Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations Concerning Long Haul COVID-19 October, November, December 2023

Prepared by Staff of the RACGWVI

RACGWVI: Long Haul COVID-19 — PubMed Citations for Oct, Nov, Dec 2023

The following is a selection of published research projects that focus on Long Haul COVID-19 for the months of October, November, December 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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Article Title: The title on each page (excluding table of contents), links to the abstract at PubMed.

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

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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 Oct;23(10):1119-1129. doi: 10.1016/S1473-3099(23)00299-2. Epub 2023 Jun 8.

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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.

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

Nat Immunol. 2023 Oct;24(10):1616-1627. doi: 10.1038/s41590-023-01601-2. Epub 2023 Sep 4.

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Erratum in

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

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Nat Immunol. 2023 Oct;24(10):1778. doi: 10.1038/s41590-023-01646-3.

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.

The immunology of long COVID

Nat Rev Immunol. 2023 Oct;23(10):618-634. doi: 10.1038/s41577-023-00904-7. Epub 2023 Jul 11.

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Erratum in

Author Correction: The immunology of long COVID.

Altmann DM, Whettlock EM, Liu S, Arachchillage DJ, Boyton RJ.

Abstract

Long COVID is the patient-coined term for the disease entity whereby persistent symptoms ensue in a significant proportion of those who have had COVID-19, whether asymptomatic, mild or severe. Estimated numbers vary but the assumption is that, of all those who had COVID-19 globally, at least 10% have long COVID. The disease burden spans from mild symptoms to profound disability, the scale making this a huge, new health-care challenge. Long COVID will likely be stratified into several more or less discrete entities with potentially distinct pathogenic pathways. The evolving symptom list is extensive, multi-organ, multisystem and relapsing-remitting, including fatigue, breathlessness, neurocognitive effects and dysautonomia. A range of radiological abnormalities in the olfactory bulb, brain, heart, lung and other sites have been observed in individuals with long COVID. Some body sites indicate the presence of microclots; these and other blood markers of hypercoagulation implicate a likely role of endothelial activation and clotting abnormalities. Diverse auto-antibody (AAB) specificities have been found, as yet without a clear consensus or correlation with symptom clusters. There is support for a role of persistent SARS-CoV-2 reservoirs and/or an effect of Epstein-Barr virus reactivation, and evidence from immune subset changes for broad immune perturbation. Thus, the current picture is one of convergence towards a map of an immunopathogenic aetiology of long COVID, though as yet with insufficient data for a mechanistic synthesis or to fully inform therapeutic pathways.

Psychosocial and Economic Impacts of the COVID-19 Pandemic on the Mental Health of Veteran Men and Women

J Womens Health (Larchmt). 2023 Oct;32(10):1041-1051. doi: 10.1089/jwh.2023.0078. Epub 2023 Aug 22.

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Abstract

Purpose: The psychosocial impacts of the coronavirus disease-2019 (COVID-19) pandemic on women Veterans' mental health compared to men are understudied, with few studies examining the differential impact of COVID-19 stressors on depression and post-traumatic stress disorder (PTSD). Furthermore, little is known about whether social support may buffer against adverse pandemic-related outcomes for this population. In the present study, we examined (1) gender differences in the impact of the COVID-19 pandemic on numerous life domains, including economic, work, home, social, and health; (2) how pandemic impacts in these domains were associated with depression and PTSD symptoms; and (3) whether social support buffered against worse mental health outcomes.

Materials and Methods: Data from 1530 Veterans enrolled in the Longitudinal Investigation of Gender, Health, and Trauma (LIGHT) study were analyzed using descriptive statistics and multiple groups' path analyses.

Results: Women reported higher pandemic impact scores across life domains. For both men and women, higher health impacts were associated with increased PTSD symptoms; differential findings emerged for depressive symptoms. Home and economic impacts were associated with increased depression for both men and women, social and health impacts were associated with depression for women, and work impacts were associated with depression for men. Higher social support was associated with decreased depressive symptoms for both men and women; however, social support moderated the relationship between pandemic impacts and both PTSD and depressive symptoms for women only.

Conclusions: Findings highlight the value of social support in mitigating effects of pandemic-related stress, particularly for women Veterans.

"I Am Not the Same as I Was Before": A Qualitative Analysis of COVID-19 Survivors

Int J Behav Med. 2023 Oct;30(5):663-672. doi: 10.1007/s12529-022-10129-y. Epub 2022 Oct 13.

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Abstract

Background: Little is known about the illness experience of patients' long-term emotional and physical recovery from severe COVID-19 infection. This study aimed to expand upon the recovery process of COVID-19 survivors up to 6 months after hospital discharge.

Methods: Qualitative analysis of free-response answers from a cohort study of 152 patients ≥ 18 years hospitalized with laboratory-confirmed SARS-CoV-2 surveyed at 1-month post hospital discharge and 6-months post hospital discharge. Responses were analyzed with a grounded theory approach to identify overarching themes.

Results: Participants described persistent complications, both physical and mental, that have affected their recovery from COVID-19. Five overarching themes of post-acute patient experiences were generated: (1) an increased awareness of a mind and body connection, (2) feelings of premature aging, (3) an overall decline in quality of life, (4) a continued fear of infection, and (5) methods of coping.

Conclusions: Patients described lasting changes to their mental health and overall quality of life in connection to physical complications after severe COVID-19 infection. Patients' reports of their experience call for a greater awareness of the psychological aspects of COVID-19 recovery to provide both physical and psychological rehabilitation services. Additional resources such as education around re-infection and financial resources are needed.

Excess mortality in US Veterans during the COVID-19 pandemic: an individual-level cohort study

Int J Epidemiol. 2023 Oct 6:dyad136. doi: 10.1093/ije/dyad136. Online ahead of print.

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Abstract

Background: Most analyses of excess mortality during the COVID-19 pandemic have employed aggregate data. Individual-level data from the largest integrated healthcare system in the US may enhance understanding of excess mortality.

Methods: We performed an observational cohort study following patients receiving care from the Department of Veterans Affairs (VA) between 1 March 2018 and 28 February 2022. We estimated excess mortality on an absolute scale (i.e. excess mortality rates, number of excess deaths) and a relative scale by measuring the hazard ratio (HR) for mortality comparing pandemic and pre-pandemic periods, overall and within demographic and clinical subgroups. Comorbidity burden and frailty were measured using the Charlson Comorbidity Index and Veterans Aging Cohort Study Index, respectively.

Results: Of 5 905 747 patients, the median age was 65.8 years and 91% were men. Overall, the excess mortality rate was 10.0 deaths/1000 person-years (PY), with a total of 103 164 excess deaths and pandemic HR of 1.25 (95% CI 1.25-1.26). Excess mortality rates were highest among the most frail patients (52.0/1000 PY) and those with the highest comorbidity burden (16.3/1000 PY). However, the largest relative mortality increases were observed among the least frail (HR 1.31, 95% CI 1.30-1.32) and those with the lowest comorbidity burden (HR 1.44, 95% CI 1.43-1.46).

Conclusions: Individual-level data offered crucial clinical and operational insights into US excess mortality patterns during the COVID-19 pandemic. Notable differences emerged among clinical risk groups, emphasizing the need for reporting excess mortality in both absolute and relative terms to inform resource allocation in future outbreaks.

Single-nuclei characterization of pervasive transcriptional signatures across organs in response to COVID-19

Elife. 2023 Oct 13:12:e81090. doi: 10.7554/eLife.81090.

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Abstract

Background: Infection by coronavirus SARS-CoV2 is a severe and often deadly disease that has implications for the respiratory system and multiple organs across the human body. While the effects in the lung have been extensively studied, less is known about the impact COVID-19 has across other organs.

Methods: Here, we contribute a single-nuclei RNA-sequencing atlas comprising six human organs across 20 autopsies where we analyzed the transcriptional changes due to COVID-19 in multiple cell types. The integration of data from multiple organs enabled the identification of systemic transcriptional changes.

Results: Computational cross-organ analysis for endothelial cells and macrophages identified systemic transcriptional changes in these cell types in COVID-19 samples. In addition, analysis of gene modules showed enrichment of specific signaling pathways across multiple organs in COVID-19 autopsies.

Conclusions: Altogether, the COVID Tissue Atlas enables the investigation of both cell type-specific and cross-organ transcriptional responses to COVID-19, providing insights into the molecular networks affected by the disease and highlighting novel potential targets for therapies and drug development.

Digital Patient Reported Outcome Measures Platform for Post-COVID-19 Condition and Other Long-Term Conditions: User-Centered Development and Technical Description

JMIR Hum Factors. 2023 Oct 20:10:e48632. doi: 10.2196/48632.

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Abstract

Background: Post-COVID-19 condition (PCC), colloquially known as long COVID, is a multisystem condition characterized by persistent symptoms beyond 4 weeks after the SARS-CoV-2 infection. More than 60 million people with PCC worldwide need prompt assessment, diagnosis, and monitoring, with many requiring specialist help from a multidisciplinary team of health care professionals (HCPs). Consequently, a scalable digital system is required for both people with PCC and HCPs to capture the breadth of symptoms and their impact on health, using patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs).

Objective: We aim to develop and implement a novel PCC digital PROM (DPROM) platform for (1) securely collecting PROM and PREM data from people with PCC, (2) enabling users to monitor symptoms longitudinally and assess response to treatment, (3) generating reports for the electronic health records (EHRs), (4) providing summary reports on PCC services based on national requirements, and (5) facilitating the sharing of relevant data with authorized research teams to accelerate our understanding of this new condition and evaluate new strategies to manage PCC.

Methods: We (1) undertook requirement analysis with people with PCC, HCPs, and researchers to identify the needs of the DPROM platform and determine its required functionalities; (2) designed and developed a clinically useful web portal for staff and a mobile app for patients, with a web-based alternative app to improve patient and staff choice, limit the risk of digital exclusion, and account for variability across services; (3) determined the PROMs and PREMs that PCC services would prefer to use on the platform; and (4) designed the summary report function that can be generated for each user for the EHR and for reporting to national health authorities.

Results: A DPROM platform to record PCC symptom profile, condition severity, functional disability, and quality of life, based on the C19-YRS (Yorkshire Rehabilitation Scale) and other PROMs and PREMs, was developed. Individual-level medical information and details on the COVID-19 illness can be captured systematically. The platform generates easy-to-understand scores, radar plots and line graphs for people with PCC to self-monitor their condition and for HCPs to assess the natural course of the condition and the response to interventions. Clinics can configure a suite of PROMs and PREMs based on their local and national service and commissioning requirements and support research studies which require large-scale data collection on PROMs. The DPROM platform enables automatic aggregate data analysis for services to undertake service evaluation and cost-effectiveness analysis. The DPROM platform generated summary report can be uploaded to the EHRs of people with PCC.

Conclusions: A multifunctional DPROM platform to assess, grade, and monitor PCC has been developed. Future research will analyze the system's usability in specialist PCC clinical services and other long-term conditions.

Role of Tau protein in long COVID and potential therapeutic targets

Front Cell Infect Microbiol. 2023 Oct 25:13:1280600. doi: 10.3389/fcimb.2023.1280600. eCollection 2023.

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Abstract

Introduction: Long COVID is an emerging public health burden and has been defined as a syndrome with common symptoms of fatigue, shortness of breath, cognitive dysfunction, and others impacting day-to-day life, fluctuating or relapsing over, occurring for at least two months in patients with a history of probable or confirmed SARS CoV-2 infection; usually three months from the onset of illness and cannot be explained by an alternate diagnosis. The actual prevalence of long-term COVID-19 is unknown, but it is believed that more than 17 million patients in Europe may have suffered from it during pandemic.

Pathophysiology: Currently, there is limited understanding of the pathophysiology of this syndrome, and multiple hypotheses have been proposed. Our literature review has shown studies reporting tau deposits in tissue samples of the brain from autopsies of COVID-19 patients compared to the control group, and the in-vitro human brain organoid model has shown aberrant phosphorylation of tau protein in response to SARS-CoV-2 infection. Tauopathies, a group of neurodegenerative disorders with the salient features of tau deposits, can manifest different symptoms based on the anatomical region of brain involvement and have been shown to affect the peripheral nervous system as well and explained even in rat model studies. Long COVID has more than 203 symptoms, with predominant symptoms of fatigue, dyspnea, and cognitive dysfunction, which tauopathy-induced CNS and peripheral nervous system dysfunction can explain. There have been no studies up till now to reveal the pathophysiology of long COVID. Based on our literature review, aberrant tau phosphorylation is a promising hypothesis that can be explored in future studies. Therapeutic approaches for tauopathies have multidimensional aspects, including targeting post-translational modifications, tau aggregation, and tau clearance through the autophagy process with the help of lysosomes, which can be potential targets for developing therapeutic interventions for the long COVID. In addition, future studies can attempt to find the tau proteins in CSF and use those as biomarkers for the long COVID.

Long-term impact of the COVID-19 pandemic on self-management of chronic conditions among high-risk adults in the USA: protocol for the C3 observational cohort study

BMJ Open. 2023 Oct 29;13(10):e077911. doi: 10.1136/bmjopen-2023-077911.

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Abstract

Introduction: COVID-19 is an unprecedented public health threat in modern times, especially for older adults or those with chronic illness. Beyond the threat of infection, the pandemic may also have longer-term impacts on mental and physical health. The COVID-19 & Chronic Conditions ('C3') study offers a unique opportunity to assess psychosocial and health/healthcare trajectories over 5 years among a diverse cohort of adults with comorbidities well-characterised from before the pandemic, at its onset, through multiple surges, vaccine rollouts and through the gradual easing of restrictions as society slowly returns to 'normal'.

Methods and analysis: The C3 study is an extension of an ongoing longitudinal cohort study of 'high-risk' adults (aged 23-88 at baseline) with one or more chronic medical conditions during the COVID-19 pandemic. Five active studies with uniform data collection prior to COVID-19 were leveraged to establish the C3 cohort; 673 adults in Chicago were interviewed during the first week of the outbreak. The C3 cohort has since expanded to include 1044 participants across eight survey waves (T1-T8). Four additional survey waves (T9-T12) will be conducted via telephone interviews spaced 1 year apart and supplemented by electronic health record and pharmacy fill data, for a total of 5 years of data post pandemic onset. Measurement will include COVID-19-related attitudes/behaviours, mental health, social behaviour, lifestyle/health behaviours, healthcare use, chronic disease self-management and health outcomes. Mental health trajectories and associations with health behaviours/outcomes will be examined in a series of latent group and mixed effects modelling, while also examining mediating and moderating factors.

Ethics and dissemination: This study was approved by Northwestern University's Feinberg School of Medicine Institutional Review Board (STU00215360). Results will be published in international peer-reviewed journals and summaries will be provided to the funders of the study.

Treatable traits for long COVID

Respirology. 2023 Nov;28(11):1005-1022. doi: 10.1111/resp.14596. Epub 2023 Sep 16.

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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.

Ramipril for the Treatment of COVID-19: RAMIC, a Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Adv Ther. 2023 Nov;40(11):4805-4816. doi: 10.1007/s12325-023-02618-7. Epub 2023 Aug 24.

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Abstract

Introduction: Retrospective studies report that angiotensin-converting enzyme inhibitors (ACEIs) may reduce the severity of COVID-19, but prospective data on de novo treatment with ACEIs are limited. The RAMIC trial was a randomized, multicenter, placebo-controlled, double-blind, allocation-concealed clinical trial to examine the efficacy of de novo ramipril versus placebo for the treatment of COVID-19.

Methods: Eligible participants were aged 18 years and older with a confirmed diagnosis of SARS-CoV-2 infection, recruited from urgent care clinics, emergency departments, and hospital inpatient wards at eight sites in the USA. Participants were randomly assigned to daily ramipril 2.5 mg or placebo orally in a 2:1 ratio, using permuted block randomization. Analyses were conducted on an intention-to-treat basis. The primary outcome was a composite of mortality, intensive care unit (ICU) admission, or invasive mechanical ventilation by day 14.

Results: Between 27 May 2020 and 19 April 2021, a total of 114 participants (51% female) were randomized to ramipril (n = 79) or placebo (n = 35). The overall mean (± SD) age and BMI were 45 (± 15) years and 33 (± 8) kg/m2. Two participants in the ramipril group required ICU admission and one died, compared with none in the placebo group. There were no significant differences between ramipril and placebo in the primary endpoint (ICU admission, mechanical ventilation, or death) (3% versus 0%, p = 1.00) or adverse events (27% versus 29%, p = 0.82). The study was terminated early because of a low event rate and subsequent Emergency Use Authorization of therapies for COVID-19.

Conclusion: De novo ramipril was not different compared with placebo in improving or worsening clinical outcomes from COVID-19 but appeared safe in non-critically ill patients with COVID-19.

Distinguishing features of long COVID identified through immune profiling

Nature. 2023 Nov;623(7985):139-148. doi: 10.1038/s41586-023-06651-y. Epub 2023 Sep 25.

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Abstract

Post-acute infection syndromes may develop after acute viral disease1. Infection with SARS-CoV-2 can result in the development of a post-acute infection syndrome known as long COVID. Individuals with long COVID frequently report unremitting fatigue, post-exertional malaise, and a variety of cognitive and autonomic dysfunctions2-4. However, the biological processes that are associated with the development and persistence of these symptoms are unclear. Here 275 individuals with or without long COVID were enrolled in a cross-sectional study that included multidimensional immune phenotyping and unbiased machine learning methods to identify biological features associated with long COVID. Marked differences were noted in circulating myeloid and lymphocyte populations relative to the matched controls, as well as evidence of exaggerated humoral responses directed against SARS-CoV-2 among participants with long COVID. Furthermore, higher antibody responses directed against non-SARS-CoV-2 viral pathogens were observed among individuals with long COVID, particularly Epstein-Barr virus. Levels of soluble immune mediators and hormones varied among groups, with cortisol levels being lower among participants with long COVID. Integration of immune phenotyping data into unbiased machine learning models identified the key features that are most strongly associated with long COVID status. Collectively, these findings may help to guide future studies into the pathobiology of long COVID and help with developing relevant biomarkers.

Space-time clustering of COVID-19 cases in the United States veteran population

Ann Epidemiol. 2023 Nov:87:9-16. doi: 10.1016/j.annepidem.2023.09.006. Epub 2023 Sep 22.

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Abstract

Purpose: To assess the distribution and clustering of coronavirus disease 2019 (COVID-19) testing and incidence over space and time, U.S. Department of Veteran's Affairs (VA) data were used to describe where and when veterans experienced highest proportions of test positivity.

Methods: Data for 6,342,455 veterans who utilized VA services between January 1, 2018, and September 30, 2021, were assessed for COVID-19 testing and test positivity. Testing and positivity proportions by county were mapped and focused-cluster tests identified significant clustering around VA facilities. Spatial cluster analysis also identified where and when veterans experienced highest proportions of test positivity.

Results: Within the veterans study population and our time window, 21.3% received at least one COVID-19 test, and 20.4% of those tested had at least one positive test. There was statistically significant clustering of testing around VA facilities, revealing regional variation in testing practices. Veterans experienced highest test positivity proportions between November 2020 and January 2021 in a cluster of states in the Midwest, compared to those who received testing outside of the identified cluster (RR: 3.45).

Conclusions: Findings reflect broad regional trends in COVID-19 positivity which can inform VA policy and resource allocation. Additional analysis is needed to understand patterns during Delta and Omicron variant periods.

Low-dose naltrexone use for the management of post-acute sequelae of COVID-19

Int Immunopharmacol. 2023 Nov;124(Pt B):110966. doi: 10.1016/j.intimp.2023.110966. Epub 2023 Oct 5.

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Abstract

The global prevalence of Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) stands at approximately 43 % among individuals who have previously had acute COVID-19. In contrast, in the United States, the National Center for Health Statistics (NCHS) estimates that around 11 % of individuals who have been infected with SARS-CoV-2 go on to experience long COVID. The underlying causes of PASC remains under investigation, and there are no currently established FDA-approved therapies. One of the leading hypotheses for the cause of PASC is the persistent activation of innate immune cells with increase systemic inflammation. Naltrexone is a medication with anti-inflammatory and immunomodulatory properties that has been used in other conditions that overlap with PASC. We performed a retrospective review of a clinical cohort of 59 patients at a single academic center who received low-dose naltrexone (LDN) off-label as a potential therapeutic intervention for PASC. The use of LDN was associated with a fewer number of symptoms, improved clinical symptoms (fatigue, post-exertional malaise, unrefreshing sleep, and abnormal sleep pattern), and a better functional status. This observation warrants testing in rigorous, randomized, placebo-controlled clinical trials.

Effectiveness of Nirmatrelvir-Ritonavir Against the Development of Post-COVID-19 Conditions Among U.S. Veterans : A Target Trial Emulation

Ann Intern Med. 2023 Nov;176(11):1486-1497. doi: 10.7326/M23-1394. Epub 2023 Oct 31.

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Abstract

Background: COVID-19 has been linked to the development of many post-COVID-19 conditions (PCCs) after acute infection. Limited information is available on the effectiveness of oral antivirals used to treat acute COVID-19 in preventing the development of PCCs.

Objective: To measure the effectiveness of outpatient treatment of COVID-19 with nirmatrelvir-ritonavir in preventing PCCs.

Design: Retrospective target trial emulation study comparing matched cohorts receiving nirmatrelvir-ritonavir versus no treatment.

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 treatment for acute COVID-19.

Measurements: Cumulative incidence of 31 potential PCCs at 31 to 180 days after treatment or a matched index date, including cardiac, pulmonary, renal, thromboembolic, gastrointestinal, neurologic, mental health, musculoskeletal, endocrine, and general conditions and symptoms.

Results: Eighty-six percent of the participants were male, with a median age of 66 years, and 17.5% were unvaccinated. Baseline characteristics were well balanced between participants treated with nirmatrelvir-ritonavir and matched untreated comparators. No differences were observed between participants treated with nirmatrelvir-ritonavir (n = 9593) and their matched untreated comparators in the incidence of most PCCs examined individually or grouped by organ system, except for lower combined risk for venous thromboembolism and pulmonary embolism (subhazard ratio, 0.65 [95% CI, 0.44 to 0.97]; cumulative incidence difference, -0.29 percentage points [CI, -0.52 to -0.05 percentage points]).

Limitations: Ascertainment of PCCs using International Classification of Diseases, 10th Revision, codes may be inaccurate. Evaluation of many outcomes could have resulted in spurious associations with combined thromboembolic events by chance.

Conclusion: Out of 31 potential PCCs, only combined thromboembolic events seemed to be reduced by nirmatrelvir-ritonavir.

Association of obesity on the outcome of critically ill patients affected by COVID-19

Med Intensiva (Engl Ed). 2023 Nov 1:S2173-5727(23)00152-2. doi: 10.1016/j.medine.2023.08.003. Online ahead of print.

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Abstract

Objective: To evaluate the impact of obesity on ICU mortality.

Design: Observational, retrospective, multicentre study.

Setting: Intensive Care Unit (ICU).

Patients: Adults patients admitted with COVID-19 and respiratory failure.

Interventions: None.

Primary variables of interest: Collected data included demographic and clinical characteristics, comorbidities, laboratory tests and ICU outcomes. Body mass index (BMI) impact on ICU mortality was studied as (1) a continuous variable, (2) a categorical variable obesity/non-obesity, and (3) as categories defined a priori: underweight, normal, overweight, obesity and Class III obesity. The impact of obesity on mortality was assessed by multiple logistic regression and Smooth Restricted cubic (SRC) splines for Cox hazard regression.

Results: 5,206 patients were included, 20 patients (0.4%) as underweight, 887(17.0%) as normal, 2390(46%) as overweight, 1672(32.1) as obese and 237(4.5%) as class III obesity. The obesity group patients (n = 1909) were younger (61 vs. 65 years, $p < 0.001$) and with lower severity scores APACHE II (13 [9-17] vs. 13[10-17, $p < 0.01$) than non-obese. Overall ICU mortality was 28.5% and not different for obese (28.9%) or non-obese (28.3%, $p = 0.65$). Only Class III obesity (OR = 2.19, 95%CI 1.44-3.34) was associated with ICU mortality in the multivariate and SRC analysis.

Conclusions: COVID-19 patients with a BMI > 40 are at high risk of poor outcomes in the ICU. An effective vaccination schedule and prolonged social distancing should be recommended.

Beyond the acute illness: Exploring long COVID and its impact on multiple organ systems

Physiol Int. 2023 Nov 9. doi: 10.1556/2060.2023.00256. Online ahead of print.

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Abstract

Unprecedented worldwide health catastrophe due to the COVID-19 pandemic has ended up resulting in high morbidity and mortality rates. Even though many people recover from acute infection, there is rising concern regarding post-COVID-19 conditions (PCCs), often referred to as post-acute sequelae of SARS-CoV-2 infection (PASC) or "long COVID." The respiratory, cardiovascular, neurological, and endocrine systems are just a few of the many organ systems that can be impacted by this multifarious, complicated illness. The clinical manifestations of long COVID can vary among individuals and may include fatigue, dyspnea, chest pain, cognitive impairment, and new-onset diabetes, among others. Although the underlying processes of long COVID are not fully understood, they probably involve unregulated immune response, persistent generation of pro-inflammatory cytokines (chronic inflammation), autoimmune-like reactions, persistent viral replication, and micro-clot formation. To create successful treatments and care plans, it is essential to comprehend the immunological mechanisms causing these difficulties. The pathogenesis of long COVID should be clarified and potential biomarkers to help with diagnosis and treatment should be sought after. To reduce the burden of long COVID on people and healthcare systems around the world, the need for long-term monitoring and management of long COVID problems should be emphasized. It also underscores the significance of a multidisciplinary approach to patient care. The goal of this review is to carefully evaluate the clinical signs and symptoms of long COVID, their underlying causes, and any potential immunological implications.

Functionality, physical activity, fatigue and quality of life in patients with acute COVID-19 and Long COVID infection

Sci Rep. 2023 Nov 14;13(1):19907. doi: 10.1038/s41598-023-47218-1.

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Abstract

A prominent feature of COVID-19, both in the short and long term, is the reduction in quality of life (QoL) due to low functionality scores and the presence of fatigue, which can hinder daily activities. The main objective of this study is to compare the functional status, level of physical activity, fatigue, and QoL of patients with Long COVID to other COVID-19 patients who did not develop persistent illness, and to determine whether there is a relationship between these variables and QoL. A cross-sectional study was conducted with 170 participants who had been infected with COVID-19 or had developed Long COVID. The main variables studied were functionality, physical activity, QoL and fatigue, measured using the PostCOVID-19 Functional Status Scale (PCFS), International Physical Activity Questionnaire (IPAQ), Short Form 12 (SF-12), and Fatigue Severity Scale (FSS). The main findings show a significant relationship ($p < 0.001$) between reduced functionality, lower physical activity levels, increased fatigue severity, and poorer QoL in Long COVID patients. Furthermore, these variables are also related to worse QoL, but only functional status predicts it. In conclusion, our results have shown highly significant correlations between the group with COVID-19 and Long COVID regarding functional status, level of physical activity, QoL, and fatigue.

Prevalence and risk factors of post-acute sequelae of COVID-19 among United States Veterans

Ann Epidemiol. 2023 Nov 15:89:1-7. doi: 10.1016/j.annepidem.2023.11.006. Online ahead of print.

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Abstract

Purpose: To better understand Post-Acute Sequelae of COVID-19 (PASC) in the Veteran population, this study aims to determine the prevalence of PASC and identify risk factors associated with its development.

Methods: This retrospective cohort study included 363,825 Veterans that tested positive for COVID-19 between February 1, 2020, and September 30, 2022. The primary outcome was the development of PASC 30-180 days following an acute infection with SARS-CoV-2. Multivariate logistic regression was utilized to examine factors associated with PASC.

Results: Of the 363,825 Veterans included in the analysis, 164,315 (45%) displayed symptoms of PASC. The Veterans in this analysis were predominantly male, non-Hispanic White, under the age of 65 years old, and lived in an urban residence. The strongest predictors for PASC included Non-Hispanic Black or African American race compared to Non-Hispanic White race (aOR=1.14), being between the ages of 50 and 64 compared to ages 50 and below (aOR=1.80), diabetes (aOR=8.46), and severe acute infection (aOR=1.42).

Conclusion: Results demonstrate potential health inequities for vulnerable individuals, as well as increased risk for individuals with pre-existing comorbidities. The prevalence of PASC provides estimates for future health care utilization. The risk factors identified can aid public health interventions to reduce the burden of PASC.

Conducting health services research during the COVID-19 pandemic: experiences from the veterans health administration

BMC Health Serv Res. 2023 Nov 16;23(1):1267. doi: 10.1186/s12913-023-10296-y.

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Abstract

Background: Health services researchers within the Veterans Health Administration (VA) seek to improve the delivery of care to the Veteran population, whose medical needs often differ from the general population. The COVID-19 pandemic and restricted access to medical centers and offices forced VA researchers and staff to transition to remote work. This study aimed to characterize the work experience of health service researchers during the COVID-19 pandemic.

Methods: A REDCap survey developed from the management literature was distributed in July 2020 to 800 HSR&D researchers and staff affiliated with VA Centers of Innovation. We requested recipients to forward the survey to VA colleagues. Descriptive analyses and logistic regression modeling were conducted on multiple choice and Likert scaled items. Manifest content analysis was conducted on open-text responses.

Results: Responses were received from 473 researchers and staff from 37 VA Medical Centers. About half (48%; n = 228) of VA HSR&D researchers and staff who responded to the survey experienced some interference with their research due to the COVID-19 pandemic, yet 55% (n = 260) reported their programs of research did not slow or stop. Clinician investigators reported significantly greater odds of interference than non-clinician investigators and support staff. The most common barriers to working remotely were loss of face-to-face interactions with colleagues (56%; n = 263) and absence of daily routines (25%; n = 118). Strategies teams used to address COVID-19 related remote work challenges included videoconferencing (79%; n = 375), virtual get-togethers (48%; n = 225), altered timelines (42%; n = 199), daily email updates (30%; n = 143) and virtual team huddles (16%; n = 74). Pre-pandemic VA information technology structures along with systems created to support multidisciplinary research teams working across a national healthcare system maintained and enhanced staff engagement and well-being.

Conclusions: This study identifies how the VA structures and systems put in place prior to the COVID-19 pandemic to support a dispersed workforce enabled the continuation of vital scientific research, staff engagement and well-being during a global pandemic. These findings can inform remote work policies and practices for researchers during the current and future crises.

Veterans and Nonveterans Coping With Stress During 4 Months of COVID-19

Ann Fam Med. 2023 Nov-Dec;21(6):508-516. doi: 10.1370/afm.3046.

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Abstract

Purpose: Identifying how people have been coping with stress during the COVID-19 pandemic allows us to anticipate how the population may react to similar stressors over time. In this study, we assessed patterns of coping styles among veterans and nonveterans, and stability and change in these strategies at 3 time points during the pandemic.

Methods: Using an online survey platform, we circulated a questionnaire at 3 time points during the period when COVID-19 vaccines became widely available (December 2-27, 2020; January 21-February 6, 2021; and March 8-23, 2021). The questionnaire asked participants about their extent of use of 11 coping strategies, and symptoms of anxiety and depression.

Results: A total of 2,085 participants (50.8% veterans) completed the questionnaire at 1 or more time points and 930 participants (62.8% veterans) completed it at all 3 time points. Cluster analysis identified 3 distinct coping styles: adaptive, distressed, and disengaged. Compared with nonveterans, veterans more commonly had adaptive and disengaged coping styles, and less commonly had a distressed coping style. The majority of the cohort (71.3%) changed coping style at least once during the study period. Participants who used the same coping style across all 3 time points reported lower levels of anxiety and depression.

Conclusions: Our data demonstrate a need to better understand the dynamic nature of coping with pandemic-level stressors across time. We did not find patterns of change in coping styles, but our findings point to potential advantages of stability in coping style. It is possible that less adaptive styles that are more stable may be advantageous for mental health. This research has implications for supporting patients dealing with stress in family medicine.

Older Adults' Quality of Life in Long-Term Care: A Cross-Sectional Comparison Before and During the COVID-19 Pandemic

Can J Aging. 2023 Dec;42(4):744-753. doi: 10.1017/S0714980823000272. Epub 2023 Jul 10.

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Abstract

This study aims to assess changes in long-term care (LTC) residents' quality of life (QoL) before and during the COVID-19 pandemic. A pre-test post-test study of 49 QoL measures, across four dimensions from the interRAI self-reported QoL survey, was conducted. Secondary data from 2019 (n = 116) and 2020 (n = 128) were analysed to assess the change in QoL. A significant decline in 12 measures was observed, indicating a change in QoL of LTC residents during the pandemic. Social life was the dimension mostly affected with residents reporting less opportunities to spend time with like-minded residents, explore new skills and interests, participate in meaningful religious activities, and have enjoyable things to do in the evenings. Several measures of personal control, staff responsiveness and care, and safety also demonstrated a significant change. The results can inform future strategies for pandemic and outbreak preparedness. Balancing the safety of residents with attention to their QoL should be a priority moving forward.

Long COVID and possible preventive options

Inflammopharmacology. 2023 Dec;31(6):2807-2817. doi: 10.1007/s10787-023-01204-1. Epub 2023 Jun 21.

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Abstract

Most of the people who suffered from COVID-19 fully recovered, but approximately 10-20% of them developed a wide variety of symptoms after they recover from their initial illness. Long COVID can develop at any patient; however, several studies suggest that the development of Long Covid syndrome may be linked to severity of acute illness. Some of the risk factors are hospitalization (with mechanical ventilation), Intensive Care Unit admission, age (over 50 years), gender (female) and comorbidities. Since the precise mechanism of Long COVID has not been clarified, neither the management of Long COVID-19 syndrome has been solved yet. Promising results have been published with vaccines as they effectively reduced the risk of Long COVID; however, other data suggest that vaccination results only partial protection in the post-acute phase of the disease. Recently, the orally effective antiviral agents (Paxlovid, molnupiravir) are preferred for outpatient management, and they highly reduce the progression of mild-to-moderate COVID-19 to severe one, and consequently, might reduce the development of Long COVID. Finally, recently, several clinical trials are in progress with either dietary supplements or drugs with different mechanisms of action. Additional information on the precise mechanisms, risk factors of Long COVID may result in successful preventive and therapeutic management of Long Covid 19 syndrome.

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

Qual Life Res. 2023 Dec;32(12):3463-3474. doi: 10.1007/s11136-023-03491-1. Epub 2023 Aug 12.

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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.

COVID-19 Vaccination Prior to SARS-CoV-2 Infection Reduced Risk of Subsequent Diabetes Mellitus: A Real-World Investigation Using U.S. Electronic Health Records

Diabetes Care. 2023 Dec 1;46(12):2193-2200. doi: 10.2337/dc23-0936.

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Abstract

Objective: Previous studies have indicated a bidirectional correlation between diabetes and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, no investigation has comprehensively explored the potential of coronavirus disease 2019 (COVID-19) vaccination to reduce the risk of new-onset diabetes in infected individuals.

Research design and methods: In the first of 2 cohorts, we compared the risk of new-onset diabetes between individuals infected with SARS-CoV-2 and noninfected individuals (N = 1,562,606) using the TriNetX database to validate findings in prior literature. For the second cohort, we identified 83,829 vaccinated and 83,829 unvaccinated COVID-19 survivors from the same period. Diabetes, antihyperglycemic drug use, and a composite of both were defined as outcomes. We conducted Cox proportional hazard regression analysis for the estimation of hazard ratios (HRs) and 95% CIs. Kaplan-Meier analysis was conducted to calculate the incidence of new-onset diabetes. Subgroup analyses based on age (18-44, 45-64, ≥65 years), sex (female, male), race (White, Black or African American, Asian), and BMI categories (<19.9, 20-29, 30-39, ≥40), sensitivities analyses, and a dose-response analysis were conducted to validate the findings.

Results: The initial cohort of patients infected with SARS-CoV-2 had a 65% increased risk (HR 1.65; 95% CI 1.62-1.68) of developing new-onset diabetes relative to noninfected individuals. In the second cohort, we observed that vaccinated patients had a 21% lower risk of developing new-onset diabetes in comparison with unvaccinated COVID-19 survivors (HR 0.79; 95% CI 0.73-0.86). Subgroup analyses by sex, age, race, and BMI yielded similar results. These findings were consistent in sensitivity analyses and cross-validation with an independent data set from TriNetX.

Conclusions: In conclusion, this study validates a 65% higher risk of new-onset diabetes in SARS-CoV-2-infected individuals compared to noninfected counterparts. Furthermore, COVID-19 survivors who received COVID-19 vaccinations experienced a reduced risk of new-onset diabetes, with a dose-dependent effect. Notably, the protective impact of COVID-19 vaccination is more pronounced among the Black/African American population than other ethnic groups. These findings emphasize the imperative of widespread vaccination to mitigate diabetes risk and the need for tailored strategies for diverse demographic groups to ensure equitable protection.

Rates of ICD-10 Code U09.9 Documentation and Clinical Characteristics of VA Patients With Post-COVID-19 Condition

JAMA Netw Open. 2023 Dec 1;6(12):e2346783. doi: 10.1001/jamanetworkopen.2023.46783.

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Abstract

Importance: A significant proportion of SARS-CoV-2 infected individuals experience post-COVID-19 condition months after initial infection.

Objective: To determine the rates, clinical setting, risk factors, and symptoms associated with the documentation of International Statistical Classification of Diseases Tenth Revision (ICD-10), code U09.9 for post-COVID-19 condition after acute infection.

Design, setting, and participants: This retrospective cohort study was performed within the US Department of Veterans Affairs (VA) health care system. Veterans with a positive SARS-CoV-2 test result between October 1, 2021, the date ICD-10 code U09.9 was introduced, and January 31, 2023 (n = 388 980), and a randomly selected subsample of patients with the U09.9 code (n = 350) whose symptom prevalence was assessed by systematic medical record review, were included in the analysis.

Exposure: Positive SARS-CoV-2 test result.

Main outcomes and measures: Rates, clinical setting, risk factors, and symptoms associated with ICD-10 code U09.9 in the medical record.

Results: Among the 388 980 persons with a positive SARS-CoV-2 test, the mean (SD) age was 61.4 (16.1) years; 87.3% were men. In terms of race and ethnicity, 0.8% were American Indian or Alaska Native, 1.4% were Asian, 20.7% were Black, 9.3% were Hispanic or Latino, 1.0% were Native Hawaiian or Other Pacific Islander; and 67.8% were White. Cumulative incidence of U09.9 documentation was 4.79% (95% CI, 4.73%-4.87%) at 6 months and 5.28% (95% CI, 5.21%-5.36%) at 12 months after infection. Factors independently associated with U09.9 documentation included older age, female sex, Hispanic or Latino ethnicity, comorbidity burden, and severe acute infection manifesting by symptoms, hospitalization, or ventilation. Primary vaccination (adjusted hazard ratio [AHR], 0.80 [95% CI, 0.78-0.83]) and booster vaccination (AHR, 0.66 [95% CI, 0.64-0.69]) were associated with a lower likelihood of U09.9 documentation. Marked differences by geographic region and facility in U09.9 code documentation may reflect local screening and care practices. Among the 350 patients undergoing systematic medical record review, the most common symptoms documented in the medical records among patients with the U09.9 code were shortness of breath (130 [37.1%]), fatigue or exhaustion (78 [22.3%]), cough (63 [18.0%]), reduced cognitive function or brain fog (22 [6.3%]), and change in smell and/or taste (20 [5.7%]).

Conclusions and relevance: In this cohort study of 388 980 veterans, documentation of ICD-10 code U09.9 had marked regional and facility-level variability. Strong risk factors for U09.9 documentation were identified, while vaccination appeared to be protective. Accurate and consistent documentation of U09.9 is needed to maximize its utility in tracking patients for clinical care and research. Future studies should examine the long-term trajectory of individuals with U09.9 documentation.

The impact of stress and well-being during the COVID-19 pandemic on mental health in U.S. veterans

Stress Health. 2023 Dec 21. doi: 10.1002/smi.3357. Online ahead of print.

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Abstract

The COVID-19 pandemic disrupted life around the globe and negatively impacted mental health (MH), including among military veterans. Building on previous research with U.S. veterans, the present study examined the association between a broad array of pandemic stressors and well-being on MH outcomes. A total of 372 veterans (51.3% women) from all service eras completed measures of posttraumatic stress disorder and depression during early (timepoint 1 [T1]) and peri-pandemic (timepoint 2 [T2]) periods. Pandemic-related stressors and well-being (satisfaction in life domains) were assessed at the peri-pandemic timepoint (T2). Logistic regression analyses were used to investigate associations between stressors and well-being with the likelihood of a probable MH diagnosis at T2 controlling for T1 MH status. More negative physical and MH impacts of the pandemic in addition to fewer positive consequences and lower satisfaction with paid work, finances, health, romantic relationships, and social life were associated with a higher likelihood of a probable T2 MH diagnosis. COVID infection was associated with lower odds of a probable T2 MH diagnosis. There were significant indirect effects, such that physical and MH impacts of the pandemic were associated with T2 MH via well-being. Overall, these findings highlight the role of stress and well-being on MH during a global pandemic. Interventions to address well-being may be important to address veteran MH during other periods of stress. Future research should examine the generalizability of study findings and further investigate factors that contribute to veterans' MH resilience during stressful life experiences.