Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations Concerning Long Haul COVID-19 January, February, March 2023

Prepared by Staff of the RACGWVI.

RACGWVI: Long Haul COVID-19 — PubMed Citations for Jan, Feb, March 2023

The following is a selected list of published research projects that focus on Long Haul COVID-19 for the months of January, February and March 2023.

This research alert supports the RACGWVI recommendation three, “Initiate research on the relationship between COVID-19, long-haul COVID-19, and their impact on GWI” of the four recommendations presented to the Secretary of Veterans Affairs. For further VA research updates please visit, VA RESEARCH CURRENTS — Research News from the U.S. Department of Veterans Affairs. VA Research Currents - Home

Please note, due to the evolving nature of COVID-19 (SARS-CoV-2) the terms Long, Long Haul, Post-acute and Post-acute Sequelae (PASC) all refer to the same long-term, multi-symptom illness caused by COVID-19 infection. Ref. Long COVID or Post-acute Sequelae …

Hyperlinks Guide:

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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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Molecular states during acute COVID-19 reveal distinct etiologies of long-term sequelae

Nat Med. 2023 Jan;29(1):236-246. doi: 10.1038/s41591-022-02107-4. Epub 2022 Dec 8.

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Abstract

Post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are debilitating, clinically heterogeneous and of unknown molecular etiology. A transcriptome-wide investigation was performed in 165 acutely infected hospitalized individuals who were followed clinically into the post-acute period. Distinct gene expression signatures of post-acute sequelae were already present in whole blood during acute infection, with innate and adaptive immune cells implicated in different symptoms. Two clusters of sequelae exhibited divergent plasma-cell-associated gene expression patterns. In one cluster, sequelae associated with higher expression of immunoglobulin-related genes in an anti-spike antibody titer-dependent manner. In the other, sequelae associated independently of these titers with lower expression of immunoglobulin-related genes, indicating lower non-specific antibody production in individuals with these sequelae. This relationship between lower total immunoglobulins and sequelae was validated in an external cohort. Altogether, multiple etiologies of post-acute sequelae were already detectable during SARS-CoV-2 infection, directly linking these sequelae with the acute host response to the virus and providing early insights into their development.

A systematic review and meta-analysis of long term physical and mental sequelae of COVID-19 pandemic: call for research priority and action

Mol Psychiatry. 2023 Jan;28(1):423-433. doi: 10.1038/s41380-022-01614-7. Epub 2022 Jun 6.

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Abstract

The long-term physical and mental sequelae of COVID-19 are a growing public health concern, yet there is considerable uncertainty about their prevalence, persistence and predictors. We conducted a comprehensive, up-to-date meta-analysis of survivors' health consequences and sequelae for COVID-19. PubMed, Embase and the Cochrane Library were searched through Sep 30th, 2021. Observational studies that reported the prevalence of sequelae of COVID-19 were included. Two reviewers independently undertook the data extraction and quality assessment. Of the 36,625 records identified, a total of 151 studies were included involving 1,285,407 participants from thirty-two countries. At least one sequelae symptom occurred in 50.1% (95% CI 45.4-54.8) of COVID-19 survivors for up to 12 months after infection. The most common investigation findings included

abnormalities on lung CT (56.9%, 95% CI 46.2-67.3) and abnormal pulmonary function tests (45.6%, 95% CI 36.3-55.0), followed by generalized symptoms, such as fatigue (28.7%, 95% CI 21.0-37.0), psychiatric symptoms (19.7%, 95% CI 16.1-23.6) mainly depression (18.3%, 95% CI 13.3-23.8) and PTSD (17.9%, 95% CI 11.6-25.3), and neurological symptoms (18.7%, 95% CI 16.2-21.4), such as cognitive deficits (19.7%, 95% CI 8.8-33.4) and memory impairment (17.5%, 95% CI 8.1-29.6). Subgroup analysis showed that participants with a higher risk of long-term sequelae were older, mostly male, living in a high-income country, with more severe status at acute infection. Individuals with severe infection suffered more from PTSD, sleep disturbance, cognitive deficits, concentration impairment, and gustatory dysfunction. Survivors with mild infection had high burden of anxiety and memory impairment after recovery. Our findings suggest that after recovery from acute COVID-19, half of survivors still have a high burden of either physical or mental sequelae up to at least 12 months. It is important to provide urgent and appropriate prevention and intervention management to preclude persistent or emerging long-term sequelae and to promote the physical and psychiatric wellbeing of COVID-19 survivors.

Long COVID: mechanisms, risk factors and recovery

Exp Physiol. 2023 Jan;108(1):12-27. doi: 10.1113/EP090802. Epub 2022 Nov 22.

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Abstract

New findings: What is the topic of this review? The emerging condition of long COVID, its epidemiology, pathophysiological impacts on patients of different backgrounds, physiological mechanisms emerging as explanations of the condition, and treatment strategies being trialled. The review leads from a Physiological Society online conference on this topic. What advances does it highlight? Progress in understanding the pathophysiology and cellular mechanisms underlying Long COVID and potential therapeutic and management strategies.

Abstract: Long COVID, the prolonged illness and fatigue suffered by a small proportion of those infected with SARS-CoV-2, is placing an increasing burden on individuals and society. A Physiological Society virtual meeting in February 2022 brought clinicians and researchers together to discuss the current understanding of long COVID mechanisms, risk factors and recovery. This review highlights the themes arising from that meeting. It considers the nature of long COVID, exploring its links with other post-viral illnesses such as myalgic encephalomyelitis/chronic fatigue

syndrome, and highlights how long COVID research can help us better support those suffering from all post-viral syndromes. Long COVID research started particularly swiftly in populations routinely monitoring their physical performance - namely the military and elite athletes. The review highlights how the high degree of diagnosis, intervention and monitoring of success in these active populations can suggest management strategies for the wider population. We then consider how a key component of performance monitoring in active populations, cardiopulmonary exercise training, has revealed long COVID-related changes in physiology - including alterations in peripheral muscle function, ventilatory inefficiency and autonomic dysfunction. The nature and impact of dysautonomia are further discussed in relation to postural orthostatic tachycardia syndrome, fatigue and treatment strategies that aim to combat sympathetic overactivation by stimulating the vagus nerve. We then interrogate the mechanisms that underlie long COVID symptoms, with a focus on impaired oxygen delivery due to micro-clotting and disruption of cellular energy metabolism, before considering treatment strategies that indirectly or directly tackle these mechanisms. These include remote inspiratory muscle training and integrated care pathways that combine rehabilitation and drug interventions with research into long COVID healthcare access across different populations. Overall, this review showcases how physiological research reveals the changes that occur in long COVID and how different therapeutic strategies are being developed and tested to combat this condition.

Post-acute sequelae of SARS-CoV-2 associates with physical inactivity in a cohort of COVID-19 survivors

Sci Rep. 2023 Jan 5;13(1):215. doi: 10.1038/s41598-022-26888-3.

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Abstract

The aim of this study was to determine whether Post-acute Sequelae of SARS-CoV-2 Infection (PASC) are associated with physical inactivity in COVID-19 survivors. This is a cohort study of COVID-19 survivors discharged from a tertiary hospital in Sao Paulo, Brazil. Patients admitted as inpatients due to laboratory-confirmed COVID-19 between March and August 2020 were consecutively invited for a follow-up in-person visit 6 to 11 months after hospitalization. Ten

symptoms of PASC were assessed using standardized scales. Physical activity was assessed by questionnaire and participants were classified according to WHO Guidelines. 614 patients were analyzed (age: 56 ± 13 years; 53% male). Frequency of physical inactivity in patients exhibiting none, at least 1, 1-4, and 5 or more symptoms of PASC was 51%, 62%, 58%, and 71%, respectively. Adjusted models showed that patients with one or more persistent PASC symptoms have greater odds of being physically inactive than those without any persistent symptoms (OR: 1.57 [95% CI 1.04-2.39], P = 0.032). Dyspnea (OR: 2.22 [1.50-3.33], P < 0.001), fatigue (OR: 2.01 [1.40-2.90], P < 0.001), insomnia (OR: 1.69 [1.16-2.49], P = 0.007), post-traumatic stress (OR: 1.53 [1.05-2.23], P = 0.028), and severe muscle/joint pain (OR: 1.53 [95% CI 1.08-2.17], P = 0.011) were associated with greater odds of being physically inactive. This study suggests that PASC is associated with physical inactivity, which itself may be considered as a persistent symptom among COVID-19 survivors. This may help in the early identification of patients who could benefit from additional interventions tailored to combat inactivity (even after treatment of PASC), with potential beneficial impacts on overall morbidity/mortality and health systems worldwide.

Patient Experiences with a Tertiary Care Post-COVID-19 Clinic

J Patient Exp. 2023 Jan 17;10:23743735231151539. doi: 10.1177/23743735231151539. eCollection 2023.

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Abstract

Post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (PASC) is a complex condition with multisystem involvement. We assessed patients' experience with a PASC clinic established at University of Iowa in June 2020. A survey was electronically mailed in June 2021 asking about (1) symptoms and their impact on functional domains using the Patient-Reported Outcomes Measurement Information System (PROMIS) measures (Global Health and Cognitive Function Abilities) (2) satisfaction with clinic services, referrals, barriers to care, and recommended support resources. Survey completion rate was 35% (97/277). Majority were women (67%), Caucasian (93%), and were not hospitalized (76%) during acute COVID-19. As many as 50% reported wait time between 1 and 3 months, 40% traveled >1 h for an appointment and referred to various subspecialities. Participants reported high symptom burden-fatigue (77%), "brain fog" (73%), exercise intolerance (73%), anxiety (63%), sleep difficulties (56%) and depression (44%). On PROMIS measures, some patients scored significantly low (≥1.5 SD below mean) in physical (22.7%), mental (15.9%), and cognitive (17.6%) domains. Approximately 61% to 93% of participants were satisfied with clinical services. Qualitative analysis added insight to their experience with healthcare. Participants suggested potential strategies for optimizing recovery, including continuity of care, a co-located multispecialty clinic, and receiving timely information from emerging research. Participants appreciated that physicians validated their symptoms and provided continuity of care and access to specialists.

Mechanisms, Effects, and Management of Neurological Complications of Post-Acute Sequelae of COVID-19 (NC-PASC)

Biomedicines. 2023 Jan 27;11(2):377. doi: 10.3390/biomedicines11020377.Ian Z Ong 1, Dennis L Kolson 2, Matthew K Schindler 2

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Abstract

With a growing number of patients entering the recovery phase following infection with SARS-CoV-2, understanding the long-term neurological consequences of the disease is important to their care. The neurological complications of post-acute sequelae of SARS-CoV-2 infection (NC-PASC) represent a myriad of symptoms including headaches, brain fog, numbness/tingling, and other neurological symptoms that many people report long after their acute infection has resolved. Emerging reports are being published concerning COVID-19 and its chronic effects, yet limited knowledge of disease mechanisms has challenged therapeutic efforts. To address these issues, we review broadly the literature spanning 2020-2022 concerning the proposed mechanisms underlying NC-PASC, outline the long-term neurological sequelae associated with COVID-19, and discuss potential clinical interventions.

Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes

Nat Med. 2023 Jan;29(1):226-235. doi: 10.1038/s41591-022-02116-3. Epub 2022 Dec 1.

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Abstract

The post-acute sequelae of SARS-CoV-2 infection (PASC) refers to a broad spectrum of symptoms and signs that are persistent, exacerbated or newly incident in the period after acute SARS-CoV-2 infection. Most studies have examined these conditions individually without providing evidence on co-occurring conditions. In this study, we leveraged the electronic health record data of two large cohorts, INSIGHT and OneFlorida+, from the national Patient-Centered Clinical Research Network. We created a development cohort from INSIGHT and a validation cohort from OneFlorida+ including 20,881 and 13,724 patients, respectively, who were SARS-CoV-2 infected, and we investigated their newly incident diagnoses 30-180 days after a documented SARS-CoV-2 infection. Through machine learning analysis of over 137 symptoms and conditions, we identified four reproducible PASC subphenotypes, dominated by cardiac and renal (including 33.75% and 25.43% of the patients in the development and validation cohorts); respiratory, sleep and anxiety (32.75% and 38.48%); musculoskeletal and nervous system (23.37% and 23.35%); and digestive and respiratory system (10.14% and 12.74%) sequelae. These subphenotypes were associated with distinct patient demographics, underlying conditions before SARS-CoV-2 infection and acute infection phase severity. Our study provides insights into the heterogeneity of PASC and may inform stratified decision-making in the management of PASC conditions.

Post-acute sequelae of SARS-CoV-2 (PASC) syndrome presenting as postural orthostatic tachycardia syndrome (POTS)

Clin Exp Emerg Med. 2023 Jan 30. doi: 10.15441/ceem.22.409. Online ahead of print.Sarah Diekman 1 2, Tae Chung 3

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Abstract

The novel SARS-CoV-2 emerged in 2019, and the global COVID-19 pandemic continues into 2022. It has been known that a subset of patients develops chronic, debilitating symptoms after otherwise complete recovery from acute infection of COVID-19. Multiple terms have been used to describe this constellation of symptoms, including long COVID, long-haul COVID, and post-acute sequelae of SARS-CoV-2 syndrome (PASC). PASC is broadly defined as a wide range of new, returning, or ongoing symptoms at least four weeks after infection. Those patients are often seen in emergency departments after acute COVID- 19 infection, but their symptoms are not adequately managed because the underlying pathophysiology of PASC is not well understood. Among patients with PASC, postural orthostatic tachycardic syndrome (POTS) has been increasingly recognized. POTS is one of the most common forms of autonomic dysfunction and defined by a sustained orthostatic tachycardia during active standing or head-up tilt test in the absence of orthostatic hypotension or other cardiopulmonary diseases. Because POTS is a treatable condition, it is important to recognize POTS among PASC patients. Herein, we reviewed the current literature on POTS and dysautonomia in PASC in order to better understand the overlap and distinction between these pathologies.

A Review of Persistent Post-COVID Syndrome (PPCS)

Clin Rev Allergy Immunol. 2023 Feb;64(1):66-74. doi: 10.1007/s12016-021-08848-3. Epub 2021 Feb 20.

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Abstract

Persistent post-COVID syndrome, also referred to as long COVID, is a pathologic entity, which involves persistent physical, medical, and cognitive sequelae following COVID-19, including persistent immunosuppression as well as pulmonary, cardiac, and vascular fibrosis. Pathologic fibrosis of organs and vasculature leads to increased mortality and severely worsened quality of life. Inhibiting transforming growth factor beta (TGF-β), an immuno- and a fibrosis modulator, may attenuate these post-COVID sequelae. Current preclinical and clinical efforts are centered on the mechanisms and manifestations of COVID-19 and its presymptomatic and prodromal periods; by comparison, the postdrome, which occurs in the aftermath of COVID-19, which we refer to as persistent post-COVID-syndrome, has received little attention. Potential long-term effects from post-COVID syndrome will assume increasing importance as a surge of treated patients are discharged from the hospital, placing a burden on healthcare systems, patients' families, and society in general to care for these medically devastated COVID-19 survivors. This review explores underlying mechanisms and possible manifestations of persistent post-COVID syndrome, and presents a framework of strategies for the diagnosis and management of patients with suspected or confirmed persistent post-COVID syndrome.

Risks and burdens of incident dyslipidaemia in long COVID: a cohort study

Lancet Diabetes Endocrinol. 2023 Feb;11(2):120-128. doi: 10.1016/S2213-8587(22)00355-2. Epub 2023 Jan 6.

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Abstract

Background: Non-clinical evidence and a few human studies with short follow-ups suggest increased risk of dyslipidaemia in the post-acute phase of COVID-19 (ie, >30 days after SARS-CoV-2 infection). However, detailed large-scale controlled studies with longer follow-ups and in-depth assessment of the risks and burdens of incident dyslipidaemia in the post-acute phase of COVID-19 are not yet available. We, therefore, aimed to examine the risks and 1-year burdens of incident dyslipidaemia in the post-acute phase of COVID-19 among people who survive the first 30 days of SARS-CoV-2 infection.

Methods: In this cohort study, we used the national health-care databases of the US Department of Veterans Affairs to build a cohort of 51 919 participants who had a positive COVID-19 test and survived the first 30 days of infection between March 1, 2020, and Jan 15, 2021; a non-infected contemporary control group (n=2 647 654) that enrolled patients between March 1, 2020, and Jan 15, 2021; and a historical control group (n=2 539 941) that enrolled patients between March 1, 2018, and Jan 15, 2019. Control groups had no evidence of SARS-CoV-2 infection, and participants in all three cohorts were free of dyslipidaemia before cohort enrolment. We then used inverse probability weighting using predefined and algorithmically-selected high dimensional variables to estimate the risks and 1-year burdens of incident dyslipidaemia, lipid-lowering medications use, and a composite of these outcomes. We reported two measures of risk: hazard ratios (HRs) and burden per 1000 people at 12 months. Additionally, we estimated the risks and burdens of incident dyslipidaemia outcomes in mutually exclusive groups based on the care setting of the acute infection (ie, participants who were non-hospitalised, hospitalised, or admitted to intensive care during the acute phase of SARS-CoV-2 infection).

Findings: In the post-acute phase of the SARS-CoV-2 infection, compared with the non-infected contemporary control group, those in the COVID-19 group had higher risks and burdens of incident dyslipidaemia, including total cholesterol greater than 200 mg/dL (hazard ratio [HR] 1·26, 95% CI 1·22-1·29; burden 22·46, 95% CI 19·14-25·87 per 1000 people at 1 year), triglycerides greater than 150 mg/dL (1·27, 1·23-1·31; 22·03, 18·85-25·30), LDL cholesterol greater than 130 mg/dL (1·24, 1·20-1·29; 18·00, 14·98-21·11), and HDL cholesterol lower than 40 mg/dL (1·20, 1·16-1·25; 15·58, 12·52-18·73). The risk and burden of a composite of these abnormal lipid laboratory outcomes were 1·24 (95% CI 1·21-1·27) and 39·19 (95% CI 34·71-43·73), respectively. There was also increased risk and burden of incident lipid-lowering medications use (HR 1·54, 95% CI 1·48-1·61; burden 25·50, 95% CI 22·61-28·50). A composite of any dyslipidaemia outcome (laboratory abnormality or lipid-lowering medications use) yielded an HR of 1·31 (95% CI 1·28-1·34) and a burden of 54·03 (95% CI 49·21-58·92). The risks and burdens of these post-acute outcomes increased in a graded fashion corresponding to the severity of the acute phase of COVID-19 infection (ie, whether patients

were non-hospitalised, hospitalised, or admitted to intensive care). The results were consistent in analyses comparing the COVID-19 group to the non-infected historical control group.

Interpretation: Our findings suggest increased risks and 1-year burdens of incident dyslipidaemia and incident lipid-lowering medications use in the post-acute phase of COVID-19 infection. Post-acute care for those with COVID-19 should involve attention to dyslipidaemia as a potential post-acute sequela of SARS-CoV-2 infection.

Current and Emerging Knowledge in COVID-19

Radiology. 2023 Feb;306(2):e222462. doi: 10.1148/radiol.222462. Epub 2023 Jan 10.

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Abstract

COVID-19 has emerged as a pandemic leading to a global public health crisis of unprecedented morbidity. A comprehensive insight into the imaging of COVID-19 has enabled early diagnosis, stratification of disease severity, and identification of potential sequelae. The evolution of COVID-19 can be divided into early infectious, pulmonary, and hyperinflammatory phases. Clinical features, imaging features, and management are different among the three phases. In the early stage, peripheral ground-glass opacities are predominant CT findings, and therapy directly targeting SARS-CoV-2 is effective. In the later stage, organizing pneumonia or diffuse alveolar damage pattern are predominant CT findings and anti-inflammatory therapies are more beneficial. The risk of severe disease or hospitalization is lower in breakthrough or Omicron variant infection compared with nonimmunized or Delta variant infections. The protection rates of the fourth dose of mRNA vaccination were 34% and 67% against overall infection and hospitalizations for severe illness, respectively. After acute COVID-19 pneumonia, most residual CT abnormalities gradually decreased in extent, but they may remain as linear or multifocal reticular or cystic lesions. Advanced insights into the pathophysiologic and imaging features of COVID-19 along with vaccine benefits have improved patient care, but emerging knowledge of post-COVID-19 condition, or long COVID, also presents radiology with new challenges.

Post-acute sequelae of COVID-19 infection

Prev Med Rep. 2023 Feb;31:102097. doi: 10.1016/j.pmedr.2022.102097. Epub 2022 Dec 21.

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Abstract

To determine if people infected with SARS-CoV-2 were at higher risk of developing selected medical conditions post-recovery, data were extracted from the database of a large health maintenance organization (HMO) in Israel between March 2020 and May 2021. For each condition, a condition-naïve group prior to COVID-19 (PCR-positive) infection were compared to a condition-naïve, non-COVID-19 infected group, matched by gender, age, socioeconomic status, minority group status and number of months visited primary care physician (PCP) in previous year. Diagnosis and recuperation dates for each COVID-19 infected participant were applied to their matched comparison participant (1:1 ratio). Incidence of each condition was measured between date of recuperation and end of study period for each group and Cox regression models developed to determine hazard ratios by group status, controlling for demographic and health variables. Crude and adjusted incidence rates were higher for the COVID-19 infected group than those not infected with COVID-19 for treatment for depression/anxiety, sleep disturbance, diagnosis of deep venous thrombosis, lung disease and fibromyalgia. Differences in incidence were no longer observed between the two groups for treatment of sleep disturbance, and diagnosis of lung disease when those hospitalized during the acute-phase of illness (any reason) were excluded. No difference was found by COVID-19 infection status for post-acute incidence of diabetes, cerebrovascular accident, myocardial infarction, acute kidney disease, hypertension and ischemic heart disease. Patients post-COVID-19 infection should be evaluated for depression, anxiety, sleep disturbance, DVT, lung disease and fibromyalgia.

Neurological post-acute sequelae of SARS-CoV-2 infection

Psychiatry Clin Neurosci. 2023 Feb;77(2):72-83. doi: 10.1111/pcn.13481. Epub 2022 Oct 17.Masaki Takao 1, Masayuki Ohira 1

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Abstract

The novel coronavirus disease 19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can have two phases: acute (generally 4 weeks after onset) and chronic (>4 weeks after onset). Both phases include a wide variety of signs and symptoms including neurological and psychiatric symptoms. The signs and symptoms that are considered sequelae of COVID-19 are termed post-COVID condition, long COVID-19, and post-acute sequelae of SARS-CoV-2 infection (PASC). PASC symptoms include fatigue, dyspnea, palpitation, dysosmia, subfever, hypertension, alopecia, sleep problems, loss of concentration, amnesia, numbness, pain, gastrointestinal symptoms, depression, and anxiety. Because the specific pathophysiology of PASC has not yet been clarified, there are no definite criteria of the condition, hence the World Health Organization's definition is quite broad. Consequently, it is difficult to correctly diagnose PASC. Approximately 50% of patients may show at least one PASC symptom up to 12 months after COVID-19 infection; however, the exact prevalence of PASC has not been determined. Despite extensive research in progress worldwide, there are currently no clear diagnostic methodologies or treatments for PASC. In this review, we discuss the currently available information on PASC and highlight the neurological sequelae of COVID-19 infection. Furthermore, we provide clinical suggestions for diagnosing and caring for patients with PASC based on our outpatient clinic experience.

Recent developments in the immunopathology of COVID-19

Allergy. 2023 Feb;78(2):369-388. doi: 10.1111/all.15593. Epub 2022 Dec 5.

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Abstract

There has been an important change in the clinical characteristics and immune profile of Coronavirus disease 2019 (COVID-19) patients during the pandemic thanks to the extensive vaccination programs. Here, we highlight recent studies on COVID-19, from the clinical and immunological characteristics to the protective and risk factors for severity and mortality of COVID-19. The efficacy of the COVID-19 vaccines and potential allergic reactions after administration are also discussed. The occurrence of new variants of concerns such as Omicron BA.2, BA.4, and BA.5 and the global administration of COVID-19 vaccines have changed the clinical scenario of COVID-19. Multisystem inflammatory syndrome in children (MIS-C) may cause severe and heterogeneous disease but with a lower mortality rate. Perturbations in immunity of T cells, B cells, and mast cells, as well as autoantibodies and metabolic reprogramming may contribute to the long-term symptoms of COVID-19. There is conflicting evidence about whether atopic diseases, such as allergic asthma and rhinitis, are associated with a lower susceptibility and better outcomes of COVID-19. At the beginning of pandemic, the European Academy of Allergy and Clinical Immunology (EAACI) developed guidelines that provided timely information for the management of allergic diseases and preventive measures to reduce transmission in the allergic clinics. The global distribution of COVID-19 vaccines and emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants with reduced pathogenic potential dramatically decreased the morbidity, severity, and mortality of COVID-19. Nevertheless, breakthrough infection remains a challenge for disease control. Hypersensitivity reactions (HSR) to COVID-19 vaccines are low compared to other vaccines, and these were addressed in EAACI statements that provided indications for the management of allergic reactions, including anaphylaxis to COVID-19 vaccines. We have gained a depth knowledge and experience in the over 2 years since the start of the pandemic, and yet a full eradication of SARS-CoV-2 is not on the horizon. Novel strategies are warranted to prevent severe disease in high-risk groups, the development of MIS-C and long COVID-19.

Long COVID: An inevitable sequela of SARS-CoV-2 infection

J Microbiol Immunol Infect. 2023 Feb;56(1):1-9. doi: 10.1016/j.jmii.2022.10.003. Epub 2022 Oct 15.

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Abstract

At present, there are more than 560 million confirmed cases of the coronavirus disease 2019 (COVID-19) worldwide. Although more than 98% of patients with severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection can survive acute COVID, a significant portion of survivors can develop residual health problems, which is termed as long COVID. Although severe COVID-19 is generally associated with a high risk of long COVID, patients with asymptomatic or mild disease can also show long COVID. The definition of long COVID is inconsistent and its clinical manifestations are protean. In addition to general symptoms, such as fatigue, long COVID can affect many organ systems, including the respiratory, neurological, psychosocial, cardiovascular, gastrointestinal, and metabolic systems. Moreover, patients with long COVID may experience exercise intolerance and impaired daily function and quality of life. Long COVID may be caused by SARS-CoV-2 direct injury or its associated immune/inflammatory response. Assessment of patients with long COVID requires comprehensive evaluation, including history taking, physical examination, laboratory tests, radiography, and functional tests. However, there is no known effective treatment for long COVID. Based on the limited evidence, vaccines may help to prevent the development of long COVID. As long COVID is a new clinical entity that is constantly evolving, there are still many unknowns, and further investigation is warranted to enhance our understanding of this disease.

"Long Haulers"

Semin Respir Crit Care Med. 2023 Feb;44(1):130-142. doi: 10.1055/s-0042-1759568. Epub 2023 Jan 16.

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Abstract

Post-COVID conditions continue to afflict patients long after acute severe acute respiratory syndrome-coronavirus-2 (SARS CoV-2) infection. Over 50 symptoms across multiple organ systems have been reported, with pulmonary, cardiovascular, and neuropsychiatric sequelae occurring most frequently. Multiple terms have been used to describe post-COVID conditions including long COVID, long-haul COVID, postacute coronavirus disease 2019 (COVID-19), postacute sequelae of SARS-CoV-2 infection, long-term effects of COVID, and chronic COVID-19; however, standardized assessments and treatment algorithms for patients have generally been lacking. This review discusses the epidemiology and risk factors for post-COVID conditions and provides a general overview of the diagnostic assessment and treatment of specific manifestations. Data derived from the multitude of observational studies and scientific investigations into pathogenesis are providing a clearer understanding of the distinct phenotypes of post-COVID conditions. Insight gained from these studies and ongoing interventional trials continues to lead to the development of clinical protocols directed toward improving COVID-19 survivors' quality of life and preventing or reducing long-term morbidity.

A comparison of pain, fatigue, and function between post-COVID-19 condition, fibromyalgia, and chronic fatigue syndrome: a survey study

Pain. 2023 Feb 1;164(2):385-401. doi: 10.1097/j.pain.0000000000002711. Epub 2022 Jun 29.

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Abstract

A growing number of individuals report prolonged symptoms following acute Coronavirus-19 (COVID-19) infection, known as post-COVID-19 condition (post-COVID-19). While studies have emerged investigating the symptom sequelae of post-COVID-19, there has been limited investigation into the characterization of pain, fatigue, and function in these individuals, despite initial reports of a clinical phenotype similar to fibromyalgia syndrome (FMS) and chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME). This study aimed to characterize multiple symptom domains in individuals reporting post-COVID-19 and compare its clinical phenotype with those with FMS and CFS. A total of 707 individuals with a single or comorbid diagnosis of post-COVID-19, FMS, and/or CFS completed multiple surveys assessing self-reported pain, fatigue, physical and cognitive function, catastrophizing, kinesiophobia, anxiety, depression, dyspnea, and sleep quality. In all 3 diagnoses, elevated pain, fatigue, anxiety, depression, catastrophizing, and kinesiophobia were reported. Physical and cognitive function were similarly impacted among individuals with post-COVID-19, FMS, and CFS; however, individuals with post-COVID-19 reported lower pain and fatigue than FMS and CFS. The comorbid diagnosis of post-COVID-19 with FMS and/or CFS further exacerbated pain, fatigue, and psychological domains when compared with post-COVID-19 alone. In summary, individuals with post-COVID-19 report a symptom phenotype similar to FMS and CFS, negatively impacting cognitive and physical function, but with less severe pain and fatigue overall. These findings may help direct future investigations of the benefit of a biopsychosocial approach to the clinical management of post-COVID-19.

Characterizing and Predicting Post-Acute Sequelae of SARS CoV-2 Infection (PASC) in a Large Academic Medical Center in the US

J Clin Med. 2023 Feb 7;12(4):1328. doi: 10.3390/jcm12041328.

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Abstract

Background: A growing number of Coronavirus Disease-2019 (COVID-19) survivors are affected by post-acute sequelae of SARS CoV-2 infection (PACS). Using electronic health record data, we aimed to characterize PASC-associated diagnoses and develop risk prediction models.

Methods: In our cohort of 63,675 patients with a history of COVID-19, 1724 (2.7%) had a recorded PASC diagnosis. We used a case-control study design and phenome-wide scans to characterize PASC-associated phenotypes of the pre-, acute-, and post-COVID-19 periods. We also integrated PASC-associated phenotypes into phenotype risk scores (PheRSs) and evaluated their predictive performance.

Results: In the post-COVID-19 period, known PASC symptoms (e.g., shortness of breath, malaise/fatigue) and musculoskeletal, infectious, and digestive disorders were enriched among PASC cases. We found seven phenotypes in the pre-COVID-19 period (e.g., irritable bowel syndrome, concussion, nausea/vomiting) and sixty-nine phenotypes in the acute-COVID-19 period (predominantly respiratory, circulatory, neurological) associated with PASC. The derived pre- and acute-COVID-19 PheRSs stratified risk well, e.g., the combined PheRSs identified a quarter of the cohort with a history of COVID-19 with a 3.5-fold increased risk (95% CI: 2.19, 5.55) for PASC compared to the bottom 50%.

Conclusions: The uncovered PASC-associated diagnoses across categories highlighted a complex arrangement of presenting and likely predisposing features, some with potential for risk stratification approaches.

Persistent Circulating Severe Acute Respiratory Syndrome Coronavirus 2 Spike Is Associated With Post-acute Coronavirus Disease 2019 Sequelae

Clin Infect Dis. 2023 Feb 8;76(3):e487-e490. doi: 10.1093/cid/ciac722.

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Abstract

The diagnosis of postacute sequelae of coronavirus disease 2019 (PASC) poses an ongoing medical challenge. To identify biomarkers associated with PASC we analyzed plasma samples collected from PASC and coronavirus disease 2019 patients to quantify viral antigens and inflammatory markers. We detect severe acute respiratory syndrome coronavirus 2 spike predominantly in PASC patients up to 12 months after diagnosis.

A case of post-COVID-19 myalgic encephalomyelitis/chronic fatigue syndrome characterized by post-exertional malaise and low serum acylcarnitine level

Clin Case Rep. 2023 Feb 10;11(2):e6930. doi: 10.1002/ccr3.6930. eCollection 2023 Feb.

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Abstract

COVID-19 afflicts patients with acute symptoms and longer term sequelae. One of the sequelae is myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which is often difficult to diagnose, having no established tests. In this article, we synthesize information from literature reviews on patients with ME/CSF that developed after recovery from COVID-19.

Racial/Ethnic Disparities in Post-acute Sequelae of SARS-CoV-2 Infection in New York: an EHR-Based Cohort Study from the RECOVER Program

J Gen Intern Med. 2023 Feb 16;1-10. doi: 10.1007/s11606-022-07997-1. Online ahead of print.

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Abstract

Background: Compared to white individuals, Black and Hispanic individuals have higher rates of COVID-19 hospitalization and death. Less is known about racial/ethnic differences in post-acute sequelae of SARS-CoV-2 infection (PASC).

Objective: Examine racial/ethnic differences in potential PASC symptoms and conditions among hospitalized and non-hospitalized COVID-19 patients.

Design: Retrospective cohort study using data from electronic health records.

Participants: 62,339 patients with COVID-19 and 247,881 patients without COVID-19 in New York City between March 2020 and October 2021.

Main measures: New symptoms and conditions 31-180 days after COVID-19 diagnosis.

Key results: The final study population included 29,331 white patients (47.1%), 12,638 Black patients (20.3%), and 20,370 Hispanic patients (32.7%) diagnosed with COVID-19. After adjusting for confounders, significant racial/ethnic differences in incident symptoms and conditions existed among both hospitalized and non-hospitalized patients. For example, 31-180 days after a positive SARS-CoV-2 test, hospitalized Black patients had higher odds of being diagnosed with diabetes (adjusted odds ratio [OR]: 1.96, 95% confidence interval [CI]: 1.50-2.56, q<0.001) and headaches (OR: 1.52, 95% CI: 1.11-2.08, q=0.02), compared to hospitalized white patients. Hospitalized Hispanic patients had higher odds of headaches (OR: 1.62, 95% CI: 1.21-2.17, q=0.003) and dyspnea (OR: 1.22, 95% CI: 1.05-1.42, q=0.02), compared to hospitalized white patients. Among non-hospitalized patients, Black patients had higher odds of being diagnosed with pulmonary embolism (OR: 1.68, 95% CI: 1.20-2.36, q=0.009) and diabetes (OR: 2.13, 95% CI: 1.75-2.58, q<0.001), but lower odds of encephalopathy (OR: 0.58, 95% CI: 0.45-0.75, q<0.001), compared to white patients. Hispanic patients had higher odds of being diagnosed with headaches (OR: 1.41, 95% CI: 1.24-1.60, q<0.001) and chest pain (OR: 1.50, 95% CI: 1.35-1.67, q < 0.001), but lower odds of encephalopathy (OR: 0.64, 95% CI: 0.51-0.80, q<0.001).

Conclusions: Compared to white patients, patients from racial/ethnic minority groups had significantly different odds of developing potential PASC symptoms and conditions. Future research should examine the reasons for these differences.

Long COVID: major findings, mechanisms and recommendations

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Abstract

Long COVID is an often debilitating illness that occurs in at least 10% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. More than 200 symptoms have been identified with impacts on multiple organ systems. At least 65 million individuals worldwide are estimated to have long COVID, with cases increasing daily. Biomedical research has made substantial progress in identifying various pathophysiological changes and risk factors and in characterizing the illness; further, similarities with other viral-onset illnesses such as myalgic encephalomyelitis/chronic fatigue syndrome and postural orthostatic tachycardia syndrome have laid the groundwork for research in the field. In this Review, we explore the current literature and highlight key findings, the overlap with other conditions, the variable onset of symptoms, long COVID in children and the impact of vaccinations. Although these key findings are critical to understanding long COVID, current diagnostic and treatment options are insufficient, and clinical trials must be prioritized that address leading hypotheses. Additionally, to strengthen long COVID research, future studies must account for biases and SARS-CoV-2 testing issues, build on viral-onset research, be inclusive of marginalized populations and meaningfully engage patients throughout the research process.

Long-COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): Potential neurophysiological biomarkers for these enigmatic entities

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No abstract available

Blood-brain barrier penetration of non-replicating SARS-CoV-2 and S1 variants of concern induce neuroinflammation which is accentuated in a mouse model of Alzheimer's disease

Brain Behav Immun. 2023 Mar;109:251-268. doi: 10.1016/j.bbi.2023.01.010. Epub 2023 Jan 20.

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Abstract

COVID-19 and especially Long COVID are associated with severe CNS symptoms and may place persons at risk to develop long-term cognitive impairments. Here, we show that two non-infective models of SARS-CoV-2 can cross the blood-brain barrier (BBB) and induce neuroinflammation, a major mechanism underpinning CNS and cognitive impairments, even in the absence of productive infection. The viral models cross the BBB by the mechanism of adsorptive transcytosis with the sugar N-acetylglucosamine being key. The delta and omicron variants cross the BB B faster than the other variants of concern, with peripheral tissue uptake rates also differing for the variants. Neuroinflammation induced by icv injection of S1 protein was greatly enhanced in young and especially in aged SAMP8 mice, a model of Alzheimer's disease, whereas sex and obesity had little effect.

Tissue injury and leukocyte changes in post-acute sequelae of SARS-CoV-2: review of 2833 post-acute patient outcomes per immune dysregulation and microbial translocation in long COVID

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Abstract

A significant number of persons with coronavirus disease 2019 (COVID-19) experience persistent, recurrent, or new symptoms several months after the acute stage of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This phenomenon, termed post-acute sequelae of SARS-CoV-2 (PASC) or long COVID, is associated with high viral titers during acute infection, a persistently hyperactivated immune system, tissue injury by NETosis-induced micro-thrombofibrosis (NETinjury), microbial translocation, complement deposition, fibrotic macrophages, the presence of autoantibodies, and lymphopenic immune environments. Here, we review the current literature on the immunological imbalances that occur during PASC. Specifically, we focus on data supporting common immunopathogenesis and tissue injury mechanisms shared across this highly heterogenous disorder, including NETosis, coagulopathy, and fibrosis. Mechanisms include changes in leukocyte subsets/functions, fibroblast activation, cytokine imbalances, lower cortisol, autoantibodies, co-pathogen reactivation, and residual immune activation driven by persistent viral antigens and/or microbial translocation. Taken together, we develop the premise that SARS-CoV-2 infection results in PASC as a consequence of acute and/or persistent single or multiple organ injury mediated by PASC determinants to include the degree of host responses (inflammation, NETinjury), residual viral antigen (persistent antigen), and exogenous factors (microbial translocation). Determinants of PASC may be amplified by comorbidities, age, and sex.

Cerebrovascular Manifestations of SARS-CoV-2: A Comprehensive Review

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Abstract

Purpose of review: The risks of cerebrovascular manifestations due to SARS-CoV-2 infection are significantly increased within the first 6 months of the infection. Our work aims to give an update on current clinical aspects of diagnosis and treatment of cerebrovascular manifestations during acute and long-term SARS-CoV-2 infection.

Recent findings: The incidence of acute ischemic stroke and haemorrhagic stroke during acute SARS-CoV-2 patients is estimated at 0.9 to 4.6% and 0.5-0.9%, respectively, and were associated with increased mortality. The majority presented with hemiparesis, dysarthria, sensory deficits, and a NIHSS score within 5-15. In addition, beyond the first 30 days of infection people with COVID-19 exhibited increased risk of stroke. During acute phase, age, hypertension, diabetes, and medical history of vascular disease were increased in patients with COVID-19 with new onset of cerebrovascular manifestations, while during long-COVID-19, the risk of cerebrovascular manifestations were found increased regardless of these factors. The management of patients with large-vessel ischemic stroke fulfilling the intravenous thrombolysis criteria are successfully treated according to the guidelines, while hyperosmolar therapy is typically administered in 4- to 6-h intervals. In addition, prophylaxis of anticoagulation therapy is associated with a better prognosis and low mortality during acute and post hospital discharge of patients with COVID-19.

Summary: In this work, we provide a comprehensive review of the current literature on acute and post-acute COVID-19 cerebrovascular sequelae, symptomatology, and its pathophysiology mechanisms. Moreover, we discuss therapeutic strategies for these patients during acute and long-term care and point populations at risk. Our findings suggest that older patients with risk factors such as hypertension, diabetes, and medical history of vascular disease are more likely to develop cerebrovascular complications.

Post-acute sequelae after SARS-CoV-2 infection by viral variant and vaccination status: a multicenter cross-sectional study

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Abstract

Background: Disentangling the effects of SARS-CoV-2 variants and vaccination on the occurrence of post-acute sequelae of SARS-CoV-2 (PASC) is crucial to estimate and reduce the burden of PASC.

Methods: We performed a cross-sectional analysis (May/June 2022) within a prospective multicenter healthcare worker (HCW) cohort in North-Eastern Switzerland. HCW were stratified by viral variant and vaccination status at time of their first positive SARS-CoV-2 nasopharyngeal swab. HCW without positive swab and with negative serology served as controls. The sum of eighteen self-reported PASC symptoms was modeled with univariable and multivariable negative-binomial

regression to analyse the association of mean symptom number with viral variant and vaccination status.

Results: Among 2'912 participants (median age 44 years, 81.3% female), PASC symptoms were significantly more frequent after wild-type infection (estimated mean symptom number 1.12, p<0.001; median time since infection 18.3 months), after Alpha/Delta infection (0.67 symptoms, p<0.001; 6.5 months), and after Omicron BA.1 infections (0.52 symptoms, p=0.005; 3.1 months) compared to uninfected controls (0.39 symptoms). After Omicron BA.1 infection, the estimated mean symptom number was 0.36 for unvaccinated individuals, compared to 0.71 with 1-2 vaccinations (p=0.028) and 0.49 with ≥3 prior vaccinations (p=0.30). Adjusting for confounders, only wild-type (adjusted rate ratio [aRR] 2.81, 95% confidence interval [CI] 2.08-3.83) and Alpha/Delta infection (aRR 1.93, 95% CI 1.10-3.46) were significantly associated with the outcome.

Conclusions: Previous infection with pre-Omicron variants was the strongest risk factor for PASC symptoms among our HCW. Vaccination prior to Omicron BA.1 infection was not associated with a clear protective effect against PASC symptoms in this population.

Pathogenic mechanisms of post-acute sequelae of SARS-CoV-2 infection (PASC)

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Abstract

COVID-19, with persistent and new onset of symptoms such as fatigue, post-exertional malaise, and cognitive dysfunction that last for months and impact everyday functioning, is referred to as Long COVID under the general category of post-acute sequelae of SARS-CoV-2 infection (PASC). PASC is highly heterogenous and may be associated with multisystem tissue damage/dysfunction including acute encephalitis, cardiopulmonary syndromes, fibrosis, hepatobiliary damages, gastrointestinal dysregulation, myocardial infarction, neuromuscular syndromes, neuropsychiatric disorders, pulmonary damage, renal failure, stroke, and vascular endothelial dysregulation. A better understanding of the pathophysiologic mechanisms underlying PASC is essential to guide

prevention and treatment. This review addresses potential mechanisms and hypotheses that connect SARS-CoV-2 infection to long-term health consequences. Comparisons between PASC and other virus-initiated chronic syndromes such as myalgic encephalomyelitis/chronic fatigue syndrome and postural orthostatic tachycardia syndrome will be addressed. Aligning symptoms with other chronic syndromes and identifying potentially regulated common underlining pathways may be necessary for understanding the true nature of PASC. The discussed contributors to PASC symptoms include sequelae from acute SARS-CoV-2 injury to one or more organs, persistent reservoirs of the replicating virus or its remnants in several tissues, re-activation of latent pathogens such as Epstein-Barr and herpes viruses in COVID-19 immune-dysregulated tissue environment, SARS-CoV-2 interactions with host microbiome/virome communities, clotting/coagulation dysregulation, dysfunctional brainstem/vagus nerve signaling, dysautonomia or autonomic dysfunction, ongoing activity of primed immune cells, and autoimmunity due to molecular mimicry between pathogen and host proteins. The individualized nature of PASC symptoms suggests that different therapeutic approaches may be required to best manage specific patients.

Association of Treatment With Nirmatrelvir and the Risk of Post-COVID-19 Condition

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Abstract

Importance: Post-COVID-19 condition (PCC), also known as long COVID, affects many individuals. Prevention of PCC is an urgent public health priority.

Objective: To examine whether treatment with nirmatrelvir in the acute phase of COVID-19 is associated with reduced risk of PCC.

Design, setting, and participants: This cohort study used the health care databases of the US Department of Veterans Affairs (VA) to identify patients who had a SARS-CoV-2 positive test result between January 3, 2022, and December 31, 2022, who were not hospitalized on the day of the positive test result, who had at least 1 risk factor for progression to severe COVID-19 illness, and who had survived the first 30 days after SARS-CoV-2 diagnosis. Those who were treated with oral nirmatrelvir within 5 days after the positive test (n = 35 717) and those who received no COVID-19 antiviral or antibody treatment during the acute phase of SARS-CoV-2 infection (control group, n = 246 076) were identified.

Exposures: Treatment with nirmatrelvir or receipt of no COVID-19 antiviral or antibody treatment based on prescription records.

Main outcomes and measures: Inverse probability weighted survival models were used to estimate the association of nirmatrelvir (vs control) with post-acute death, post-acute hospitalization, and a prespecified panel of 13 post-acute COVID-19 sequelae (components of PCC) and reported in relative scale as relative risk (RR) or hazard ratio (HR) and in absolute scale as absolute risk reduction in percentage at 180 days (ARR).

Results: A total of 281 793 patients (mean [SD] age, 61.99 [14.96]; 242 383 [86.01%] male) who had a positive SARS-CoV-2 test result and had at least 1 risk factor for progression to severe COVID-19 illness were studied. Among them, 246 076 received no COVID-19 antiviral or antibody treatment during the acute phase of SARS-CoV-2 infection, and 35 717 received oral nirmatrelvir within 5 days after the positive SARS-CoV-2 test result. Compared with the control group, nirmatrelvir was associated with reduced risk of PCC (RR, 0.74; 95% CI, 0.72-0.77; ARR, 4.51%; 95% CI, 4.01-4.99), including reduced risk of 10 of 13 post-acute sequelae (components of PCC) in the cardiovascular system (dysrhythmia and ischemic heart disease), coagulation and hematologic disorders (pulmonary embolism and deep vein thrombosis), fatigue and malaise, acute kidney disease, muscle pain, neurologic system (neurocognitive impairment and dysautonomia), and shortness of breath. Nirmatrelvir was also associated with reduced risk of post-acute death (HR, 0.53; 95% CI, 0.46-0.61); ARR, 0.65%; 95% CI, 0.54-0.77), and post-acute hospitalization (HR, 0.76; 95% CI, 0.73-0.80; ARR, 1.72%; 95% CI, 1.42-2.01). Nirmatrelvir was associated with reduced risk of PCC in people who were unvaccinated, vaccinated, and boosted, and in people with primary SARS-CoV-2 infection and reinfection.

Conclusions and relevance: This cohort study found that in people with SARS-CoV-2 infection who had at least 1 risk factor for progression to severe disease, treatment with nirmatrelvir within 5 days of a positive SARS-CoV-2 test result was associated with reduced risk of PCC across the risk spectrum in this cohort and regardless of vaccination status and history of prior infection; the totality of findings suggests that treatment with nirmatrelvir during the acute phase of COVID-19 may reduce the risk of post-acute adverse health outcomes.