Advancing Toward Recovery from Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

NIH’s RECOVER Initiative

Progress Update

December 15, 2022
Frequency of PASC varies widely depending on time from infection and severity of illness (e.g., 5-80%).

Heterogeneous symptom set.

Groff et al., *JAMA Network Open*, October 2021

At six month time point 55% were judged to have at least one sequelae of COVID-19 infection.
Short- and Long-term Rates of Post-acute Sequelae of SARS-CoV-2 Infection: A Systematic Review
(57 studies, Total n=250,351 COVID-19 survivors, 79% hospitalized)
At six month time point 55% were judged to have at least one sequelae of COVID-19 infection.

- Frequency of PASC varies widely depending on time from infection and severity of illness (e.g., 5-80%).
- Heterogeneous symptom set.
How prevalent is PASC?

Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021

Proportion of Individuals Who Survived Symptomatic SARS-CoV-2 Infection and Who Experienced at Least 1 of the 3 Long COVID Symptom Clusters in 2020 and 2021

The estimated mean Long COVID symptom cluster duration was 9.0 months (95% UI, 7.0-12.0 months) among hospitalized individuals and 4.0 months (95% UI, 3.6-4.6 months) among nonhospitalized individuals.

JAMA. Published online October 10, 2022. doi:10.1001/jama.2022.18931
Persistent symptoms after 12 weeks of acute infection are **3.0% based on tracking specific symptoms, to 11.7% based on self-classification** of long COVID, using data to 1 August 2021.

Among study participants **with COVID-19, 5.0% reported any of 12 common symptoms** 12 to 16 weeks after infection; however, **prevalence was 3.4% in a control** group of participants without a positive test for COVID-19, demonstrating the relative commonness of these symptoms in the population at any given time.

Among study participants with COVID-19, **3.0%** experienced any of 12 common symptoms for a **continuous period of at least 12 weeks** from infection, compared with **0.5% in the control** group.

Prevalence of **self-reported long COVID is 11.7%** of study subjects experiencing long COVID (based on self-classification rather than reporting one of the 12 common symptoms) 12 weeks after infection, falling to 7.5% when considering long COVID that resulted in limitation to day-to-day activities; these percentages increased to 17.7% and 11.8% respectively when considering only participants who were symptomatic at the acute phase of infection.

Prevalence was highest in **females, adults aged 50 to 69 years, people with a pre-existing health condition, and those with signs of high viral load at the time of infection**.
How does prevalence of PASC vary by variant?

Approximately 4% of triple-vaccinated adults reported experiencing long COVID 12 weeks after being infected with the Omicron BA.1 or BA.2 variants.

### Triple-vaccinated

<table>
<thead>
<tr>
<th>Severity</th>
<th>Delta</th>
<th>Omicron BA.1</th>
<th>Omicron BA.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any severity</td>
<td><img src="#" alt="Bar Chart" /></td>
<td><img src="#" alt="Bar Chart" /></td>
<td><img src="#" alt="Bar Chart" /></td>
</tr>
<tr>
<td>Activity-limiting</td>
<td><img src="#" alt="Bar Chart" /></td>
<td><img src="#" alt="Bar Chart" /></td>
<td><img src="#" alt="Bar Chart" /></td>
</tr>
</tbody>
</table>

### Double-vaccinated

<table>
<thead>
<tr>
<th>Severity</th>
<th>Delta</th>
<th>Omicron BA.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any severity</td>
<td><img src="#" alt="Bar Chart" /></td>
<td><img src="#" alt="Bar Chart" /></td>
</tr>
<tr>
<td>Activity-limiting</td>
<td><img src="#" alt="Bar Chart" /></td>
<td><img src="#" alt="Bar Chart" /></td>
</tr>
</tbody>
</table>
Followed patients in Cerner Electronic Health Records for incident conditions occurring after 30 days of infection vs. control group without infection. Hospitalization status not defined.

- 38% of previously infected individuals developed an incident condition compared with 16% of controls.
- One in five COVID-19 survivors > 18 years old experienced an incident condition that might be attributable to previous COVID-19.
- One in four survivors aged > 65 did so.

correctCOVID.org
Hypothesized etiologies of PASC

- PASC is very likely a set of multiple conditions with varied underlying causes

- **Examples of hypothesized causes:**
  - Persistence of SARS-CoV-2 virus or antigens and/or reactivation of other viruses stimulating ongoing immune response
  - Viral infection and/or antigenic stimulation setting in motion a **dysregulated immune response** affecting various organs and tissues
  - Viral infection and/or inflammatory responses cause **damage to organs and tissues** that in turn results in dysfunction (e.g., neurologic, cardiac, pulmonary, renal, metabolic, GI)

2. https://www.nature.com/articles/s41590-021-01113-x
4. https://www.biorxiv.org/content/10.1101/2022.01.07.475453v1
Patients with Long Covid had:

- highly activated innate immune cells,
- lacked naive T and B cells and
- showed elevated expression of type I IFN (IFN-β) and type III IFN (IFN-λ1) that remained persistently high at 8 months after infection.
Potential role for autoimmunity in PASC.

• Auto antibodies to multiple self antigens are observed during acute COVID-19 infection.
  • Diverse functional autoantibodies in patients with COVID-19 (Nature) 10.1038/s41586-021-03631-y ;
  • New-onset IgG autoantibodies in hospitalized patients with COVID-19 (Nat Commun) 10.1038/s41467-021-25509-3;

A number of small studies suggesting autoimmunity in some persons with PASC.

• Dysregulated autoantibodies targeting vaso- and immunoregulatory receptors in Post COVID Syndrome correlate with symptom severity. DOI: 10.3389/fimmu.2022.981532
• Autoimmune Effect of Antibodies against the SARS-CoV-2 Nucleoprotein DOI: 10.3390/v14061141
• Reaction of Human Monoclonal Antibodies to SARS-CoV-2 Proteins With Tissue Antigens: Implications for Autoimmune Diseases DOI: 10.3389/fimmu.2020.617089
• Autoimmunity is a hallmark of post-COVID syndrome doi: 10.1186/s12967-022-03328-4
• Persistent Autoimmune Activation and Proinflammatory State in Post-Coronavirus Disease 2019 Syndrome DOI: 10.1093/infdis/jiac017
• Persistent IgG anticardiolipin autoantibodies are associated with post-COVID syndrome DOI: 10.1016/j.ijid.2021.09.079
Elevated vascular transformation blood biomarkers in Long-COVID indicate angiogenesis as a key pathophysiological mechanism

<table>
<thead>
<tr>
<th>Feature Ranking</th>
<th>% Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyte</td>
<td></td>
</tr>
<tr>
<td>1 ANG-1</td>
<td>21.7</td>
</tr>
<tr>
<td>2 P-SEL</td>
<td>15.4</td>
</tr>
<tr>
<td>3 MMP-1</td>
<td>12.5</td>
</tr>
<tr>
<td>4 VE-Cad</td>
<td>9.3</td>
</tr>
<tr>
<td>5 Syn-1</td>
<td>7.8</td>
</tr>
<tr>
<td>6 Endoglin</td>
<td>6.0</td>
</tr>
<tr>
<td>7 PECAM-1</td>
<td>5.4</td>
</tr>
<tr>
<td>8 VEGF-A</td>
<td>5.4</td>
</tr>
<tr>
<td>9 ICAM-1</td>
<td>5.3</td>
</tr>
<tr>
<td>10 VLA-4</td>
<td>3.3</td>
</tr>
<tr>
<td>11 E-SEL</td>
<td>3.1</td>
</tr>
<tr>
<td>12 Thrombomodulin</td>
<td>1.8</td>
</tr>
<tr>
<td>13 VEGF-R2</td>
<td>1.7</td>
</tr>
<tr>
<td>14 VEGF-R3</td>
<td>1.5</td>
</tr>
</tbody>
</table>

dimensionality reduction of all fourteen significant biomarkers, shows separation cluster of Long-COVID outpatients with some mixing with acutely ill COVID-19 inpatients and healthy control subjects

dimensionality reduction of two selected biomarkers, ANG-1 and P-SEL, showed distinct separation and clustering of Long-COVID outpatients from acutely ill COVID-19 inpatients and healthy control subjects
Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation

Authors
Anthony Fernández-Castañeda,
Peiwen Lu, Anna C. Geraghty, ..., 
Avindra Nath, Akiko Iwasaki, 
Michelle Monje

Correspondence
akiko.iwasaki@yale.edu (A.I.), 
monje@stanford.edu (M.M.)

In brief
Mild respiratory COVID causes neuroinflammation and multi-lineage cellular dysregulation in the central nervous system, a phenomenon mirroring cancer-therapy-related cognitive impairment.
Is there persistence of viral material?

SARS-CoV-2 infection and persistence throughout the human body and brain

Daniel Chertow (chertowd@cc.nih.gov)
National Institutes of Health  https://orcid.org/0000-0002-1675-1728

Autopsies on 44 COVID-19 patients from acute infection through over 7 months following symptom onset.

- SARS-CoV-2 is widely distributed even in patients who died with asymptomatic or mild infection
- Virus replication is present in multiple pulmonary and extrapulmonary tissues early in infection
- RNA in multiple anatomic sites, including brain, for up to 230 days after symptom onset.
- Paucity of inflammation or viral cytopathology outside the lung

Chertow et al. Research Square (preprint), Posted December 2021
Exocytic Vesicle (EV) numbers (i) and EV-linked Spike protein (ii) in the plasma from individuals with and without PASC as measured by Nanoparticle Tracking Analysis and ELISA, respectively.
NIH RECOVER Initiative

**Goal**
Rapidly improve our understanding of and ability to predict, treat, and prevent PASC

**Key Scientific Aims**

1. Understand clinical spectrum/biology underlying recovery over time
2. Define risk factors, incidence/prevalence, and distinct PASC sub-phenotypes
3. Study pathogenesis over time and possible relation to other organ dysfunction/disorders
4. Identify interventions to treat and prevent PASC

**Guiding Principles**

- Patient-centered, participants as partners
- National Scale with Inclusive, diverse participation & community engagement
- Platform protocols, standardized methodologies, and common data elements
- Adaptive approaches based on emerging science
Key Progress in 2022 (as of September)

- ~10,000 adult patients enrolled in past 9 months
- 8 longitudinal clinical cohort studies and related sub-studies
- 42+ pathobiology studies
- 5 master protocol-driven platform clinical trials under development
- EHR study results: ~40 reports (17 draft, 9 submitted, 11 preprint, 3 published)

- Data repositories and shared analytic workbench; initial RECOVER data release to consortium in process
- Study of potential PASC biomarker
- Launched mobile health platform; designed patient registry
- Collaborative patient community engagement and research seminar series
- RECOVER-All of Us precision medicine collaboration
Proportion of RECOVER participants developing PASC symptoms of varying severity

- **EHR Studies:**
  - Hospitalization for COVID-19 and PASC incidence
    - Incidence of PASC over time higher among people who were hospitalized for COVID-19 (8-20%) than non-hospitalized (4-8%)
  - PASC incidence in children
    - 3.7% SARS-CoV-2 infected children go on to develop PASC ([Link](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8359016/), *JAMA Pediatrics*)

- **Cohort Study:** Significant % of adult participants enrolled during acute infection report persistent and/or new onset symptoms months after acute infection compared to uninfected individuals
  - Among participants recruited during acute infection, 20-30% report symptoms at 3 months, whereas 5-15% of uninfected participants develop these symptoms
RECOVER Study: Preliminary Findings

What are the impacts of different variants and vaccination?

**EHR Studies:**
- Higher peaks of PASC early in the pandemic (a period with more severe acute illness) and with Delta variant (Link: In preparation)
- **Vaccination decreases a patient’s predicted probability of PASC** (Link: The Lancet and Link: Long COVID Risk and Pre-COVID Vaccination: An EHR-Based Cohort Study from the RECOVER Program)
- **Vaccination protects against cardiac complications of SARS-CO-V-2 infections in male teens and young adults:** Teen boys (12-17) and young men (18-29) had 2-6x and 7-8x respective higher risk of heart complications after COVID-19 infection compared to after vaccination (Link: Morbidity and Mortality Weekly Report)

**Cohort Studies:**
- Predominant symptoms are fairly consistent across infection waves
- Lower overall rates of symptoms observed in participants infected in later years
- Vaccinated individuals infected with Omicron variant continue to be at risk for PASC, though the chance of PASC is lower than individuals infected pre-Omicron
PASC Master Protocol-Driven Platform Clinical Trials Span Range of Dominant Symptom Clusters and Proposed Etiologic Pathways

- Solicited clinical trial concepts from clinical research community
- Analyzed data from RECOVER clinical cohorts to identify major symptom clusters and inform trial endpoint selection
- Engaged key stakeholders and agencies in development process: patients, clinicians, FDA, CMS, PCORI and others as appropriate, including industry
- 5 platform protocols under development and, as appropriate, regulatory review and spanning major PASC symptom clusters and proposed etiologic pathways

RECOVER Clinical Trial Platforms Portfolio

Staged roll-out starting end of 2022 and early 2023
RECOVER: Researching COVID to Enhance Recovery

What is PASC?

SARS-CoV-2 is a virus that can infect the body and is referred to as a SARS-CoV-2 infection. Recovery from SARS-CoV-2 infection can vary from person to person.

Acute Infection:
Most people recover quickly from acute SARS-CoV-2 infection. People who have a PASC (Post-Acute COVID-19 Syndrome) may experience symptoms for 2 or more months after initial infection. Typical symptoms include:

- Cough
- Shortness of breath
- Chest pain
- Difficulty breathing
- Fatigue
- Muscle and body aches
- Headache
- Sore throat
- Loss of taste or smell

Chronic Systemic Inflammatory Condition (CSIC)

Some people may develop a chronic systemic inflammatory condition (CSIC) that lasts for months or even years after initial infection. This can manifest as:

- Joint pain and muscle aches
- Fatigue
- Shortness of breath
- Headache
- Dizziness
- Fainting
- Loss of appetite
- Loss of weight
- Dry mouth

To ensure this research is informed by patients, RECOVER will engage regularly with people who have experienced SARS-CoV-2 infection.

What types of updates would you like to receive?

- Information about volunteering for RECOVER studies
- RECOVER updates and the latest research findings
- Announcements on related research funding, training, and technical assistance opportunities

Together we can learn more. The more voices.

recoverCOVID.org