Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI) — PubMed Research Citations Concerning Long Haul COVID-19 April, May, June 2022

Prepared by Staff of the RACGWVI.

RACGWVI: Long Haul COVID-19 — PubMed Citations for April, May, June 2022

The following is a list of published research projects that focus on Long Haul COVID-19 for the months of April, May and June 2022.

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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Post COVID fatigue: Can we really ignore it?

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Abstract

Long-COVID, also referred to as post-acute COVID-19, chronic COVID-19, post-COVID syndrome, or post-acute sequelae of SARS-CoV-2 infection (PASC), generally refers to symptoms that develop during or after acute COVID-19 illness, continue for ≥12 weeks, and are not explained by an alternative diagnosis. It is not yet known whether "long-COVID" represents a new syndrome unique to COVID-19 or overlaps with recovery from similar illnesses. It's difficult for physicians to predict when symptoms will improve as it varies differently in different people. Patient's recovery depends on various factors including age, associated comorbidities, severity of COVID-19 infection. Some symptoms, like fatigue, might continue even while others improve or go away. This review addresses the pathogenesis, presentation of post covid fatigue, its severity and its management.

Clinical patterns of somatic symptoms in patients suffering from post-acute long COVID: a systematic review

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Abstract

Background: Long COVID-19 may affect patients after hospital discharge.

Aims: This study aims to describe the burden of the long-term persistence of clinical symptoms in COVID-19 patients.

Methods: We conducted a systematic review by using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline. The PubMed and Google Scholar databases were searched for studies that included information on the prevalence of somatic clinical symptoms lasting at least 4 weeks after the onset of a PCR- or serology-confirmed diagnosis of COVID-19. The prevalence of persisting clinical symptoms was assessed and risk factors were described when investigated. Psychological symptoms and cognitive disorders were not evaluated in this study.

Results: Thirty-seven articles met the inclusion criteria. Eighteen studies involved in-patients only with a duration of follow-up of either less than 12 weeks, 12 weeks to 6 months, or more. In these studies, fatigue (16-64%), dyspnea (15-61%), cough (2-59%), arthralgia (8-55%), and thoracic pain (5-62%) were the most frequent persisting symptoms. In nineteen studies conducted in a majority of out-patients, the persistence of these symptoms was lower and 3% to 74% of patients reported prolonged smell and taste disorders. The main risk factors for persisting symptoms were being female, older, having comorbidities and severity at the acute phase of the disease.

Conclusion: COVID-19 patients should have access to dedicated multidisciplinary healthcare allowing a holistic approach. Effective outpatient care for patients with long-COVID-19 requires coordination across multiple sub-specialties, which can be proposed in specialized post-COVID units.

Gastrointestinal post-acute COVID-19 syndrome

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No abstract available

Post-acute Sequelae in COVID-19 Survivors: an Overview

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Abstract

In the acute phase of SARS-CoV-2 infection, varying degrees of clinical manifestations have been noticed in patients. Some patients who recovered from the infection developed long-term effects which have become of interest to the scientific and medical communities, as it relates to pathogenesis and the multidisciplinary approach to treatment. Long COVID (long-term or long-haul) is the collective term used to define recovered individuals of SARS-CoV-2 infection who have presented with persistent COVID symptoms, as well as the emergence of disorders and complications. Following the review of literature from major scientific databases, this paper investigated long COVID and the resulting post-sequela effects on survivors, regardless of initial disease severity. The clinical manifestations and multisystem complications of the disease specifically, cardiovascular, neurologic and psychologic, hematologic, pulmonary, dermatologic, and other ailments were discussed. Patients with chronic COVID-19 were found to experience heart thrombosis leading to myocardial infarction, inflammation, lung fibrosis, stroke, venous thromboembolism, arterial thromboembolism, "brain fog", general mood dysfunctions, dermatological issues, and fatigue. As the disease continues to progress and spread, and with the emergence of new variants the management of these persisting symptoms will pose a challenge for healthcare providers and medical systems in the next period of the pandemic. However, more information is needed about long COVID, particularly concerning certain patient populations, variability in follow-up times, the prevalence of comorbidities, and the evolution of the spread of infection. Thus, continued research needs to be conducted concerning the disease pathology to develop preventative measures and management strategies to treat long COVID.

Neurological Sequelae of COVID-19

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Abstract

Background: Though primarily a pulmonary disease, Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus can generate devastating disease states that affect multiple organ systems including the central nervous system (CNS). The various neurological disorders associated with COVID-19 range in severity from mild symptoms such as headache, or myalgias to more severe symptoms such as stroke, psychosis, and anosmia. While some of the COVID-19 associated neurological complications are mild and reversible, a significant number of patients suffer from stroke. Studies have shown that COVID-19 infection triggers a wave of inflammatory cytokines that induce endothelial cell dysfunction and generate coagulopathy that increases the risk of stroke or thromboses. Inflammation of the endothelium following infection may also destabilize atherosclerotic plaque and induce thrombotic stroke. Although uncommon, there have also been reports of hemorrhagic stroke associated with COVID-19. The proposed mechanisms include a blood pressure increase caused by infection leading to a reduction in angiotensin converting enzyme-2 (ACE-2) levels that results in an imbalance of the renin-angiotensin system ultimately manifesting inflammation and vasoconstriction. Coagulopathy, as demonstrated by elevated prothrombin time (PT), has also been posited as a factor contributing to hemorrhagics stroke in patients with COVID-19. Other neurological conditions associated with COVID-19 include encephalopathy, anosmia, encephalitis, psychosis, brain fog, headache, depression, and anxiety. Though there are several hypotheses reported in the literature, a unifying pathophysiological mechanism of many of these disorders remains unclear. Pulmonary dysfunction leading to poor oxygenation of the brain may explain encephalopathy and other disorders in COVID-19 patients. Alternatively, a direct invasion of the CNS by the virus or breach of the blood-brain barrier by the systemic cytokines released during infection may be responsible for these conditions. Notwithstanding, the relationship between the inflammatory cytokine levels and conditions such as depression and anxiety is contradictory and perhaps the social isolation during the pandemic may in part be a contributing factor to some of the reported CNS disorders.

Objective: In this article, we review the current literature pertaining to some of the most significant and common neurological disorders such as ischemic and hemorrhagic stroke, encephalopathy, encephalitis, brain fog, Long COVID, headache, Guillain-Barre syndrome, depression, anxiety, and sleep disorders in the setting of COVID-19. We summarize some of the most relevant literature to provide a better understanding of the mechanistic details regarding these disorders in order to help physicians monitor and treat patients for significant COVID-19 associated neurologic impairments.

Methods: A literature review was carried out by the authors using PubMed with the search terms "COVID-19" and "Neurology", "Neurological Manifestations", "Neuropsychiatric Manifestations", "Stroke", "Encephalopathy", "Headache", "Guillain-Barre syndrome", "Depression", "Anxiety", "Encephalitis", "Seizure", "Spasm", and "ICUAW". Another search was carried out for "Long-COVID" and "Post-Acute COVID-19" and "Neurological Manifestations" or "Neuropsychiatric Manifestations". Articles such as case reports, case series, and cohort studies were included as references. No language restrictions were enforced. In the case of anxiety and depression, attempts were made to focus mainly on articles describing these conditions in infected patients.

Results: A total of 112 articles were reviewed. The incidence, clinical outcomes, and pathophysiology of selected neurological disorders are discussed below. Given the recent advent of this disease, the incidence of certain neurologic sequelae was not always available. Putative mechanisms for each condition in the setting of COVID-19 are outlined.

Million Veteran Program's response to COVID-19: Survey development and preliminary findings

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Abstract

Background: In response to the novel Coronavirus Disease 2019 (COVID-19) pandemic, the Department of Veterans Affairs (VA) Million Veteran Program (MVP) organized efforts to better understand the impact of COVID-19 on Veterans by developing and deploying a self-reported survey.

Methods: The MVP COVID-19 Survey was developed to collect COVID-19 specific elements including symptoms, diagnosis, hospitalization, behavioral and psychosocial factors and to augment existing MVP data with longitudinal collection of key domains in physical and mental health. Due to the rapidly evolving nature of the pandemic, a multipronged strategy was implemented to widely disseminate the COVID-19 Survey and capture data using both the online platform and mailings.

Results: We limited the findings of this paper to the initial phase of survey dissemination which began in May 2020. A total of 729,625 eligible MVP Veterans were invited to complete version 1 of the COVID-19 Survey. As of October 31, 2020, 58,159 surveys have been returned. The mean and standard deviation (SD) age of responders was 71 (11) years, 8.6% were female, 8.2% were Black, 5.6% were Hispanic, and 446 (0.8%) self-reported a COVID-19 diagnosis. Over 90% of responders reported wearing masks, practicing social distancing, and frequent hand washing.

Conclusion: The MVP COVID-19 Survey provides a systematic collection of data regarding COVID-19 behaviors among Veterans and represents one of the first large-scale, national

surveillance efforts of COVID-19 in the Veteran population. Continued work will examine the overall response to the survey with comparison to available VA health record data.

Epipharyngeal Abrasive Therapy (EAT) Has Potential as a Novel Method for Long COVID Treatment

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Abstract

COVID-19 often causes sequelae after initial recovery, referred to collectively as long COVID. Long COVID is considered to be caused by the persistence of chronic inflammation after acute COVID-19 infection. We found that all long COVID patients had residual inflammation in the epipharynx, an important site of coronavirus replication, and some long COVID symptoms are similar to those associated with chronic epipharyngitis. Epipharyngeal abrasive therapy (EAT) is a treatment for chronic epipharyngitis in Japan that involves applying zinc chloride as an anti-inflammatory agent to the epipharyngeal mucosa. In this study, we evaluated the efficacy of EAT for the treatment of long COVID. The subjects in this study were 58 patients with long COVID who were treated with EAT in the outpatient department once a week for one month (mean age = 38.4 ± 12.9 years). The intensities of fatigue, headache, and attention disorder, which are reported as frequent symptoms of long COVID, were assessed before and after EAT using the visual analog scale (VAS). EAT reduced inflammation in the epipharynx and significantly improved the intensity of fatigue, headache, and attention disorder, which may be related to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). These results suggest that EAT has potential as a novel method for long COVID treatment.

Restless legs syndrome is associated with long-COVID in women

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Abstract

Study objectives: Sleep disturbance is common in long-COVID (LC). Restless legs syndrome (RLS) is characterized by sleep disturbance and has been reported after viral infections. Therefore, we evaluated RLS symptoms cross-sectionally in individuals with LC at both current and pre-coronavirus disease 2019 (pre-COVID-19) time points.

Methods: Adults on LC-focused Facebook pages were recruited for an online assessment of symptoms before COVID-19 infection and during their present LC state in a cross-sectional manner. The LC group documented baseline symptoms retrospectively. Questions were included about the presence/severity of RLS symptoms and assessments of fatigue, quality of life, and sleep apnea. A control group was recruited and included individuals ≥ 18 years of age who never had overt symptoms of COVID-19. Pregnancy was an exclusion criterion for both groups.

Results: There were 136 participants with LC (89.7% females, age 46.9 ± 12.9 years) and 136 controls (65.4% females, age 49.2 ± 15.5). RLS prevalence in females with LC was 5.7% pre-COVID-19 and 14.8% post-COVID-19 (P < .01) vs 6.7% in control females. Severity of RLS was moderate in both groups. Logistic regression predicting post-COVID-19 RLS among females with LC failed to find significant effects of hospitalization, sleep apnea, neuropathic pain severity, or use of antihistamines and antidepressants.

Conclusions: The baseline prevalence of RLS in females with LC was similar to the general population group as well as to patients in epidemiological studies. The prevalence significantly increased in the LC state. Postinfectious immunological mechanisms may be at play in the production for RLS symptoms.

Long COVID: A proposed hypothesis-driven model of viral persistence for the pathophysiology of the syndrome

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Abstract

Background: Long COVID (coronavirus disease 2019) syndrome includes a group of patients who, after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), exhibit lingering mild-to-moderate symptoms and develop medical complications that can have lasting health problems. In this report, we propose a model for the pathophysiology of the long COVID presentation based on increased proinflammatory cytokine production that results from the persistence of the SARS-CoV-2 virus or one of its molecular components. Associated with this hyperproduction of inflammatory cytokines is a heightened activity of nuclear factor κ B (NF-κB) and p38 mitogen-activated protein kinase signaling pathways that regulate cytokine production. Objective: The purpose of the present report was to review the causes of long COVID syndrome and suggest ways that can provide a basis for a better understanding of the clinical symptomatology for the of improved diagnostic and therapeutic procedures for the condition. Methods: Extensive research was conducted in medical literature data bases by applying terms such as "long COVID" associated with "persistence of the SARS-CoV-2 virus" "spike protein' "COVID-19" and "biologic therapies." Results and Conclusions: In this model of the long COVID syndrome, the persistence of SARS-CoV-2 is hypothesized to trigger a dysregulated immune system with subsequent heightened release of proinflammatory cytokines that lead to chronic low-grade inflammation and multiorgan symptomatology. The condition seems to have a genetic basis, which predisposes individuals to have a diminished immunologic capacity to completely clear the virus, with residual parts of the virus persisting. This persistence of virus and resultant hyperproduction of proinflammatory cytokines are proposed to form the basis of the syndrome.

Long-Term Cardiovascular Effects of COVID-19: Emerging Data Relevant to the Cardiovascular Clinician

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Abstract

Purpose of review: COVID-19 is now a global pandemic and the illness affects multiple organ systems, including the cardiovascular system. Long-term cardiovascular consequences of COVID-19 are not yet fully characterized. This review seeks to consolidate available data on long-term cardiovascular complications of COVID-19 infection.

Recent findings: Acute cardiovascular complications of COVID-19 infection include myocarditis, pericarditis, acute coronary syndrome, heart failure, pulmonary hypertension, right ventricular dysfunction, and arrhythmia. Long-term follow-up shows increased incidence of arrhythmia, heart failure, acute coronary syndrome, right ventricular dysfunction, myocardial fibrosis, hypertension, and diabetes mellitus. There is increased mortality in COVID-19 patients after hospital discharge, and initial myocardial injury is associated with increased mortality. Emerging data demonstrates increased incidence of cardiovascular illness and structural changes in recovered COVID-19 patients. Future research will be important in understanding the clinical significance of these structural abnormalities, and to determine the effect of vaccines on preventing long-term cardiovascular complications.

Post-acute sequelae of SARS-CoV-2 infection: relationship of central nervous system manifestations with physical disability and systemic inflammation

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No abstract available

Impaired Vagal Activity in Long-COVID-19 Patients

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Abstract

Long-COVID-19 refers to the signs and symptoms that continue or develop after the "acute COVID-19" phase. These patients have an increased risk of multiorgan dysfunction, readmission, and mortality. In Long-COVID-19 patients, it is possible to detect a persistent increase in D-Dimer, NT-ProBNP, and autonomic nervous system dysfunction. To verify the dysautonomia hypothesis in Long-COVID-19 patients, we studied heart rate variability using 12-lead 24-h ECG monitoring in 30 Long-COVID-19 patients and 20 No-COVID patients. Power spectral analysis of heart rate variability was lower in Long-COVID-19 patients both for total power (7.46 ± 0.5 vs. 8.08 ± 0.6; $p < 0.0001$; Cohens-d = 1.12) and for the VLF (6.84 ± 0.8 vs. 7.66 ± 0.6; $p < 0.0001$; Cohens-d = 1.16) and HF (4.65 ± 0.9 vs. 5.33 ± 0.9; $p = 0.015$; Cohens-d = 0.76) components. The LF/HF ratio was significantly higher in Long-COVID-19 patients (1.46 ± 0.27 vs. 1.23 ± 0.13; $p = 0.001$; Cohens-d = 1.09). On multivariable analysis, Long-COVID-19 is significantly correlated with D-dimer (standardized β-coefficient = 0.259), NT-ProBNP (standardized β-coefficient = 0.281), HF component of spectral analysis (standardized β-coefficient = 0.696), and LF/HF ratio (standardized β-coefficient = 0.820). Dysautonomia may explain the persistent symptoms in Long COVID-19 patients. The persistence of a procoagulative state and an elevated myocardial strain could explain vagal impairment in these patients. In Long-COVID-19 patients, impaired vagal activity, persistent increases of NT-ProBNP, and a prothrombotic state require careful monitoring and appropriate intervention.

Persistent Symptoms among Frontline Health Workers Post-Acute COVID-19 Infection

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Abstract

Growing evidence shows that a significant number of patients with COVID-19 experience persistent symptoms, also known as long COVID-19. We sought to identify persistent symptoms of COVID-19 in frontline workers at Right to Care South Africa, who are past the acute phase of illness, using a cross-sectional survey. We analysed data from 207 eligible COVID-19 positive frontline workers who participated in a two-month post-COVID-19 online self-administered survey. The survey response rate was 30%; of the 62 respondents with a median age of 33.5 years (IQR= 30-44 years), 47 (76%) were females. The majority (n = 55; 88.7%) self-isolated and 7 (11.3%) were admitted to hospital at the time of diagnosis. The most common comorbid condition reported was hypertension, particularly among workers aged 45-55 years. The most reported persistent symptoms were characterised by fatigue, anxiety, difficulty sleeping, chest pain, muscle pain, and brain fog. Long COVID-19 is a serious phenomenon, of which much is still unknown, including its causes, how common it is especially in non-hospitalised healthcare workers, and how to treat it. Given the rise in COVID-19 cases, the prevalence of long COVID-19 is likely to be substantial; thus, the need for rehabilitation programs targeted at each persistent COVID-19 symptom is critical.

Identifying who has long COVID in the USA: a machine learning approach using N3C data

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Abstract

Background: Post-acute sequelae of SARS-CoV-2 infection, known as long COVID, have severely affected recovery from the COVID-19 pandemic for patients and society alike. Long COVID is characterised by evolving, heterogeneous symptoms, making it challenging to derive an unambiguous definition. Studies of electronic health records are a crucial element of the US National Institutes of Health's RECOVER Initiative, which is addressing the urgent need to understand long COVID, identify treatments, and accurately identify who has it-the latter is the aim of this study.

Methods: Using the National COVID Cohort Collaborative's (N3C) electronic health record repository, we developed XGBoost machine learning models to identify potential patients with long COVID. We defined our base population (n=1 793 604) as any non-deceased adult patient (age ≥18 years) with either an International Classification of Diseases-10-Clinical Modification COVID-19 diagnosis code (U07.1) from an inpatient or emergency visit, or a positive SARS-CoV-2 PCR or antigen test, and for whom at least 90 days have passed since COVID-19 index date. We examined

demographics, health-care utilisation, diagnoses, and medications for 97 995 adults with COVID-19. We used data on these features and 597 patients from a long COVID clinic to train three machine learning models to identify potential long COVID among all patients with COVID-19, patients hospitalised with COVID-19, and patients who had COVID-19 but were not hospitalised. Feature importance was determined via Shapley values. We further validated the models on data from a fourth site.

Findings: Our models identified, with high accuracy, patients who potentially have long COVID, achieving areas under the receiver operator characteristic curve of 0·92 (all patients), 0·90 (hospitalised), and 0·85 (non-hospitalised). Important features, as defined by Shapley values, include rate of health-care utilisation, patient age, dyspnoea, and other diagnosis and medication information available within the electronic health record.

Interpretation: Patients identified by our models as potentially having long COVID can be interpreted as patients warranting care at a specialty clinic for long COVID, which is an essential proxy for long COVID diagnosis as its definition continues to evolve. We also achieve the urgent goal of identifying potential long COVID in patients for clinical trials. As more data sources are identified, our models can be retrained and tuned based on the needs of individual studies.

LOng COvid Multidisciplinary consortium Optimising Treatments and servIces acrOss the NHS (LOCOMOTION): protocol for a mixed-methods study in the UK

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Abstract

Introduction: Long COVID, a new condition whose origins and natural history are not yet fully established, currently affects 1.5 million people in the UK. Most do not have access to specialist long COVID services. We seek to optimise long COVID care both within and outside specialist clinics, including improving access, reducing inequalities, helping self-management and providing guidance and decision support for primary care. We aim to establish a 'gold standard' of care by systematically analysing current practices, iteratively improving pathways and systems of care.

Methods and analysis: This mixed-methods, multisite study is informed by the principles of applied health services research, quality improvement, co-design, outcome measurement and learning health systems. It was developed in close partnership with patients (whose stated priorities are prompt clinical assessment; evidence-based advice and treatment and help with returning to work and other roles) and with front-line clinicians. Workstreams and tasks to optimise assessment, treatment and monitoring are based in three contrasting settings: workstream 1 (qualitative research, up to 100 participants), specialist management in 10 long COVID clinics across the UK,

via a quality improvement collaborative, experience-based co-design and targeted efforts to reduce inequalities of access, return to work and peer support; workstream 2 (quantitative research, up to 5000 participants), patient self-management at home, technology-supported monitoring and validation of condition-specific outcome measures and workstream 3 (quantitative research, up to 5000 participants), generalist management in primary care, harnessing electronic record data to study population phenotypes and develop evidence-based decision support, referral pathways and analysis of costs. Study governance includes an active patient advisory group.

Ethics and dissemination: LOng COvid Multidisciplinary consortium Optimising Treatments and servIces acrOss the NHS study is sponsored by the University of Leeds and approved by Yorkshire & The Humber-Bradford Leeds Research Ethics Committee (ref: 21/YH/0276). Participants will provide informed consent. Dissemination plans include academic and lay publications, and partnerships with national and regional policymakers.

Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study

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Abstract

Objective: To estimate associations between covid-19 vaccination and long covid symptoms in adults with SARS-CoV-2 infection before vaccination.

Design: Observational cohort study.

Setting: Community dwelling population, UK.

Participants: 28 356 participants in the Office for National Statistics COVID-19 Infection Survey aged 18-69 years who received at least one dose of an adenovirus vector or mRNA covid-19 vaccine after testing positive for SARS-CoV-2 infection.
Main outcome measure: Presence of long covid symptoms at least 12 weeks after infection over the follow-up period 3 February to 5 September 2021.

Results: Mean age of participants was 46 years, 55.6% (n=15 760) were women, and 88.7% (n=25 141) were of white ethnicity. Median follow-up was 141 days from first vaccination (among all participants) and 67 days from second vaccination (83.8% of participants). 6729 participants (23.7%) reported long covid symptoms of any severity at least once during follow-up. A first vaccine dose was associated with an initial 12.8% decrease (95% confidence interval -18.6% to -6.6%, P<0.001) in the odds of long covid, with subsequent data compatible with both increases and decreases in the trajectory (0.3% per week, 95% confidence interval -0.6% to 1.2% per week, P=0.51). A second dose was associated with an initial 8.8% decrease (95% confidence interval -14.1% to -3.1%, P=0.003) in the odds of long covid, with a subsequent decrease by 0.8% per week (-1.2% to -0.4% per week, P<0.001). Heterogeneity was not found in associations between vaccination and long covid by sociodemographic characteristics, health status, hospital admission with acute covid-19, vaccine type (adenovirus vector or mRNA), or duration from SARS-CoV-2 infection to vaccination.

Conclusions: The likelihood of long covid symptoms was observed to decrease after covid-19 vaccination and evidence suggested sustained improvement after a second dose, at least over the median follow-up of 67 days. Vaccination may contribute to a reduction in the population health burden of long covid, although longer follow-up is needed.

Symptoms and signs of long COVID: A rapid review and meta-analysis

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Abstract

Background: Long COVID is defined as symptoms and signs related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that are present at least four weeks following acute infection. These symptoms and signs are poorly characterised but may be associated with significant morbidity. We sought to synthesise the evidence on their incidence to guide future research, policy and practice.

Methods: We searched Medline and Embase for longitudinal cohort studies from January 2020 to July 2021 that investigated adults with long COVID at least four weeks after acute infection. Risk of bias was assessed using the Joanna Briggs Institute checklist for cohort studies. Random-effects meta-analyses were performed with subgroup analysis by follow-up time (4-12 vs more than 12 weeks).

Results: 19 studies were included, 13 of which included patients hospitalised with COVID-19. The total sample size was 10 643 and the follow-up time ranged from 30 to 340 days. Risk of bias was assessed as high in one study, moderate in two studies and low in the remaining 16 studies. The most common symptoms and signs seen at any time point in long COVID were fatigue (37%; 95% confidence interval (CI) = 23-55), dyspnoea (21%; 95% CI = 14-30), olfactory dysfunction (17%; 95% CI = 9-29), myalgia (12%; 95% CI = 5-25), cough (11%; 95% CI = 6-20) and gustatory dysfunction (10%; 95% CI = 7-17). High heterogeneity was seen for all meta-analyses and the presence of some funnel plot asymmetry may indicate reporting bias. No effect of follow-up time was found for any symptom or sign included in the subgroup analysis.

Conclusions: We have summarised evidence from longitudinal cohort studies on the most common symptoms and signs associated with long COVID. High heterogeneity seen in the meta-analysis means pooled incidence estimates should be interpreted with caution. This heterogeneity may be attributable to studies including patients from different health care settings and countries.

Inflammation, immunity, and antigen persistence in post-acute sequelae of SARS-CoV-2 infection

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Abstract

SARS-CoV-2 infection is known to result in a range of symptoms with varying degrees of acute-phase severity. In a subset of individuals, an equally diverse collection of long-term sequelae has been reported after convalescence. As survivorship and therefore the number of individuals with 'long-COVID' continues to grow, an understanding of the prevalence, origins, and mechanisms of post-acute sequelae manifestation is critically needed. Here, we will explore proposed roles of the anti-SARS-CoV-2 immune response in the onset, severity, and persistence of SARS-CoV-2 post-acute sequelae. We discuss the potential roles of persistent virus and autoantigens in this syndrome, as well as the contributions of unresolved inflammation and tissue injury. Furthermore, we highlight recent evidence demonstrating the potential benefits of vaccination and immunity in the resolution of post-acute symptoms.

A Longitudinal Study of COVID-19 Sequelae and Immunity: Baseline Findings

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Abstract

Background: A substantial proportion of persons who develop COVID-19 report persistent symptoms after acute illness. Various pathophysiologic mechanisms have been implicated in the pathogenesis of postacute sequelae of SARS-CoV-2 infection (PASC).

Objective: To characterize medical sequelae and persistent symptoms after recovery from COVID-19 in a cohort of disease survivors and controls.

Design: Cohort study. (ClinicalTrials.gov: NCT04411147).

Setting: National Institutes of Health Clinical Center, Bethesda, Maryland.

Participants: Self-referred adults with laboratory-documented SARS-CoV-2 infection who were at least 6 weeks from symptom onset were enrolled regardless of presence of PASC. A control group comprised persons with no history of COVID-19 or serologic evidence of SARS-CoV-2 infection, recruited regardless of their current health status. Both groups were enrolled over the same period and from the same geographic area.

Measurements: All participants had the same evaluations regardless of presence of symptoms, including physical examination, laboratory tests and questionnaires, cognitive function testing, and cardiopulmonary evaluation. A subset also underwent exploratory immunologic and virologic evaluations.

Results: 189 persons with laboratory-documented COVID-19 (12% of whom were hospitalized during acute illness) and 120 antibody-negative control participants were enrolled. At enrollment, symptoms consistent with PASC were reported by 55% of the COVID-19 cohort and 13% of control participants. Increased risk for PASC was noted in women and those with a history of anxiety disorder. Participants with findings meeting the definition of PASC reported lower quality of life on standardized testing. Abnormal findings on physical examination and diagnostic testing were uncommon. Neutralizing antibody levels to spike protein were negative in 27% of the unvaccinated COVID-19 cohort and none of the vaccinated COVID-19 cohort. Exploratory studies found no evidence of persistent viral infection, autoimmunity, or abnormal immune activation in participants with PASC.

Limitations: Most participants with COVID-19 had mild to moderate acute illness that did not require hospitalization. The prevalence of reported PASC was likely overestimated in this cohort because persons with PASC may have been more motivated to enroll. The study did not capture PASC that resolved before enrollment.

Conclusion: A high burden of persistent symptoms was observed in persons after COVID-19. Extensive diagnostic evaluation revealed no specific cause of reported symptoms in most cases. Antibody levels were highly variable after COVID-19.

Long COVID after breakthrough SARS-CoV-2 infection

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Abstract

The post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-also referred to as Long COVID-have been described, but whether breakthrough SARS-CoV-2 infection (BTI) in vaccinated people results in post-acute sequelae is not clear. In this study, we used the US Department of Veterans Affairs national healthcare databases to build a cohort of 33,940 individuals with BTI and several controls of people without evidence of SARS-CoV-2 infection, including contemporary (n = 4,983,491), historical (n = 5,785,273) and vaccinated (n = 2,566,369) controls. At 6 months after infection, we show that, beyond the first 30 days of illness, compared to contemporary controls, people with BTI exhibited a higher risk of death (hazard ratio (HR) = 1.75, 95% confidence interval (CI): 1.59, 1.93) and incident post-acute sequelae (HR = 1.50, 95% CI: 1.46, 1.54), including cardiovascular, coagulation and hematologic, gastrointestinal, kidney, mental health, metabolic, musculoskeletal and neurologic disorders. The results were consistent in comparisons versus the historical and vaccinated controls. Compared to people with SARS-CoV-2 infection who were not previously vaccinated (n = 113,474), people with BTI exhibited lower risks of death (HR = 0.66, 95% CI: 0.58, 0.74) and incident post-acute sequelae (HR = 0.85, 95% CI: 0.82, 0.89). Altogether, the findings suggest that vaccination before infection confers only partial protection in the post-acute phase of the disease; hence, reliance on it as a sole mitigation strategy may not optimally reduce long-term health consequences of SARS-CoV-2 infection. The findings emphasize the need for continued optimization of strategies for primary prevention of BTI and will guide development of post-acute care pathways for people with BTI.

Symptom burden correlates to impairment of diffusion capacity and exercise intolerance in long COVID patients

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Abstract

After acute infection with the SARS-CoV-2 virus, a considerable number of patients remains symptomatic with pathological changes in various organ systems. This study aimed to relate the physical and mental burden of symptoms of long COVID patients to the findings of a somatic evaluation. In patients with persistent long COVID symptoms three months after acute infection we assessed physical and mental health status using the SF-36 questionnaire. The cohort was dichotomised by the results (upper two quartiles vs. lower to quartiles) and compared with regard to transthoracic echocardiography, body plethysmography (including diffusion capacity), capillary blood gas analysis and 6-min walk test (6-MWT). From February 22 to September 13, 2021, 463 patients were prospectively examined, of which 367 completed the SF-36 questionnaire. A positive correlation between initial disease severity (need for hospitalization, intensive care medicine) and resulting symptom burden at follow-up could be demonstrated. Patients with impaired subjective physical and mental status were significantly more likely to be women. There was a significant correlation between symptom severity and reduced exercise tolerance in the 6-MWT (495.6 ± 83.7 m vs 549.7 ± 71.6 m, $p < 0.001$) and diffusion capacity for carbon monoxide ($85.6 \pm 14.3\%$ of target vs 94.5 ± 14.4, $p < 0.001$). In long COVID patients, initial disease severity is correlated with symptom burden after at least 3 months of follow-up. Highly symptomatic long COVID patients show impaired diffusion capacity and 6-MWT despite average or mildly affected mechanical lung parameters. It must be further differentiated whether this corresponds to a transient functional impairment or whether it is a matter of defined organ damage.

Long COVID in children and young people: uncertainty and contradictions

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No abstract available

SARS-CoV-2-specific T cells associate with inflammation and reduced lung function in pulmonary post-acute sequalae of SARS-CoV-2

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Abstract

As of January 2022, at least 60 million individuals are estimated to develop post-acute sequelae of SARS-CoV-2 (PASC) after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While elevated levels of SARS-CoV-2-specific T cells have been observed in non-specific PASC, little is known about their impact on pulmonary function which is compromised in the majority of these individuals. This study compares frequencies of SARS-CoV-2-specific T cells and inflammatory markers with lung function in participants with pulmonary PASC and resolved COVID-19 (RC). Compared to RC, participants with respiratory PASC had between 6- and 105-fold higher frequencies of IFN-γ- and TNF-α-producing SARS-CoV-2-specific CD4+ and CD8+ T cells in peripheral blood, and elevated levels of plasma CRP and IL-6. Importantly, in PASC participants the frequency of TNF-α-producing SARS-CoV-2-specific CD4+ and CD8+ T cells, which exhibited the highest levels of Ki67 indicating they were activity dividing, correlated positively with plasma IL-6 and negatively with measures of lung function, including forced expiratory volume in one second (FEV1), while increased frequencies of IFN-γ-producing SARS-CoV-2-specific T cells associated with prolonged dyspnea. Statistical analyses stratified by age, number of comorbidities and hospitalization status demonstrated that none of these factors affect differences in the frequency of SARS-CoV-2 T cells and plasma IL-6 levels measured between PASC and RC cohorts. Taken together, these findings demonstrate elevated frequencies of SARS-CoV-2-specific T cells in individuals with pulmonary PASC are associated with increased systemic inflammation and decreased lung function, suggesting that SARS-CoV-2-specific T cells contribute to lingering pulmonary symptoms. These findings also provide mechanistic insight on the pathophysiology of PASC that can inform development of potential treatments to reduce symptom burden.

Application of Kampo Medicines for Treatment of General Fatigue Due to Long COVID

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Abstract

Evidence regarding treatment for the acute phase of COVID-19 has been accumulating, but specific treatment for long COVID/post-COVID-19 condition has not yet been established. Treatment with herbal medicine might be one treatment option for long COVID, but there has been little research on the effectiveness of herbal medicine for long COVID. The aim of this study was to clarify the prescription patterns of Kampo medicines, which are herbal medicines that originated in China and were developed in Japan, for the treatment of general fatigue due to long COVID. A retrospective descriptive study was performed for patients who visited a COVID-19 aftercare clinic established in Okayama University Hospital during the period from Feb 2021 to Dec 2021 with a focus on symptoms accompanying general fatigue and prescriptions of Kampo medicine. Among the clinical data obtained from medical records of 195 patients, clinical data for 102 patients with general fatigue and accompanying symptoms were analyzed. The patients had various symptoms, and the most frequent symptoms accompanying general fatigue were dysosmia, dysgeusia, headache, insomnia, dyspnea, and hair loss. Prescriptions of Kampo medicine accounted for 24.1% of the total prescriptions (n = 609). The most frequently prescribed Kampo medicine was hochuekkito (71.6%) and other prescribed Kampo medicines were tokishakuyakusan, ryokeijutsukanto, juzentaihoto, hangekobokuto, kakkonto, ninjin'yoeito, goreisan, rikkunshito, and keishibukuryogan. Since the pathophysiology of general fatigue after an infectious disease is, in general, considered a qi deficiency in Kampo medicine, treatments with such compensation agents can be the major prescription as a complement for the qi. In conclusion, Kampo medicine can be one of the main pharmacological treatments for long COVID accompanying general fatigue.

Connecting the Dots in Emerging Mast Cell Research: Do Factors Affecting Mast Cell Activation Provide a Missing Link between Adverse COVID-19 Outcomes and the Social Determinants of Health?

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Abstract

Evidence continues to emerge that the social determinants of health play a role in adverse outcomes related to COVID-19, including increased morbidity and mortality, increased risk of long COVID, and vaccine adverse effects. Therefore, a more nuanced understanding of the biochemical and cellular pathways of illnesses commonly associated with adverse social determinants of health is urgently needed. We contend that a commitment to understanding adverse outcomes in historically marginalized communities will increase community-level confidence in public health measures. Here, we synthesize emerging literature on mast cell disease, and the role of mast cells in chronic illness, alongside emerging research on mechanisms of COVID illness and vaccines. We propose that a focus on aberrant and/or hyperactive mast cell behavior associated with chronic underlying health conditions can elucidate adverse COVID-related outcomes and contribute to the pandemic recovery. Standards of care for mast cell activation syndrome (MCAS), as well as clinical reviews, experimental research, and case reports, suggest that effective and cost-efficient remedies are available, including antihistamines, vitamin C, and quercetin, among others. Primary care physicians, specialists, and public health workers should consider new and emerging evidence from the biomedical literature in tackling COVID-19. Specialists and researchers note that MCAS is likely grossly under-diagnosed; therefore, public health agencies and policy makers should urgently attend to community-based experiences of adverse COVID outcomes. It is essential that we extract and examine experiential evidence of marginalized communities from the broader political-ideological discourse.

Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection

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Abstract

Postacute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or long coronavirus disease (COVID) is an emerging syndrome characterized by multiple persisting or newly emergent symptoms following the acute phase of SARS-CoV-2 infection. For affected patients, these prolonged symptoms can have a relapsing and remitting course and may be associated with disability and frequent health care utilization. Although many symptom-driven treatments are available, management remains challenging and often requires a multidisciplinary approach. This article summarizes the emerging consensus on definitions, epidemiology, and pathophysiology of long COVID and discusses what is understood about prevention, evaluation, and treatment of this syndrome.

116 not out: A Case of long COVID Syndrome

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Abstract

COVID-19 pandemic has caused havoc worldwide with huge health and financial losses to patients and relatives. It has wide clinical spectrum with acute respiratory distress syndrome (ARDS) as its primary manifestation. This also includes secondary infections developing post-COVID. Overall 10-15% of patients develop severe COVID and 5% become critically ill. Usually it takes 2-4 weeks to resolve. But few patients take unusually longer period to recover due to severe and serious complications. Some of them require prolonged ventilatory support and home oxygen and recover gradually with very high morbidity rates. We report a case of a 35-year-old male patient who was COVID-19 positive and took a long period of 116 days in-hospital stay to recover from illness in spite of having all possible complications.

116 not out: A Case of long COVID Syndrome

Ongoing Dizziness Following Acute COVID-19 Infection: A Single Center Pediatric Case Series

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Abstract

Dizziness is a common concern discussed at adolescent medical visits. In this series, we describe 9 pediatric patients with Post-Acute Sequelae of SARS-CoV-2 (PASC) who presented with persistent, debilitating dizziness for weeks to months after their acute infection. Among the 9 patients, median age was 14 years (range: 11-17), 6 were female, and 8 had not received any SARS-CoV-2 vaccines. Five patients met diagnostic criteria for postural orthostatic tachycardia syndrome (POTS) by active standing testing and benefited from a combination of non-pharmacologic therapy (NPT) and medication. NPT alone did not improve symptoms in any patients. Patients who did not meet conventional criteria for POTS, but continued to have symptoms despite NPT compliance, also demonstrated subjective improvement in dizziness when medications were initiated. The majority of patients experienced improvement in dizziness and quality of life, including returning to sports teams and a regular school schedule. A review of the PACS literature demonstrates increasing recognition of a subset of patients who develop autonomic dysfunction, including POTS, although the etiology and prognosis are not completely understood. Our case series aims to highlight the phenomenon of dysautonomia after acute SARS-CoV-2 infection and its response to therapy.

Multi-Disciplinary Collaborative Consensus Guidance Statement on the Assessment and Treatment of Cardiovascular Complications in Patients with Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

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No abstract available

Protracted headache after COVID-19: A case series of 31 patients from a tertiary headache center

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Abstract

Background: Headache can be a prominent feature of Post-Acute Sequelae of SARS-Cov2 infection (PASC) and previous studies have centered around PASC headaches that have resolved within a month of infection.

Methods: We performed a retrospective chart review of 31 adults evaluated at the Stanford Headache Clinic between September 2020 and January 2022 who developed new or worsening headaches after COVID-19 infection that were unresolved at time of evaluation for demographics, medical history, and headache diagnosis.

Results: Headache had been present for a mean duration of 7.4±4.8 months after infection. Notably, 25/31 (81%) had a previous history of headache. The specific features of the headache varied considerably, but 23/31 (74%) met International Classification of Headache Disorders, Third Edition (ICHD-3) criteria for migraine, with 20/31 (65%) meeting ICHD-3 criteria for chronic migraine, while only 5/31 (16%) met these criteria before COVID infection. Additionally, full-time employment decreased from 25/31 (81%) to 17/31 (55%). Prior to establishing care at our clinic, 13/18 (72%) of the patients who were started on preventive medications currently indicated for migraine management, reported a decrease in frequency and/or severity of headaches.

Conclusions: Our study presents a group of patients with protracted headache after COVID-19 infection that includes both patients with a previously lower headache burden who largely exhibited chronification from episodic to chronic migraine, as well as patients with no previous history of headache who meet ICHD-3 criteria for headache attributed to a systemic viral illness, mostly with a migrainous phenotype.

The effect of SARS-CoV-2 vaccination on post-acute sequelae of COVID-19 (PASC): A prospective cohort study

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Abstract

Background: Symptoms of post-acute sequelae of COVID-19 (PASC) may improve following SARS-CoV-2 vaccination. However few prospective data that also explore the underlying biological mechanism are available. We assessed the effect of vaccination on symptomatology of participants with PASC, and compared antibody dynamics between those with and without PASC.

Methods: RECoVERED is a prospective cohort study of adult patients with mild to critical COVID-19, enrolled from illness onset. Among participants with PASC, vaccinated participants were exact-matched 1:1 on age, sex, obesity status and time since illness onset to unvaccinated participants. Between matched pairs, we compared the monthly mean numbers of symptoms over a 3-month follow-up period, and, using exact logistic regression, the proportion of participants who fully recovered from PASC. Finally, we assessed the association between PACS status and rate of decay of spike- and RBD-binding IgG titers up to 9 months after illness onset using Bayesian hierarchical linear regression.

Findings: Of 349 enrolled participants, 316 (90.5%) had ≥3 months of follow-up, of whom 186 (58.9%) developed PASC. Among 36 matched pairs with PASC, the mean number of symptoms reported each month during 3 months of follow-up were comparable between vaccinated and

unvaccinated groups. Odds of full recovery from PASC also did not differ between matched pairs (OR 1.57 [95%CI 0.46-5.84]) within 3 months after the matched time-point. The median half-life of spike- and RBD-binding IgG levels were, in days (95%CrI), 233 (183-324) and 181 (147-230) among participants with PASC, and 170 (125-252) and 144 (113-196) among those without PASC, respectively.

Interpretation: Our study found no strong evidence to suggest that vaccination improves symptoms of PASC. This was corroborated by comparable spike- and RBD-binding IgG waning trajectories between those with and without PASC, refuting any immunological basis for a therapeutic effect of vaccination on PASC.

Long-COVID syndrome and the lung

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No abstract available

Intermittent left bundle branch block with septal flash and postural orthostatic tachycardia syndrome in a young woman with long COVID-19

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Abstract

The emerging entity, long COVID -19 is characterised by long-lasting dyspnoea, fatigue, cognitive dysfunction and other symptoms. Cardiac involvement manifested as conduction abnormalities, left ventricle mechanical dyssynchrony, dyspnoea, palpitation and postural orthostatic tachycardia syndrome (POTS) are common in long COVID-19. The direct viral damage to the myocardium or immune-mediated inflammation are postulated mechanisms. A woman in her forties presented with a 2-month history of chest pain, functional dyspnoea, palpitation and an episode of syncope after having been home-isolated for mild COVID infection. During clinical workup, a clustering of ECG and echocardiographic abnormalities including left bundle branch block, septal flash, and presystolic wave on spectral Doppler echocardiography, and POTS were detected. The echocardiographic findings together with POTS and persistent dyspnoea indicated the presence of a long COVID-19 state. The prevalence and clinical significance of these finding, as well as the impact on long-term prognosis, should be investigated in future studies.

Characterization of long COVID-19 manifestations and its associated factors: A prospective cohort study from Iran

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Abstract

The prevalence and variety complaints of COVID-19 cases in a long term have been investigated in recent studies. The symptoms over the time are various and unpredictable which may persist several weeks after full recovery. The importance of long-COVID-19 manifestations includes its effect on the recovered cases which requires a rational management based on an accurate guideline to handle post-acute COVID-19 state. The aim of this study was to evaluate the incidence of post-acute COVID-19 syndrome and to identify the associated risk factors as well as to compare new and persistent symptoms at different post-acute phases. Totally 254 individuals from Pasteur Institute of Iran (or/and their relatives) were investigated who had a previously confirmed COVID-19 PCR test. The long-term manifestations of the virus were categorized through a time window as acute, ongoing, post-COVID and persistent phases and the individuals were assessed by the face-to-face or the phone call interview according to their complaints. The data were then statistically analyzed to determine the frequency of the symptoms and also the associated factors in which a p value < 0.05 was considered significant. Except a small asymptotic group of five, 249 cases progressed the symptoms to acute phase among which 64.1% reported at least one symptom in post-acute phase. Neurological sequelae were found as the most frequent symptom (91.6%). Furthermore, there was a significant association between the underlying diseases, age and acute phase symptoms to the post-acute phase syndrome susceptibility (p < 0.05). In conclusion, the increasing number of the reports and studies on long COVID-19 which can hugely affect the life quality should be more investigated and explored in terms of the pathophysiology to achieve appropriate treatments in time. The clusters of symptoms, specially a combination of neurological signs, presenting over months after the recovery impose a huge difficulty to the recovered population.

Functional Status, Mood State, and Physical Activity Among Women With Post-Acute COVID-19 Syndrome

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Abstract

Objectives: While organ-specific pathophysiology has been well-described in SARS-CoV-2 infection, less is known about the attendant effects on functional status, mood state and leisure-time physical activity (PA) in post-acute COVID-19 syndrome (PASC). Methods: A case-control design was employed to recruit 32 women (n = 17 SARS-CoV-2; n = 15 controls) matched on age (54 ± 12 years) and body mass index (27 ± 6 kg/m2) that did not differ by smoking status or history of cardiopulmonary disease. Participants completed a series of assessments including Profile of Mood States (POMS), Modified Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ-M), and Godin-Shephard Leisure-Time PA. Results: Significant between-group differences were detected for the POMS total mood disturbance with sub-scale analyses revealing elevated tension, confusion, and lower vigor among SARS-CoV-2 participants (all p-values < 0.05). The number of SARS-CoV-2 symptoms (e.g., loss of taste/smell, muscle aches etc.) were associated (r = 0.620, p = 0.008) with confusion. SARS-CoV-2 participants exhibited poorer functional status (p = 0.008) and reduced leisure-time PA (p = 0.004) compared to controls. Conclusion: The sequela of persistent SARS-CoV-2 symptoms elicit clear disturbances in functional status, mood state, and leisure-time PA among women with PASC. Ongoing symptom presentation affects recovery time-course and PA participation.

Alteration of Inflammatory Parameters and Psychological Post-Traumatic Syndrome in Long-COVID Patients

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Abstract

The aim of our study is to evaluate the correlation between the psychological status of patients recovered from SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) infection (long-COVID patients) and their inflammatory status. Three months after hospital discharge, ninety-three patients were recruited and categorized into two distinct populations: control and long-COVID (COrona VIrus Disease) group. Patients belonging to the control group presented with an entering diagnosis of cardiovascular, metabolic, or respiratory disease and a negative history of SARS-CoV-2 infection, whereas the long-COVID population presented with a severe SARS-CoV-2 infection treated in the sub-intensive Care Unit. Psychological evaluation was performed through the administration of the Symptom Checklist-90 (SCL90) and LDH (Lactate dehydrogenase), ferritin, CRPhs (C-high sensitivity Reactive Protein), NLR (Neutrophil-to-lymphocyte ratio), PLR (Platelet-to-lymphocyte ratio), and SII (systemic immune-inflammation index) were investigated. We highlighted that beyond the first three months after contagion, patients recovered from SARS-CoV-2 infection are characterized by the persistence of a systemic inflammatory state and are at high risk for developing somatization, depression, anxiety, and sleep disturbances. Interestingly, ferritin value was strongly correlated with sleep disorders (p < 0.05). Our study emphasizes how COVID-19 strategies for risk stratification, prognosis, and therapy management of patients should be implemented with a psychological follow-up.

Post-Acute Sequelae of SARS-CoV-2 Infection: A Descriptive Clinical Study

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Abstract

Objective: The investigators aimed to describe the clinical experience of a single center reporting on neuropsychiatric findings among patients experiencing persistent symptoms as part of post-acute sequelae of SARS-CoV-2 (PASC) infection.

Methods: Data were collected retrospectively (between February 2020 and May 2021) from a cohort (N=100) within a COVID-19 survivors study of patients with persistent symptoms enrolled after a short inpatient stay or who had been outpatients never hospitalized. Patients without confirmatory positive PCR or antibody diagnostic test results were grouped separately as presumptive cases (N=13).

Results: Of the 87 patients with confirmed SARS-CoV-2, 63 (72.4%) were female, and 65 (74.7%) were White. The mean age was 49.2 years (SD=14.9). The most prevalent symptoms after COVID-19 infection were fatigue, "brain fog," headache, anxiety, and sleep issues. Attention and executive function were frequently impaired. The mean Montreal Cognitive Assessment score was 26.0 (SD=2.8). Concentration and attention as well as memory issues were both significantly correlated with the complaint of brain fog.

Conclusions: These preliminary findings suggest that post-acute sequelae of SARS-CoV-2 vary in frequency and duration with relation to premorbid history and that these conditions affect functional domains and patients' ability to return to work. Longitudinal research with larger cohorts is needed to characterize PASC and to optimize care, especially for vulnerable populations.

Remodeling of T Cell Dynamics During Long COVID Is Dependent on Severity of SARS-CoV-2 Infection

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Abstract

Several COVID-19 convalescents suffer from the post-acute COVID-syndrome (PACS)/long COVID, with symptoms that include fatigue, dyspnea, pulmonary fibrosis, cognitive dysfunctions or even stroke. Given the scale of the worldwide infections, the long-term recovery and the integrative health-care in the nearest future, it is critical to understand the cellular and molecular mechanisms as well as possible predictors of the longitudinal post-COVID-19 responses in convalescent individuals. The immune system and T cell alterations are proposed as drivers of post-acute COVID syndrome. However, despite the number of studies on COVID-19, many of them addressed only the severe convalescents or the short-term responses. Here, we performed longitudinal studies of mild, moderate and severe COVID-19-convalescent patients, at two time points (3 and 6 months from the infection), to assess the dynamics of T cells immune landscape, integrated with patients-reported symptoms. We show that alterations among T cell subsets exhibit different, severity- and time-dependent dynamics, that in severe convalescents result in a polarization towards an exhausted/senescent state of CD4+ and CD8+ T cells and perturbances in CD4+ Tregs. In particular, CD8+ T cells exhibit a high proportion of CD57+ terminal effector cells, together with significant decrease of naïve cell population, augmented granzyme B and IFN-γ production and unresolved inflammation 6 months after infection. Mild convalescents showed increased naïve, and decreased central memory and effector memory CD4+ Treg subsets. Patients from all severity groups can be predisposed to the long COVID symptoms, and fatigue and cognitive dysfunctions are not necessarily related to exhausted/senescent state and T cell dysfunctions, as well as unresolved inflammation that was found only in severe convalescents. In conclusion, the post-COVID-19 functional remodeling of T cells could be seen as a two-step process, leading to distinct convalescent immune states at 6 months after infection. Our data imply that attenuation of the functional polarization together with blocking granzyme B and IFN-γ in CD8+ cells might influence post-COVID alterations in severe convalescents. However, either the search for long COVID predictors or any treatment to prevent PACS and further complications is mandatory in all patients with SARS-CoV-2 infection, and not only in those suffering from severe COVID-19.

Comprehensive clinical assessment identifies specific neurocognitive deficits in working-age patients with long-COVID

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Abstract

There have been more than 425 million COVID-19 infections worldwide. Post-COVID illness has become a common, disabling complication of this infection. Therefore, it presents a significant challenge to global public health and economic activity.

Methods: Comprehensive clinical assessment (symptoms, WHO performance status, cognitive testing, CPET, lung function, high-resolution CT chest, CT pulmonary angiogram and cardiac MRI) of previously well, working-age adults in full-time employment was conducted to identify physical and neurocognitive deficits in those with severe or prolonged COVID-19 illness.

Results: 205 consecutive patients, age 39 (IQR30.0-46.7) years, 84% male, were assessed 24 (IQR17.1-34.0) weeks after acute illness. 69% reported ≥3 ongoing symptoms. Shortness of breath (61%), fatigue (54%) and cognitive problems (47%) were the most frequent symptoms, 17% met criteria for anxiety and 24% depression. 67% remained below pre-COVID performance status at 24 weeks. One third of lung function tests were abnormal, (reduced lung volume and transfer factor, and obstructive spirometry). HRCT lung was clinically indicated in <50% of patients, with COVID-associated pathology found in 25% of these. In all but three HRCTs, changes were graded 'mild'. There was an extremely low incidence of pulmonary thromboembolic disease or significant cardiac pathology. A specific, focal cognitive deficit was identified in those with ongoing symptoms of fatigue, poor concentration, poor memory, low mood, and anxiety. This was notably more common in patients managed in the community during their acute illness.

Conclusion: Despite low rates of residual cardiopulmonary pathology, in this cohort, with low rates of premorbid illness, there is a high burden of symptoms and failure to regain pre-COVID performance 6-months after acute illness. Cognitive assessment identified a specific deficit of the

same magnitude as intoxication at the UK drink driving limit or the deterioration expected with 10 years ageing, which appears to contribute significantly to the symptomatology of long-COVID.

Sarcopenia as potential biological substrate of long COVID-19 syndrome: prevalence, clinical features, and risk factors

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Abstract

Background: Severe clinical pictures and sequelae of COVID-19 disease are immune mediated and characterized by a 'cytokine storm'. Skeletal muscle has emerged as a potent regulator of immune system function. The aim of the present study is to define the prevalence of sarcopenia among COVID-19 survivors and the negative impact of sarcopenia on the post-acute COVID-19 syndrome and its related risk factors.

Methods: A total of 541 subjects recovered from COVID-19 disease were enrolled in the Gemelli Against COVID-19 Post-Acute Care between April 2020 and February 2021. They underwent a multidisciplinary clinical evaluation and muscle strength and physical performance assessment.

Results: Mean age was 53.1 years (SD 15.2, range from 18 to 86 years), and 274 (51%) were women. The prevalence of sarcopenia was 19.5%, and it was higher in patients with a longer hospital stay and lower in patients who were more physically active and had higher levels of serum albumin. Patients with sarcopenia had a higher number of persistent symptoms than non-sarcopenic patients (3.8 ± 2.9 vs. 3.2 ± 2.8, respectively; $P = 0.06$), in particular fatigue, dyspnoea, and joint pain.

Conclusions: Sarcopenia identified according to the EWGSOP2 criteria is high in patients recovered from COVID-19 acute illness, particularly in those who had experienced the worst clinical picture reporting the persistence of fatigue and dyspnoea. Our data suggest that sarcopenia, through the persistence of inflammation, could be the biological substrate of long COVID-19 syndrome. Physical activity, especially if associated with adequate nutrition, seems to be an important protective factor.

The Impact of Iron Dyshomeostasis and Anaemia on Long-Term Pulmonary Recovery and Persisting Symptom Burden after COVID-19: A Prospective Observational Cohort Study

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Abstract

Coronavirus disease 2019 (COVID-19) is frequently associated with iron dyshomeostasis. The latter is related to acute disease severity and COVID-19 convalescence. We herein describe iron dyshomeostasis at COVID-19 follow-up and its association with long-term pulmonary and symptomatic recovery. The prospective, multicentre, observational cohort study "Development of Interstitial Lung Disease (ILD) in Patients With Severe SARS-CoV-2 Infection (CovILD)" encompasses serial extensive clinical, laboratory, functional and imaging evaluations at 60, 100, 180 and 360 days after COVID-19 onset. We included 108 individuals with mild-to-critical acute COVID-19, whereas 75% presented with severe acute disease. At 60 days post-COVID-19 follow-up, hyperferritinaemia (35% of patients), iron deficiency (24% of the cohort) and anaemia (9% of the patients) were frequently found. Anaemia of inflammation (AI) was the predominant feature at early post-acute follow-up, whereas the anaemia phenotype shifted towards iron deficiency anaemia (IDA) and combinations of IDA and AI until the 360 days follow-up. The prevalence of anaemia significantly decreased over time, but iron dyshomeostasis remained a frequent finding throughout the study. Neither iron dyshomeostasis nor anaemia were related to persisting structural lung impairment, but both were associated with impaired stress resilience at long-term COVID-19 follow-up. To conclude, iron dyshomeostasis and anaemia are frequent findings after COVID-19 and may contribute to its long-term symptomatic outcome.

Longitudinal evaluation of neurologic-post acute sequelae SARS-CoV-2 infection symptoms

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Abstract

Objective: To assess the initial features and evolution of neurologic Postacute Sequelae of SARS-CoV-2 infection (neuro-PASC) in patients with and without prior neurologic disease.

Methods: Participants with neurologic symptoms following acute SARS-CoV-2 infection were recruited from October 9, 2020 to October 11, 2021. Clinical data included a SARS-CoV-2 infection history, neurologic review of systems, neurologic exam, Montreal cognitive assessment (MoCA), and symptom-based self-reported surveys at baseline (conducted after acute infection) and 6-month follow-up assessments.

Results: Fifty-six participants (69% female, mean age 50 years, 29% with prior neurologic disease such as multiple sclerosis) were enrolled, of which 27 had completed the 6-month follow-up visit in this ongoing study. SARS-CoV-2 infection severity was largely described as mild (39.3%) or moderate (42.9%). At baseline, following acute infection, the most common neurologic symptoms were fatigue (89.3%) and headaches (80.4%). At the 6-month follow-up, memory impairment (68.8%) and decreased concentration (61.5%) were the most prevalent, though on average all symptoms showed a reduction in reported severity score at the follow-up. Complete symptom resolution was reported in 33.3% of participants by 6 months. From baseline to 6 months, average MoCA scores improved overall though 26.3% of participants' scores decreased. A syndrome consisting of tremor, ataxia, and cognitive dysfunction (PASC-TAC) was observed in 7.1% of patients.

Interpretation: Early in the neuro-PASC syndrome, fatigue and headache are the most commonly reported symptoms. At 6 months, memory impairment and decreased concentration were most prominent. Only one-third of participants had completed resolution of neuro-PASC at 6 months, although persistent symptoms trended toward improvement at follow-up.

Covid-19: Long covid risk is lower with omicron than delta, researchers find

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No abstract available

Clues to long COVID

Jennifer Couzin-Frankel

Abstract

Scientists strive to unravel what is driving disabling symptoms.

The Greek Collaborative Long COVID Study: Non-Hospitalized and Hospitalized Patients Share Similar Symptom Patterns

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Abstract

Long COVID-19 syndrome refers to persisting symptoms (>12 weeks) after the initial coronavirus infection and is estimated to affect 3% to 12% of people diagnosed with the disease globally.

Aim: We conducted a collaborative study with the Long COVID patient organization in Greece, in order to estimate the characteristics, symptoms, and challenges these patients confront.

Methods: Data were collected from 208 patients using unstructured qualitative free-text entries in an anonymized online questionnaire.

Results: The majority of respondents (68.8%) were not hospitalized and reported lingering symptoms (66.8%) for more than six months. Eighteen different symptoms (fatigue, palpitations, shortness of breath, parosmia, etc.) were mentioned in both hospitalized and community patients. Awareness of Long COVID sequelae seems to be low even among medical doctors. Treatment options incorporating targeted rehabilitation programs are either not available or still not included in the management plan of Long COVID patients.

Conclusions: Patients infected with coronavirus with initial mild symptoms suffer from the same persistent symptoms as those who were hospitalized. Long COVID syndrome appears to be a multi-systemic entity and a multidisciplinary medical approach should be adopted in order to correctly diagnose and successfully manage these patients.

Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2

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No abstract available

The evolving picture of long COVID

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No abstract available

Markers of fungal translocation are elevated during post-acute sequelae of SARS-CoV-2 and induce NF-κB signaling

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Abstract

Long COVID, a type of Post-Acute Sequelae of SARS-CoV-2 (PASC), has been associated with sustained elevated levels of immune activation and inflammation. However, the mechanisms that drive this inflammation remain unknown. Inflammation during acute Coronavirus Disease 2019 could be exacerbated by microbial translocation (from gut and/or lung) to blood. Whether microbial translocation contributes to inflammation during PASC is unknown. We did not observe a significant elevation in plasma markers of bacterial translocation during PASC. However, we observed higher levels of fungal translocation - measured as β-glucan, a fungal cell wall polysaccharide - in the plasma of individuals experiencing PASC compared to those without PASC or SARS-CoV-2 negative controls. The higher β-glucan correlated with higher inflammation and elevated levels of host metabolites involved in activating N-Methyl-D-aspartate receptors (such as metabolites within the tryptophan catabolism pathway) with established neuro-toxic properties. Mechanistically, β-glucan can directly induce inflammation by binding to myeloid cells (via Dectin-1) and activating Syk/NF-κB signaling. Using a Dectin-1/NF-κB reporter model, we found that plasma from individuals experiencing PASC induced higher NF-κB signaling compared to plasma from negative controls. This higher NF-κB signaling was abrogated by Piceatannol (Syk inhibitor). These data suggest a potential targetable mechanism linking fungal translocation and inflammation during PASC.

The IL-1β, IL-6, and TNF cytokine triad is associated with post-acute sequelae of COVID-19

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Abstract

Post-acute sequelae of COVID-19 (PASC) is emerging as global problem with unknown molecular drivers. Using a digital epidemiology approach, we recruited 8,077 individuals to the cohort study for digital health research in Germany (DigiHero) to respond to a basic questionnaire followed by a PASC-focused survey and blood sampling. We report the first 318 participants, the majority thereof after mild infections. Of those, 67.8% report PASC, predominantly consisting of fatigue, dyspnea, and concentration deficit, which persists in 60% over the mean 8-month follow-up period and resolves independently of post-infection vaccination. PASC is not associated with autoantibodies, but with elevated IL-1β, IL-6, and TNF plasma levels, which we confirm in a validation cohort with 333 additional participants and a longer time from infection of 10 months. Blood profiling and single-cell data from early infection suggest the induction of these cytokines in COVID-19 lung pro-inflammatory macrophages creating a self-sustaining feedback loop.

Examining the Long-Term Sequelae of SARS-CoV2 Infection in Patients Seen in an Outpatient Psychiatric Department

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Abstract

Background: The acute phase of Coronavirus disease-19 (COVID-19) is well known. However, there is now an increasing number of patients suffering from the post-acute sequelae of COVID-19 (PASC Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis), including neuropsychiatric symptoms. The purpose of this report is to describe the sociodemographic, diagnostic and treatment characteristics of patients evaluated in an outpatient psychiatric setting for PASC.

Methods: A retrospective review of 30 individuals with documented COVID-19 illness treated at a university hospital-based Post-COVID-19 Recovery Program were referred to an outpatient psychiatric department for consultation and treatment from December 2020 to July 2021. All individuals complained of neuropsychiatric symptoms including anxiety, depression, fatigue and cognitive problems. Data on sociodemographic characteristics, psychiatric diagnosis, prominent psychological themes and treatment prescribed were described and, where applicable, analyzed with SPSS software.

Results: The study population consisted of patients between 25 and 82 years old, with a predominance of women between 46 and 60 years. Approximately half of the patient population had a primary diagnosis of major depressive disorder, often combined with prominent anxiety. Over two-thirds of the patient population reported a combination of depression, fatigue and cognitive complaints, predominantly memory and slowed processing speed. Prominent stressors and psychological themes included social and occupational decline, isolation, lack of empathy and understanding from family, friends and employers, and apprehension about future ability to return to their baseline level of function. Treatments recommended included individual and group psychotherapy, medication and cognitive rehabilitation. Modafinil and antidepressants, often in combination, were the most commonly used medications, intended to target the pervasive fatigue, depressive, and anxiety these individuals were facing.

Conclusion: Clinical experience from this patient population underscored the significant medical, emotional, neurocognitive and functional sequelae of PASC. Management of these individuals requires a collaborative approach with the availability of psychotherapeutic interventions, pharmacologic treatment, neurocognitive assessment and remediation to address these symptoms.

Long-COVID in children and adolescents: a systematic review and meta-analyses

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Abstract

The objective of this systematic review and meta-analyses is to estimate the prevalence of long-COVID in children and adolescents and to present the full spectrum of symptoms present after acute COVID-19. We have used PubMed and Embase to identify observational studies published before February 10th, 2022 that included a minimum of 30 patients with ages ranging from 0 to 18 years that met the National Institute for Healthcare Excellence (NICE) definition of long-COVID, which consists of both ongoing (4 to 12 weeks) and post-COVID-19 (≥ 12 weeks) symptoms. Random-effects meta-analyses were performed using the MetaXL software to estimate the pooled prevalence with a 95% confidence interval (CI). Heterogeneity was assessed using I2 statistics. The Preferred Reporting Items for Systematic Reviewers and Meta-analysis (PRISMA) reporting guideline was followed (registration PROSPERO CRD42021275408). The literature search yielded 8373 publications, of which 21 studies met the inclusion criteria, and a total of 80,071 children and adolescents were included. The prevalence of long-COVID was 25.24%, and the most prevalent clinical manifestations were mood symptoms (16.50%), fatigue (9.66%), and sleep disorders (8.42%). Children infected by SARS-CoV-2 had a higher risk of persistent dyspnea, anosmia/ageusia, and/or fever compared to controls. Limitations of the studies analyzed include lack of standardized definitions, recall, selection, misclassification, nonresponse and/or loss of follow-up, and a high level of heterogeneity.

Rationale for Nicotinamide Adenine Dinucleotide (NAD+) Metabolome Disruption as a Pathogenic Mechanism of Post-Acute COVID-19 Syndrome

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Abstract

Many acute COVID-19 convalescents experience a persistent sequelae of infection, called post-acute COVID-19 syndrome (PACS). With incidence ranging between 31% and 69%, PACS is becoming increasingly acknowledged as a new disease state in the context of SARS-CoV-2 infection. As SARS-CoV-2 infection can affect several organ systems to varying degrees and durations, the cellular and molecular abnormalities contributing to PACS pathogenesis remain unclear. Despite our limited understanding of how SARS-CoV-2 infection promotes this persistent disease state, mitochondrial dysfunction has been increasingly recognized as a contributing factor to acute SARS-CoV-2 infection and, more recently, to PACS pathogenesis. The biological mechanisms contributing to this phenomena have not been well established in previous literature; however, in this review, we summarize the evidence that NAD+ metabolome disruption and subsequent mitochondrial dysfunction following SARS-CoV-2 genome integration may contribute to PACS biological pathogenesis. We also briefly examine the coordinated and complex relationship between increased oxidative stress, inflammation, and mitochondrial dysfunction and speculate as to how SARS-CoV-2-mediated NAD+ depletion may be causing these abnormalities in PACS. As such, we present evidence supporting the therapeutic potential of intravenous administration of NAD+ as a novel treatment intervention for PACS symptom management.

Vasospastic Angina: A Cause of Post-acute COVID-19 Syndrome

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No abstract available

Functional decline, long term symptoms and course of frailty at 3-months follow-up in COVID-19 older survivors, a prospective observational cohort study

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Abstract

Background: Aging is one of the most important prognostic factors increasing the risk of clinical severity and mortality of COVID-19 infection. However, among patients over 75 years, little is known about post-acute functional decline.

Objective: The aim of this study was to identify factors associated with functional decline 3 months after COVID-19 onset, to identify long term COVID-19 symptoms and transitions between frailty states after COVID-19 onset in older hospitalized patients.

Methods: This prospective observational study included COVID-19 patients consecutively hospitalized from March to December 2020 in Acute Geriatric Ward in Nantes University Hospital. Functional decline, frailty status and long term symptoms were assessed at 3 month follow up. Functional status was assessed using the Activities of Daily Living simplified scale (ADL). Frailty status was evaluated using Clinical Frailty Scale (CFS). We performed multivariable analyses to identify factors associated with functional decline.

Results: Among the 318 patients hospitalized for COVID-19 infection, 198 were alive 3 months after discharge. At 3 months, functional decline occurred in 69 (36%) patients. In multivariable analysis, a significant association was found between functional decline and stroke (OR = 4,57, p = 0,003), history of depressive disorder (OR = 3,05, p = 0,016), complications (OR = 2,24, p = 0,039), length of stay (OR = 1,05, p = 0,025) and age (OR = 1,08, p = 0,028). At 3 months, 75 patients described long-term symptoms (49.0%). Of those with frailty (CFS scores ≥5) at 3-months follow-up, 30% were not frail at baseline. Increasing frailty defined by a worse CFS state between baseline and 3 months occurred in 41 patients (26.8%).

Conclusions: This study provides evidence that both the severity of the COVID-19 infection and preexisting medical conditions correlates with a functional decline at distance of the infection. This encourages practitioners to establish discharge personalized care plan based on a multidimensional geriatric assessment and in parallel on clinical severity evaluation.