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.

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

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• 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**.
ICD-10 code for “post COVID-19” condition (U09.9) available October 1, 2021

• Large, mostly private, insurance database with 1,959,982 COVID-19 patients.

• 4% with diagnosis of Post COVID condition (U09.9)10/1/21-1/31/22
  • 24% of those with Post COVID dx. were hospitalized vs. 8.4% of total infected
    • 75.8 % of those with Post COVID dx. were not hospitalized
    • 81.6% of females with Post COVID dx. were not hospitalized

• Most common co-occurring conditions
  • Breathing abnormality 23.2%
  • Cough 18.9%
  • Malaise and fatigue 16.7%
  • Increased risk of: “unspecified myopathy” (11x’s), Pulmonary embolism (2x’s), other disorders of the brain (2x’s)
Memorandum on Addressing the Long-Term Effects of COVID-19

MEMORANDUM FOR THE HEADS OF EXECUTIVE DEPARTMENTS AND AGENCIES

SUBJECT: Addressing the Long-Term Effects of COVID-19

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. Policy. My Administration has made combating the coronavirus disease 2019 (COVID-19) pandemic, and guiding the Nation through the worst public health crisis in many decades, a priority of the highest national importance.
• Study of 175 COVID-19 patients.
• In contrast to the elevated IgG3 levels in both mild and severe COVID-19 cases, IgG3 showed a trend to being lower in patients developing PACS.
• Patients with both high IgM and high IgG3 were less likely to develop PACS.
From online data collection to identification of disease mechanisms: The IL-1β, IL-6 and TNF-α cytokine triad is associated with post-acute sequelae of COVID-19 in a digital research cohort. Christoph Schultheiß, Edith Willscher, Lisa Paschold, Lidia Bosurgi, Jochen Dutzmann, Daniel Sedding, Thomas Frese, Matthias Girndt, Jessica Höll, Michael Gekle, Rafael Mikolajczyk, Mascha Binder

- The analysis is based on 258 persons eight months after mostly mild infection from Halle Germany. PASC were reported in 40% of cases at 6 months and consisted predominantly in fatigue, dyspnea and concentration deficit.

- Correlation of TNF-α, IL-1β and IL-6 plasma levels in patients with ongoing PASC. Concentrations shown as pg/ml.

- The recovery from PASC was not associated with post-infection vaccination suggesting that it may not be driven by a cryptic SARS-CoV-2 reservoir.

- We confirmed the high percentage of individuals with autoantibodies after COVID-19, but found no association with PASC.

- Data show that a broad range of cytokines remain deregulated long after infection; IL-1β, IL-6 and TNF-α represented a triad that was associated with PASC.

- Blood profiling and single-cell data from early infection indicated that these cytokines are induced in COVID-19 lung pro-inflammatory macrophages creating a feedback loop that may trigger their long-term activation.
Is there persistence of viral material?

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

Daniel Chertow (chartowd@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.

recoverCOVID.org  https://videocast.nih.gov/watch=45296
Advancing Toward Recovery from Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

NIH RECOVER Initiative
RECOVER Listening Sessions

Listening Session Timeline

Listening Session #1
June 2, 2021
Long COVID Alliance / Advocacy Groups

Listening Session #2
January 21, 2022
Communities of Color and Those Most Impacted by COVID

Listening Session #3
May 3, 2022
Engaging Participants in the Health Sector serving American Indian/Alaskan Native Communities

Listening Session #3
June 23, 2022
Engaging Participants in the Health Sector serving American Indian/Alaskan Native Communities

Videos available: https://recovercovid.org/news-events
RECOVER Patient-Centered Approach

Patient perspectives are a critical element of the RECOVER Initiative and patient engagement is integral to every element of the program.

Examples of Patient Involvement

- Representation Across Governance Structure
- 35+ Patients Participated in Common Protocol Design
- Participant Portal 10,000+ participants
- Social Media Outreach
- 860+ Attendees at Discussions of Patient Experiences
- Mobile Health Platform for Patient Reported Outcomes
- 500+ Direct Email Inquiries
- 15,000+ Website Subscribers

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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
RECOVER Study Components

RECOVER Cores
- Clinical Trial Data Cord. Center
- Clinical Science Core
- Data Resource Core
- Biorepository Core

Elements
- RECOVER Clinical Trials: Clinical Platform with Multi-therapeutic domains
- RECOVER Enrolling Cohorts: ~40,000 participants
- EHR/ Health Systems Studies: 60 million+ records; ~4 million+ COVID cases
- Pathobiology Studies: Mechanistic studies of pathogenesis
- Autopsy Pathology Studies: 50+ tissue types

Data Resources
- Clinical
- Imaging
- Mobile and Digital Health
- EHR / Other Real-World Data
- Pathology

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RECOVER Cohorts: A National Scale Platform

- Clinical Cohort Studies, Adult and Pediatric
  - 30 Hubs:
    - 15 Adult Cohorts
    - 2 Pregnancy Cohorts
    - 8 Pediatric Cohorts
    - 5 Autopsy Centers

- EHR Studies, Adult and Pediatric
  - 60,000,000+ patient records

Enrolling participants from 200+ sites across the Nation

(Will also include clinical trials and patient registry)
RECOVER Cohorts: A National Scale Platform

Current Enrollment (as of May 31, 2022)

Clinical Cohort Studies, Adult and Pediatric

- Adult Population
  - 3,712 participants across 58 sites
- Pediatric cohort
  - 91 participants across 8 sites
- Autopsy cohort
  - 15 participants across 3 sites
Achieving Depth and Breadth in RECOVER Cohorts

Acute and post-acute cohort studies will use platform-protocol driven tiered approach to characterize the trajectory of recovery over time and compare those who make a good recovery with those that develop PASC.

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<th>ACUTE INFECTION COHORT</th>
<th>POST-ACUTE INFECTION COHORT</th>
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<td>9k, including 200+ pregnant persons</td>
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<td>1k</td>
<td>18k, including 800 with MIS-C</td>
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**Adult Study Overview**

- **Recruitment in 33 states + Washington, DC and Puerto Rico**
  - Hospitals/Clinics/Communities/Electronic Health Records
  - Diverse population with and without COVID-19
  - Adults/Pregnant women

- **Tier 1**
  - Surveys, Labs, Biospecimens, Minimal Exam
  - (17,680 participants)

- **Tier 2**
  - Low Risk Clinical Tests
  - (5,300 participants)

- **Tier 3**
  - Advanced Testing
  - (3,500 participants)
Overview of Enrollment for RECOVER Meta-Cohort

- **Congenital exposure cohort**: N=2,500
  - Infants born in the context of maternal SARS-CoV-2 infection N=2,000
  - Infants not born in the context of maternal SARS-CoV-2 infection N=500

- **Main Cohort Infected**: N=4,800
  - Acute Infected N=800
  - Post-Acute Infected N=4,000

- **Main Cohort Uninfected**: N=1,200
  - Uninfected N=1,200

- **ABCD Cohort**: N=10,000
  - Infected N=1,500
  - Uninfected N=8,500

- **MIS-C**: N=800
  - MIS-C N=800

- **Post-Vax MC**: N=200
  - MIS-C N=800

- **Tier 1**
  - N=19,500
  - Infants born in the context of maternal SARS-CoV-2 infection N=2,000
  - Infants not born in the context of maternal SARS-CoV-2 infection N=500

- **Tier 2**
  - N=9,500
  - Infants born in the context of maternal SARS-CoV-2 infection N=2,000
  - Infants not born in the context of maternal SARS-CoV-2 infection N=500
  - NO TIER 3

- **Tier 3**
  - N=1,400
  - NO TIER 3

- **Additional cohorts**
  - PASC+ N=3,600
  - PASC- N=1,800
  - Uninfected N=600
  - NO TIER 3

- **Post-Vax MC**
  - MIS-C N=800
  - PVMC N=200

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Welcome to RECOVER Studies

Funded by the NIH, RECOVER is a research project that aims to learn about the long-term health effects of COVID, including what is sometimes called Long COVID. We need adults and kids who have and have not had COVID to join RECOVER and help us find answers to Long COVID.

Together, we can make progress towards recovery.

Find a RECOVER study site and join today

There are more than 80 sites in over 30 states, with more sites opening up all the time.

How to use this map

You can join any study site.
1. Select a study site that is enrolling the study group you want to join
2. Enter a zip code
3. Click "Find study site"
4. Click the "Ask to join" button to contact a study site
Challenges

• Dynamic nature of pandemic
• Hurdles in enrollment
• Need for urgency
• Breadth and depth of protocol questionnaires and testing; frequency of multiple symptoms
• Wide heterogeneity of symptoms and clinical course within and across age group → will need
  • Adequate breadth and depth in clinical trial portfolio
  • Additional ancillary studies and assays to diagnose and monitor
RECOVER Electronic Health Record Studies: Addressing Key Public Health Questions at National Scale

• NC3 and PCORnet- major electronic health record systems encompassing 60 million+ adult and pediatric patient records

• Addressed key issues such as:
  • PASC and PASC sub-phenotypes
  • PASC Cardiac complications
  • Development of new onset diabetes as part of PASC
  • Syndromic, systemic, and medication features of PASC
  • Impact of COVID-19 Vaccination and Viral Variants on PASC
  • PASC in children and adolescents
  • Racial, ethnic, and socioeconomic disparities in PASC

• Advanced and accelerated public health research by developing for broad use:
  • Validated machine learning methods and usage of ICD-10 codes for identifying PASC
  • Post-acute SARS-CoV-2 computable phenotype definitions
  • Best practices in use of AI, ML, NLP in analysis of COVID EHR and RWD

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PCORnet & RECOVER (n=41) Sites
Funded by PCORI in 2014

- 15B+ rows of data
  - Electronic health records
  - >10m patients
  - structured
  - unstructured (Q3)
- Public payor data
- Exposome data
  - race/ethnicity
  - socio-economic
  - environmental
- Vaccine data
RECOVER Clinical Pathobiology ROA

Overview

ROA released to Consortium Investigators on 12/7/2021
Focuses on examining the clinical pathobiology of PASC by leveraging the RECOVER cohort samples and data, limited to sites participating in the RECOVER PASC Consortium

Objectives:

1) To make rapid progress in understanding the clinical manifestations of PASC and the mechanisms leading to the various symptoms, dysfunction of multiple organs and biologic systems, and phenotypes seen in PASC patients

2) To inform the diagnosis, prevention, mitigation, and/or treatment of PASC through elucidating the pathobiological mechanisms and pathways underpinning PASC, the molecular mediators of its protean symptomology, and possible multiple clinical clusters/sub-phenotypes

Application deadline was 1/31/2022

Requirements

- Be part of a RECOVER Cohort Site with a fully executed contract with the NYU CSC OR RECOVER Enrolling Sites operating under a RECOVER hub

- Have the potential to lead to rapid delineation of the pathogenesis of PASC clinical symptomatology, multi-organ dysfunction, and patients’ sub-phenotypes to foster progress in diagnostic, therapeutic, and preventative avenues for PASC

- Rapidly share data and biospecimens with the NIH RECOVER data and biospecimen repositories and broader research community

- Pledge to rapidly submit results for publication

- Have a budget that does not exceed maximum direct cost of $500K per year and maximum total costs of $800K per year

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RECOVER Pathobiology NOSI

Overview

NOSI released to Consortium Investigators on 12/7/2021

Focuses on advancing understanding of the pathobiological underpinnings of PASC; limited to series of activity codes for parent award

Objectives:

1) To make rapid progress in understanding the biological mechanisms underlying the pathogenesis of PASC (including the viral-host interactions that result in PASC)

2) To inform the diagnosis, prevention, mitigation, and/or treatment of PASC through elucidating the pathogenesis of PASC and the identification of associated mechanistic pathways

Application deadline was 1/24/2022

Requirements

- Have an active NIH parent award
- Describe how the project will inform the diagnosis, prevention, mitigation, and/or treatment of PASC through elucidating the pathogenesis of PASC and identification of associated mechanistic pathways
- Provide rationale to justify the use and appropriateness of NHP or animal models (if utilizing)
- Describe plans to address relevant biological variables, such as sex
- Describe plan for rapidly sharing data and biospecimens with NIH RECOVER data and biospecimen repositories and broader research community
- Describe plan to rapidly submit results for publication
- Have a budget that does not exceed a maximum direct cost of $750K
RECOVER Clinical Trials for Identifying Treatment and Preventive Strategies for PASC: Key Features

- Informed by patient and practitioner views on symptoms/symptom clusters and meaningful outcomes.
- Interventions addressing symptoms/symptom clusters and targeting specific disease/biologic pathways leading to PASC.
Preparing for PASC Clinical Trials: Prioritization PASC Interventions

Landscape Analysis
Patient and Practitioner Perspectives on Health Impact of Symptoms/Symptom Clusters
Intervention & Outcomes Inventory Across RECOVER clinicians
EHR Analysis of Interventions in Use

Set of candidate interventions evaluated according to evidence of safety, efficacy for PASC-relevant sx, MOA, availability, feasibility

- Pharmacological Drugs
- Pharmacological Biologic
- PASC Interventions
- Cognitive Behavioral
- Complementary and Integrative Medicine
- Device
RECOVER Clinical Trials Research
Opportunity Announcement – clinical trials in those over 18 years old in the prevention and/or treatment of Post-Acute Sequelae of SARS-CoV-2 infection (PASC)
Opportunity

Critical, time sensitive, and unique opportunity to:

• Fully characterize clinical course, phenotypes, and underlying pathobiology across all populations and age groups
  ➢ Enabling treatment of symptoms and modifying the course of PASC to cure or prevent it