group reported worse scores on 19 measures (d = 0.41-0.89) compared to the No Impact group and 18 measures (d = 0.31-0.62) compared to the Mild Impact group (d = 0.31-0.38). The Mild Impact group reported worse scores on two measures compared to the No Impact group (d = 0.42-0.43). Using the entire sample, the majority of HRQOL measures were classified as Asymptomatic (47.2-94.7%), followed by Persistent (2.4-27.2%). Few were classified as Developed (0.4-12.6%) or Improved (2.4-13.8%). Using repeated measures ANOVA, no meaningful effects sizes were found for mean scores on all measures completed pre-pandemic compared to during the pandemic (d ≤ 0.17).

Conclusion: The vast majority of caregivers reported stability in HRQOL pre-pandemic compared to during the pandemic. The COVID-19 pandemic was not associated with a high prevalence of decline in caregiver HRQOL.

Inflammatory and mental health sequelae of COVID-19

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Abstract

The COVID-19 pandemic has caused significant negative consequences to mental health. Increased inflammatory factors and neuropsychiatric symptoms, such as cognitive impairment ("brain fog"), depression, and anxiety are associated with long COVID [post-acute sequelae of SARS-CoV-2 infection (PASC), termed neuro-PASC]. The present study sought to examine the role of inflammatory factors as predictors of neuropsychiatric symptom severity in the context of COVID-19. Adults (n = 52) who tested negative or positive for COVID-19 were asked to complete self-report questionnaires and to provide blood samples for multiplex immunoassays. Participants who tested negative for COVID-19 were assessed at baseline and at a follow-up study visit (~4 weeks later). Individuals without COVID-19 reported significantly lower PHQ-4 scores at the follow-up visit, as compared to baseline (p = 0.03; 95% CI-1.67 to -0.084). Individuals who tested positive for COVID-19 and experienced neuro-PASC had PHQ-4 scores in the moderate range. The majority of people with neuro-PASC reported experiencing brain fog (70% vs. 30%). Those with more severe COVID-19 had significantly higher PHQ-4 scores, as compared to those with mild disease (p = 0.008; 95% CI 1.32 to 7.97). Changes in neuropsychiatric symptom severity were accompanied by alterations in immune factors, particularly monokine induced by gamma interferon (IFN-γ) (MIG, a. k.a. CXCL9). These findings add to the growing evidence supporting the usefulness of circulating MIG levels as a biomarker reflecting IFN-γ production, which is important because individuals with neuro-PASC have elevated IFN-γ responses to internal SARS-CoV-2 proteins.

Too tired to think: Relationship between post-COVID-19 fatigue and cognition in a veteran sample

Neuropsychol Rehabil. 2023 Aug 16;1-22. doi: 10.1080/09602011.2023.2244159. Online ahead of print.

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Abstract

COVID-19 survivors often endorse persistent physical and neuropsychiatric problems following disease recovery, a phenomenon described as "long COVID." Research exploring long-COVID continues to evolve in large-scale studies but remains limited among smaller populations (e.g., veterans). We explored the relationship between persistent post-COVID-19 fatigue and cognition among a sample of 246 veterans who voluntarily enrolled in a COVID-19 Convalescence Programme and completed a mental health evaluation of post-illness mood (depression, anxiety, PTSD), cognition (subjective complaints, Modified Telephone Interview for Cognitive Status [TICS-M] performance), fatigue, pain, and sleep. In concert with our hypotheses, subjective cognitive complaints are not significantly correlated with TICS-M performance, but rather are strongly correlated with long-COVID fatigue. Although cognitive changes are common post-COVID complaints, these are likely better predicted by other factors, (e.g., fatigue, mood, pain, and sleep disruption). Furthermore, comorbid mood, sleep, and pain complaints appeared to mediate the relationship between subjective cognitive complaints and fatigue. Limitations to this study included use of retrospective chart review data, limited access to pre-disease data for comparison, and lack of healthy controls. Clinicians should consider the impact of modifiable conditions associated with cognitive and functional decline, as these conditions may be targets for interdisciplinary treatment in a long-COVID veteran population.

Long-term symptom severity and clinical biomarkers in post-COVID-19/chronic fatigue syndrome: results from a prospective observational cohort

EClinicalMedicine. 2023 Aug 19;63:102146. doi: 10.1016/j.eclinm.2023.102146. eCollection 2023 Sep.

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7Si-M / "Der Simulierte Mensch" a Science Framework of Technische Universität Berlin and Charité - Universitätsmedizin Berlin, 10117 Berlin, Germany.

Abstract

Background: Post-COVID-19 syndrome (PCS) is characterised by a wide range of symptoms, primarily fatigue and exertion intolerance. While disease courses in the early months post-infection have been well-described, the long-term health consequences for patients with PCS with disabling fatigue remain unclear.

Methods: In this prospective observational cohort study, we evaluated symptom severity and various biomarkers, including hand grip strength (HGS), cardiovascular function, and laboratory parameters, in 106 patients with PCS with moderate to severe fatigue and exertion intolerance at three time points after infection (3-8, 9-16, and 17-20 months). The study was conducted at the Charité's Fatigue Centre and the Charité's outpatient clinic for neuroimmunology at Berlin, Germany from July 16, 2020, to February 18, 2022. A subset of patients (PCS-ME/CFS) met the diagnostic criteria for myalgic encephalomyelitis/chronic fatigue syndrome according to the Canadian Consensus Criteria (CCC). The aim was to determine differences in the disease course between the two patient groups (i.e., PCS vs PCS-ME/CFS) and identify correlating biomarkers.

Findings: Patients with PCS-ME/CFS reported persistently high severity of most symptoms up to 20 months after infection, while patients with PCS showed overall health improvement. Although fatigue and post-exertional malaise (PEM), hallmarks of post-infectious fatigue syndromes, were still evident in both groups, they remained more pronounced in PCS-ME/CFS. Inflammatory biomarkers decreased in both groups, but not antinuclear antibodies. Lower HGS at onset correlated with symptom persistence, particularly in patients with PCS-ME/CFS.

Interpretation: Our findings suggest that PCS can persist beyond 20 months post-infection and encompass the full scope of post-infectious ME/CFS as defined by the CCC. Sub-classifying

patients with PCS based on the CCC can assist in the management and monitoring of patients with PCS-ME/CFS due to their persistently higher symptom severity.

Late Mortality After COVID-19 Infection Among US Veterans vs Risk-Matched Comparators: A 2-Year Cohort Analysis

JAMA Intern Med. 2023 Aug 21;e233587. doi: 10.1001/jamainternmed.2023.3587. Online ahead of print.

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Abstract

Importance: Despite growing evidence of persistent problems after acute COVID-19, how long the excess mortality risk associated with COVID-19 persists is unknown.

Objective: To measure the time course of differential mortality among Veterans who had a first-documented COVID-19 infection by separately assessing acute mortality from later mortality among matched groups with infected and uninfected individuals who survived and were uncensored at the start of each period.

Design, settings, and participants: This retrospective cohort study used prospectively collected health record data from Veterans Affairs hospitals across the US on Veterans who had COVID-19 between March 2020 and April 2021. Each individual was matched with up to 5 comparators who had not been infected with COVID-19 at the time of matching. This match balanced, on a month-by-month basis, the risk of developing COVID-19 using 37 variables measured in the 24 months before the date of the infection or match. A primary analysis censored comparators when they developed COVID-19 with inverse probability of censoring weighting in Cox regression. A secondary analysis did not censor. Data analyses were performed from April 2021 through June 2023.

Exposure: First-documented case of COVID-19 (SARS-CoV-2) infection.

Main outcome measures: Hazard ratios for all-cause mortality at clinically meaningful intervals after infection: 0 to 90, 91 to 180, 181 to 365, and 366 to 730 days.

Results: The study sample comprised 208 061 Veterans with first-documented COVID-19 infection (mean [SD] age, 60.5 (16.2) years; 21 936 (10.5) women; 47 645 [22.9] Black and 139 604 [67.1] White individuals) and 1 037 423 matched uninfected comparators with similar characteristics. Veterans with COVID-19 had an unadjusted mortality rate of 8.7% during the 2-year period after the initial infection compared with 4.1% among uninfected comparators, with censoring if the comparator later developed COVID-19-an adjusted hazard ratio (aHR) of 2.01 (95% CI, 1.98-2.04). The risk of excess death varied, being highest during days 0 to 90 after infection (aHR, 6.36; 95% CI, 6.20-6.51) and still elevated during days 91 to 180 (aHR, 1.18; 95% CI, 1.12-1.23). Those who survived COVID-19 had decreased mortality on days 181 to 365 (aHR, 0.92; 95% CI, 0.89-0.95) and 366 to 730 (aHR, 0.89; 95% CI, 0.85-0.92). These patterns were consistent across sensitivity analyses.

Conclusion and relevance: The findings of this retrospective cohort study indicate that although overall 2-year mortality risk was worse among those infected with COVID-19, by day 180 after infection they had no excess mortality during the next 1.5 years.

WASF3 disrupts mitochondrial respiration and may mediate exercise intolerance in myalgic encephalomyelitis/chronic fatigue syndrome

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Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterized by various disabling symptoms including exercise intolerance and is diagnosed in the absence of a specific cause, making its clinical management challenging. A better understanding of the molecular mechanism underlying this apparent bioenergetic deficiency state may reveal insights for developing targeted treatment strategies. We report that overexpression of Wiskott-Aldrich Syndrome Protein Family Member 3 (WASF3), here identified in a 38-y-old woman suffering from long-standing fatigue and exercise intolerance, can disrupt mitochondrial respiratory supercomplex formation and is associated with endoplasmic reticulum (ER) stress. Increased expression of WASF3 in transgenic mice markedly decreased their treadmill running capacity with concomitantly impaired respiratory supercomplex assembly and reduced complex IV levels in skeletal muscle mitochondria. WASF3 induction by ER stress using endotoxin, well known to be associated with fatigue in humans, also decreased skeletal muscle complex IV levels in mice, while decreasing WASF3 levels by pharmacologic inhibition of ER stress improved mitochondrial function in the cells of the patient with chronic fatigue. Expanding on our findings, skeletal muscle biopsy samples obtained from a cohort of patients with ME/CFS showed increased WASF3 protein levels and aberrant ER stress activation. In addition to revealing a potential mechanism for the bioenergetic deficiency in ME/CFS, our study may also provide insights into other disorders associated with fatigue such as rheumatic diseases and long COVID.

The Potential Role of Hypothalamic Phospholipid Liposomes in the Supportive Therapy of Some Manifestations of Post-COVID-19 Condition: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Brain Fog

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Abstract

Post-COVID-19 condition (commonly known as Long COVID) is a heterogeneous clinical condition in which Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and brain fog stand out among the different clinical symptoms and syndromes. Cerebral metabolic alterations and neuroendocrine disorders seem to constitute an important part of the pathophysiology of Post-COVID-19 condition (PCC). Given the substantial lack of specific drugs and effective therapeutic strategies, hypothalamic phospholipid liposomes, which have been on the market for several years as adjuvant therapy for cerebral metabolic alterations resulting from neuroendocrine disorders, might represent a potential option in an overall therapeutic strategy that aims to control PCC-associated symptoms and syndromes. Their pharmacological mechanisms and clinical effects strongly support their potential effectiveness in PCC. Our initial clinical experience seems to corroborate this rationale. Further controlled clinical research is warranted in order to verify this hypothesis.

Neuroimmunological Effect of Vitamin D on Neuropsychiatric Long COVID Syndrome: A Review

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the coronavirus disease 2019 (COVID-19). COVID-19 is now recognized as a multiorgan disease with a broad spectrum of manifestations. A substantial proportion of individuals who have recovered from COVID-19 are experiencing persistent, prolonged, and often incapacitating sequelae, collectively referred to as long COVID. To date, definitive diagnostic criteria for long COVID diagnosis remain elusive. An emerging public health threat is neuropsychiatric long COVID, encompassing a broad range of manifestations, such as sleep disturbance, anxiety, depression, brain fog, and fatigue. Although the precise mechanisms underlying the neuropsychiatric complications of long COVID are presently not fully elucidated, neural cytolytic effects, neuroinflammation, cerebral microvascular compromise, breakdown of the blood-brain barrier (BBB), thrombosis, hypoxia, neurotransmitter dysregulation, and provoked neurodegeneration are pathophysiologically linked to long-term neuropsychiatric consequences, in addition to systemic hyperinflammation and maladaptation of the renin-angiotensin-aldosterone system. Vitamin D, a fat-soluble secosteroid, is a potent immunomodulatory hormone with potential beneficial effects on anti-inflammatory responses, neuroprotection, monoamine neurotransmission, BBB integrity, vasculometabolic functions, gut microbiota, and telomere stability in different phases of SARS-CoV-2 infection, acting through both genomic and nongenomic pathways. Here, we provide an up-to-date review of the potential mechanisms and pathophysiology of neuropsychiatric long COVID syndrome and the plausible neurological contributions of vitamin D in mitigating the effects of long COVID.

The perceived impact of pandemic scale (PIPS): Initial development and examination among U.S. military veterans

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Abstract

The COVID-19 pandemic has had significant impacts, including increases in mental health problems, distress, interpersonal conflict, unemployment, loss of income, housing instability, and food insecurity. Veterans may be particularly vulnerable to such impacts given their burden of mental and physical health problems. Few existing measures assess pandemic impact, and none have been validated for use with Veterans. We developed such a measure (the Perceived Impact of the Pandemic Scale; PIPS) and examined its psychometric performance in a national sample of US Veterans. Survey data from 567 Veterans were collected between 12/2020 and 2/2021. To examine PIPS factor structure, split sample exploratory/confirmatory factor analyses (EFA/CFA) were conducted to identify and test the most plausible model among an initial set of 18 items. Based on tests of factor extraction and factor loadings, 15 items clearly loaded onto three distinct factors. Internal reliability of all factors was $\omega > 0.8$ and CFA model fit was good ($\chi2(87) = 167.39$, $p < .001$; SRMR = 0.068; RMSEA = 0.060 [95% CI: 0.05, 0.07], CFI = 0.92). Mean factor scores were significantly positively correlated with measures of depression and loneliness, and negatively correlated with perceived social support. Results suggest the PIPS assesses three internally reliable factors comprised of perceived impact of the pandemic on interpersonal relationships, financial impact, and personal health and well-being. Construct validity with US Veterans was supported. The PIPS may be useful for examining the potentially disparate impact of pandemics on different populations. Research is needed to validate the PIPS in non-Veteran populations.

Postacute sequelae of COVID-19 at 2 years

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can lead to postacute sequelae in multiple organ systems, but evidence is mostly limited to the first year postinfection. We built a cohort of 138,818 individuals with SARS-CoV-2 infection and 5,985,227 noninfected control group from the US Department of Veterans Affairs and followed them for 2 years to estimate the risks of death and 80 prespecified postacute sequelae of COVID-19 (PASC) according to care setting during the acute phase of infection. The increased risk of death was not significant beyond 6 months after infection among nonhospitalized but remained significantly elevated through the 2 years in hospitalized individuals. Within the 80 prespecified sequelae, 69% and 35% of them became not significant at 2 years after infection among nonhospitalized and hospitalized individuals, respectively. Cumulatively at 2 years, PASC contributed 80.4 (95% confidence interval (CI): 71.6-89.6) and 642.8 (95% CI: 596.9-689.3) disability-adjusted life years (DALYs) per 1,000 persons among nonhospitalized and hospitalized individuals; 25.3% (18.9-31.0%) and 21.3% (18.2-24.5%) of the cumulative 2-year DALYs in nonhospitalized and hospitalized were from the second year. In sum, while risks of many sequelae declined 2 years after infection, the substantial cumulative burden of health loss due to PASC calls for attention to the care needs of people with long-term health effects due to SARS-CoV-2 infection.

Chronic inflammation, neuroglial dysfunction, and plasmalogen deficiency as a new pathobiological hypothesis addressing the overlap between post-COVID-19 symptoms and myalgic encephalomyelitis/chronic fatigue syndrome

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Abstract

After five waves of coronavirus disease 2019 (COVID-19) outbreaks, it has been recognized that a significant portion of the affected individuals developed long-term debilitating symptoms marked by chronic fatigue, cognitive difficulties ("brain fog"), post-exertional malaise, and autonomic dysfunction. The onset, progression, and clinical presentation of this condition, generically named post-COVID-19 syndrome, overlap significantly with another enigmatic condition, referred to as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Several pathobiological mechanisms have been proposed for ME/CFS, including redox imbalance, systemic and central nervous system inflammation, and mitochondrial dysfunction. Chronic inflammation and glial pathological reactivity are common hallmarks of several neurodegenerative and neuropsychiatric disorders and have been consistently associated with reduced central and peripheral levels of plasmalogens, one of the major phospholipid components of cell membranes with several homeostatic functions. Of great interest, recent evidence revealed a significant reduction of plasmalogen contents, biosynthesis, and metabolism in ME/CFS and acute COVID-19, with a strong association to symptom severity and other relevant clinical outcomes. These bioactive lipids have increasingly attracted attention due to their reduced levels representing a common pathophysiological manifestation between several disorders associated with aging and chronic inflammation. However, alterations in plasmalogen levels or their lipidic metabolism have not yet been examined in individuals suffering from post-COVID-19 symptoms. Here, we proposed a pathobiological model for post-COVID-19 and ME/CFS based on their common inflammation and dysfunctional glial reactivity, and highlighted the emerging implications of plasmalogen deficiency in the underlying mechanisms. Along with the promising outcomes of plasmalogen replacement therapy (PRT) for various neurodegenerative/neuropsychiatric disorders, we sought to propose PRT as a simple, effective, and safe strategy for the potential relief of the debilitating symptoms associated with ME/CFS and post-COVID-19 syndrome.

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

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Abstract

Topic importance: Postacute sequelae of SARS-CoV-2 (PASC) is a long-term consequence of acute infection from 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 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 illustrates exercise pathophysiologic commonalities between PASC and ME/CFS that will help guide future diagnostics and treatment.

Long-term safety of COVID vaccination in individuals with idiopathic inflammatory myopathies: results from the COVAD study

Rheumatol Int. 2023 Sep;43(9):1651-1664. doi: 10.1007/s00296-023-05345-y. Epub 2023 Jun 23.

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Abstract

Limited evidence on long-term COVID-19 vaccine safety in patients with idiopathic inflammatory myopathies (IIMs) continues to contribute to vaccine hesitancy. We studied delayed-onset vaccine adverse events (AEs) in patients with IIMs, other systemic autoimmune and inflammatory disorders (SAIDs), and healthy controls (HCs), using data from the second COVID-19 Vaccination in

Autoimmune Diseases (COVAD) study. A validated self-reporting e-survey was circulated by the COVAD study group (157 collaborators, 106 countries) from Feb-June 2022. We collected data on demographics, comorbidities, IIM/SAID details, COVID-19 history, and vaccination details. Delayed-onset (> 7 day) AEs were analyzed using regression models. A total of 15165 respondents undertook the survey, of whom 8759 responses from vaccinated individuals [median age 46 (35-58) years, 74.4% females, 45.4% Caucasians] were analyzed. Of these, 1390 (15.9%) had IIMs, 50.6% other SAIDs, and 33.5% HCs. Among IIMs, 16.3% and 10.2% patients reported minor and major AEs, respectively, and 0.72% (n = 10) required hospitalization. Notably patients with IIMs experienced fewer minor AEs than other SAIDs, though rashes were expectedly more than HCs [OR 4.0; 95% CI 2.2-7.0, p < 0.001]. IIM patients with active disease, overlap myositis, autoimmune comorbidities, and ChadOx1 nCOV-19 (Oxford/AstraZeneca) recipients reported AEs more often, while those with inclusion body myositis, and BNT162b2 (Pfizer) recipients reported fewer AEs. Vaccination is reassuringly safe in individuals with IIMs, with AEs, hospitalizations comparable to SAIDs, and largely limited to those with autoimmune multimorbidity and active disease. These observations may inform guidelines to identify high-risk patients warranting close monitoring in the post-vaccination period.

Effect of serious infectious threat response initiative (SITRI) during the coronavirus disease 2019 (COVID-19) pandemic at the Veterans Affairs North Texas Health Care System

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Abstract

Background: Health care-associated infections (HAIs) increased worldwide as health care facilities struggled through the pandemic. We describe our methods in the implementation of a programmatic initiative called serious infectious threat response initiative (SITRI) that was conceptualized to support our staff, to facilitate day-to-day clinical operations related to COVID-19 and to shield our infection prevention and control program (IPC) from excessive COVID-19 work burden to the extent possible to retain routine prevention focused efforts. Post implementation, we sought to understand and quantify the workload and utility of SITRI, IPC burnout and HAI incidence during the implementation period.

Methods: We correlated the number of weekly phone calls with inpatient COVID-19 census, assessed types of calls, staff feedback, IPC burnout, pre- and postpandemic HAI incidence, and the cost.

Results: There was significant correlation between SITRI calls and the weekly average COVID-19 census (P = .00026). IPC burnout evaluation indicated improvement in scores for exhaustion and reduced achievement and worsening in score for depersonalization. HAI incidence did not increase. SITRI's cost was $360,000.

Conclusions: Staff solicited SITRI's support in tandem with the COVID-19 burden. Our HAI during the pandemic did not increase while SITRI was operational in contrast to what is published in literature.

Rates of Covid 19 testing and positivity in US military veterans with SMI

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Abstract

Objective: to compare differences in COVID-19 testing rates and rates of positive test results between Veterans with and without SMI and identify the sociodemographic and clinical characteristics affecting COVID-19 testing/results.

Methods: Cohort study on data from the VA Corporate Data Warehouse (CDW), a data repository from clinical and administrative VA systems. The sample included Veterans who had ≥1 outpatient encounters nationally between 01/01/2019 and 12/31/2020. SMI diagnoses were derived as relevant ICD codes within the calendar years 2019-2020. Non-SMI Veterans were matched to SMI Veterans by age, gender, race and ethnicity for comparisons.

Results: The study included 1,018,047 Veterans, 339,349 had a diagnosis of SMI, and 83% were male. In unadjusted analyses, Veterans with SMI were more likely to receive testing for Covid 19 than non-SMI, however after adjusting for age, sex, race/ethnicity, region, and service utilization, Veterans with SMI were 6% less likely to receive testing for Covid 19 than non-SMI, with differences by type of SMI diagnosis: patients with psychosis (9.8%, P = .008) and schizophrenia (12.2%, P < .0001) were significantly less likely to receive an order for testing, compared to controls. Veterans with SMI were also less likely to receive a positive test result compared to controls.

Conclusions: Differences in access to testing exist across a nationally representative sample of US military Veterans with and without SMI. The finding that individuals with SMI are less likely to receive a positive test result can help reduce stigma.

SARS-CoV-2 reservoir in post-acute sequelae of COVID-19 (PASC)

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Erratum in

Author Correction: SARS-CoV-2 reservoir in post-acute sequelae of COVID-19 (PASC).

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Abstract

Millions of people are suffering from Long COVID or post-acute sequelae of COVID-19 (PASC). Several biological factors have emerged as potential drivers of PASC pathology. Some individuals with PASC may not fully clear the coronavirus SARS-CoV-2 after acute infection. Instead, replicating virus and/or viral RNA-potentially capable of being translated to produce viral proteins-persist in tissue as a 'reservoir'. This reservoir could modulate host immune responses or release viral proteins into the circulation. Here we review studies that have identified SARS-CoV-2 RNA/protein or immune responses indicative of a SARS-CoV-2 reservoir in PASC samples. Mechanisms by which a SARS-CoV-2 reservoir may contribute to PASC pathology, including coagulation, microbiome and neuroimmune abnormalities, are delineated. We identify research priorities to guide the further study of a SARS-CoV-2 reservoir in PASC, with the goal that clinical trials of antivirals or other therapeutics with potential to clear a SARS-CoV-2 reservoir are accelerated.

COVID-19 and Long COVID: Disruption of the Neurovascular Unit, Blood-Brain Barrier, and Tight Junctions

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), could affect brain structure and function. SARS-CoV-2 can enter the brain through different routes, including the olfactory, trigeminal, and vagus nerves, and through blood and immunocytes. SARS-CoV-2 may also enter the brain from the peripheral blood through a disrupted blood-brain barrier (BBB). The neurovascular unit in the brain, composed of neurons, astrocytes, endothelial cells, and pericytes, protects brain parenchyma by regulating the entry of substances from the blood. The endothelial cells, pericytes, and astrocytes highly express angiotensin converting enzyme 2 (ACE2), indicating that the BBB can be disturbed by SARS-CoV-2 and lead to derangements of tight junction and adherens junction proteins. This leads to increased BBB permeability, leakage of blood components, and movement of immune cells into the brain parenchyma. SARS-CoV-2 may also cross microvascular endothelial cells through an ACE2 receptor-associated pathway. The exact mechanism of BBB dysregulation in COVID-19/neuro-COVID is not clearly known, nor is the development of long COVID. Various blood biomarkers could indicate disease severity and neurologic complications in COVID-19 and help objectively diagnose those developing long COVID. This review highlights the importance of neurovascular and BBB disruption, as well as some potentially useful biomarkers in COVID-19, and long COVID/neuro-COVID.

Long COVID: what is known and what gaps need to be addressed

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Abstract

Introduction: Long COVID is a chronic condition that follows after acute COVID-19 and is characterized by a wide range of persistent, cyclic symptoms.

Sources of data: PubMed search for publications featuring 'Long COVID' or 'post-acute sequelae of COVID-19'.

Areas of agreement: Long COVID occurs frequently post-acute COVID-19, with a majority of people experiencing at least one symptom (such as cough, fatigue, myalgia, anosmia and dyspnoea) 4 weeks after infection.

Areas of controversy: The specific symptoms and the minimum duration of symptoms required to be defined as Long COVID.

Growing points: There is a consistent reduction in Long COVID incidence amongst vaccinated individuals, although the extent of this effect remains unclear.

Areas timely for developing research: There is an urgent need to understand the causes of Long COVID, especially extreme fatigue more than 6 months after infection. We must understand who is at risk and whether reinfections similarly risk Long COVID.

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

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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.

Prevalence and Correlates of Cannabis Use among U.S. Veterans during the Second Wave of the COVID-19 Pandemic

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Abstract

Introduction: Military veterans are at increased risk of substance use disorders. Limited research is available about veterans' cannabis use (CU) during the coronavirus disease 2019 (COVID-19) pandemic. This study estimated the prevalence of past 30-day CU, investigated individual-level correlates of past 30-day CU, and evaluated the reasons (medical, recreational, or both) of past 30-day CU among U.S. Veterans during the second wave of the COVID-19 pandemic.

Materials and methods: We used population-based, cross-sectional data from the 2021 Behavioral Risk Factor Surveillance System Survey Marijuana Use model. The sample included nationally representative military veterans aged 18+ years (n = 11,167). The outcome was past 30-day CU. Individual-level demographic, socioeconomic, behavioral, and clinical correlates were examined. Analyses were weighted to account for the survey's complex design with results generalizable to nearly 2.9 million veterans. We conducted weighted descriptive statistics, prevalence estimates, and multivariable logistic regression analyses.

Results: Out of 2.9 million veterans, 11.1% self-reported as non-Hispanic Black, 3.7% Hispanic, and 79.1% non-Hispanic White; 88.5% were men, and 72.8% were aged 50+ years. About 14.6% were current tobacco smokers, 4.7% were current e-cigarette users, 12.5% were binge alcohol drinkers, and 43.4% had three or more comorbid conditions. Overall, 8.5% reported CU in the past 30 days, of which 30.4% used it for medical reasons and 25.8% used it for nonmedical reasons. The prevalence of past 30-day CU decreased with age, education, and income level. Compared to their counterparts, the odds of past 30-day CU were greater among men, those living in urban areas, those with frequent mental distress, infrequent physical distress, and those who had at least one comorbid condition. Non-Hispanic Black veterans had 89% increased odds of past 30-day CU (adjusted odds ratio [AOR] =1.89, 95% confidence interval [CI], 1.19-3.0) compared with non-Hispanic White veterans. Current tobacco smokers had 3.54 (95% CI, 2.40-5.24) and former smokers had 1.78 (95% CI, 1.28-2.47) times higher odds of reporting past 30-day CU than never smokers. Current e-cigarette use (AOR = 3.37, 95% CI, 2.20-5.16) and binge drinking (AOR = 3.18, 95% CI, 2.29-4.41) were also statistically significantly associated with increased odds of past 30-day CU compared to no e-cigarette use and no binge drinking.

Conclusions: CU is prevalent among veterans, and certain subgroups are at higher risk of CU. Thus, identifying high-risk subgroups of veterans and adequately educating them about CU's benefits, risks, and safety is crucial.

Treatable traits for long COVID

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Abstract

Long COVID, or post-acute COVID-19 sequelae, is experienced by an estimated one in eight adults following acute COVID-19. Long COVID is a new and complex chronic health condition that typically includes multiple symptoms that cross organ systems and fluctuate over time; a one-size-fits-all approach is, therefore, not likely to be appropriate nor relevant for long COVID treatment. 'Treatable Traits' is a personalized medicine approach, purpose-built to address the complexity and heterogeneity of complex chronic conditions. This comprehensive review aimed to understand how a treatable traits approach could be applied to long COVID, by first identifying the most prevalent long COVID treatable traits and then the available evidence for strategies to target these traits. An umbrella review of 22 systematic reviews identified 34 symptoms and complications common with long COVID, grouped into eight long COVID treatable trait clusters: neurological, chest, psychological, pain, fatigue, sleep impairment, functional impairment and other. A systematic review of randomized control trials identified 18 studies that explored different intervention approaches for long COVID prevention (k = 4) or management (k = 14). While a single study reported metformin as effective for long COVID prevention, the findings need to be replicated and consensus is required around how to define long COVID as a clinical trial endpoint. For long COVID management, current evidence supports exercise training or respiratory muscle training for long COVID treatable traits in the chest and functional limitation clusters. While there are studies exploring interventions targeting other long COVID treatable traits, further high-quality RCTs are needed, particularly targeting treatable traits in the clusters of fatigue, psychological, pain and sleep impairment.

Covid-19 Outcomes Among US Veterans

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Abstract

Comparing Covid-19 mortality among the U.S. population overall with mortality among Veterans Affairs patients and U.S. military patients.

Frailty as a risk factor for post-acute sequelae of COVID-19 among US veterans during the Delta and Omicron waves

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Abstract

Background: Older populations have suffered the highest rates of SARS-CoV-2 infection and associated complications, including Post-Acute Sequelae of SARS-CoV-2 infection (PASC). Frailty is a geriatric syndrome that often coexists with COVID-19 infection. The vulnerability to stressors caused by multisystemic dysfunction that characterizes frailty may predispose older adults to develop PASC.

Methods: Retrospective cohort study using the VA COVID-19 Shared Data Resource to identify US veterans testing positive for SARS-CoV-2 between July 2021 and February 2022, without prior positive tests and who were alive 30 days after infection. Frailty was calculated using a 31-item VA Frailty Index generated from electronic health records. We categorized Veterans into robust (FI ≤ 0.10), prefrail (FI: >0.10- < 0.21), and frail (FI ≥ 0.21). We assessed the association between frailty and PASC and vaccination and PASC using Cox survival model, adjusting for covariates.

Results: We identified 245,857 COVID-19-positive veterans surviving 30 days after infection. The mean age was 57.5 ± 16.5 years; 87.2% were males, 68.1% were white, and 9.0% were Hispanic. Almost half of the sample (48.9%) were classified as robust, while 28.3% were pre-frail and 22.7% were frail; 99,886 (40.6%) were fully vaccinated, and 33,516 (13.6%) received booster doses. Over a median follow-up of 143 days (IQR = 101), 23,890 (9.7%) patients developed PASC. Within 6 months after infection, frailty and pre-frailty were associated with a 41% (adjusted HR [aHR]:1.40 (95% CI: 1.35-1.47) and 15% (aHR: 1.17 (95% CI: 1.11-1.19) increase in the risk of PASC compared with the robust, respectively. Vaccination and booster doses before infection were associated with a 27% (aHR: 0.73 (95% CI: 0.71-0.75) and 33% (aHR: 0.66 (95% CI: 0.63-0.69) reduction in the risk of developing PASC, respectively.

Conclusions: Frailty was associated with an increased risk of developing PASC. Vaccination was associated with a decreased risk of PASC, further reduced by booster doses. Early recognition of frailty in patients with COVID-19 may assist in the early identification and management of PASC.