

Summary of COVID-19 Long-term Health Effects: Emerging Evidence and Ongoing Investigation

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COVID-19 Literature Report Team:

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Understanding the course of patients' recovery from COVID-19 is critical for health system planning and for guiding public health prevention efforts. At less than one year into the COVID-19 pandemic, many long-term effects of SARS-CoV-2 infection remain unknown. However, new evidence is emerging rapidly about symptom profiles and rehabilitation needs of COVID-19 survivors in the initial months of their recovery. **This document is a brief summary of published evidence about the sequelae of COVID-19 and ongoing studies of its long-term health effects. Included are manuscripts published in peer-reviewed journals or on pre-print servers through August 31, 2020.** References summarized in this report were drawn from the COVID-19 Literature Report (Lit Rep) team database. **References that appeared in the daily Lit Rep are marked with an asterisk***, and the summary is shown in the annotated bibliography below. This list was cross-referenced with the Infectious Disease Society of America COVID-19 Expanded Reference Center, a search of Clinicaltrials.gov for observational studies on COVID-19, and supplemented with studies mentioned in media articles.¹ We encourage readers to consult these sites and the daily Lit Rep for evidence that emerges following the date of this report.

Executive Summary of COVID-19 Long-term effects

- **Emerging evidence indicates that a majority of people who require hospitalization for COVID-19 experience sequelae such as fatigue and shortness of breath in the months following their hospital discharge.**
- **Evidence on the long-term sequelae of COVID-19 among non-hospitalized but symptomatic individuals remains limited. Short-term follow-up indicates that recovery to usual state of health may be faster for this group than among their hospitalized counterparts.**
- **Many epidemiologic studies are ongoing to systematically investigate the long-term effects of COVID-19.**

Emerging evidence of COVID-19 Sequelae

The majority of studies that have reported on sequelae of COVID-19 included participants whose COVID-19 illness was severe enough to require hospitalization. There is limited evidence of sequelae in asymptomatic persons, or those with mild illness. The sections below highlight studies of cardiopulmonary function, mental health and neurologic symptoms, and general functional status of COVID-19 survivors who required hospitalization, and evidence to-date of sequelae in persons who did not require hospitalization.

Post-hospitalization cardiopulmonary function

An early report on COVID-19 sequelae by Wang et al. found that among patients (n=131) who had been admitted to a COVID-19 designated hospital in Wuhan, China, in February, 2020, most had experienced

resolution of their COVID-19 symptoms by 28 days following hospital discharge, with only 18/131 (14%) reporting any ongoing COVID-19 symptoms, most commonly cough (10%).²

In contrast, subsequent cohort studies from Italy, France, the UK, and the US of patients surveyed 1-4 months following hospital discharge found that the majority of participants reported persistent symptoms consistent with COVID-19, with further detail below.^{3-7*}

- Among hospitalized adults (n=143) with COVID-19 in Italy who were assessed at a mean of 60 days following symptom onset, only 18/143 (12.6%) were free of symptoms. The most commonly reported symptoms were fatigue (53%), shortness of breath (43%), joint pain (27%) and chest pain (22%).³
- At a median of 110 days following the date of hospitalization for COVID-19 for patients hospitalized in France (n=120), the most common symptoms were fatigue (55%) and shortness of breath (42%).^{4*}
- Among adults surveyed (n=100) at a mean of 48 days (range 29-71) following discharge from a university hospital in the UK, the most commonly reported symptoms were fatigue and breathlessness, with 72% of post-ICU patients and 60% of non-ICU patients reporting fatigue, and 66% of post-ICU patients and 43% of non-ICU patients reporting new breathlessness.^{5*}
- Adults with COVID-19 who had required a high level of oxygen support during their hospitalization (≥ 6 L/minute) in New York City (n=191) were surveyed 30-40 days after hospital discharge. They reported shortness of breath at more than twice their pre-COVID prevalence (31% affected pre-COVID-19 vs. 74% post-COVID-19). Additionally, 52/148 (35%) participants without pre-COVID supplemental oxygen requirements needed home oxygen after discharge from their COVID hospitalization, including 20 (13.5%) who still required supplemental oxygen at the time of the survey.⁶
- At eight to twelve weeks after admission, among discharged patients with COVID-19 in a UK study (n=110), most (74%) reported some persistent symptoms, with breathlessness (39%), fatigue (39%), and insomnia (24%) being the most common. Sixteen (59%) patients with mild COVID-19 reported ongoing symptoms, compared to 49 (75%) with moderate COVID-19 and 16 (89%) with severe COVID-19. Chest radiographs performed at follow-up were normal in the majority of patients (n=95, 86%).⁷

Post-hospitalization mental health challenges and neurological symptoms

COVID-19 survivors frequently have reported mental health challenges and persistent neurological symptoms following hospital discharge.

- Memory loss (34%), and concentration and sleep disorders (28% and 31%, respectively) followed fatigue and breathlessness as the most commonly reported symptoms among people in France surveyed at a median of 110 days following the date of hospitalization.^{4*}
- Forty-seven percent of post-ICU patients and 24% of non-ICU patients from a study in the UK (n=100) reported symptoms of post-traumatic stress disorder (PTSD) related to their COVID-19 illness at follow-up at a mean of 48 days following hospital discharge.^{5*}
- Among patients with COVID-19 (n=675) discharged from hospitals in Wuhan, China who were surveyed at a mean of 37 days after discharge, 70 (10%) patients reported symptoms of moderate to severe anxiety, with another 218 (32%) reporting mild anxiety symptoms. In the same study, 128 (19%) had symptoms of moderate to severe depression and 315 (48%) had mild depression. The researchers also found that more severe COVID-19 illness was associated with worse mental health outcomes after discharge, and that perceived discrimination by family or neighbors was a strong risk factor for PTSD, anxiety, and depression.⁸

Post-hospitalization functional status

- Among the participants in France who had been active workers prior to COVID-19 (n=56), 38/56 (68%) had returned to work at the time of a follow-up survey at a median of 110 days post-hospitalization.^{4*}
- Twenty-two of 32 (69%) post-ICU patients from a cohort in the UK reported new problems in mobility, self-care or usual activities.^{5*}
- More than half of participants who had required a high level of oxygen (≥ 6 L/minute) during their hospitalization in New York City received visiting nurse services after their hospitalization.⁶

Mild illness not requiring hospitalization

There are few studies to-date that report sequelae for people with COVID-19 who did not require hospitalization. The first two included here report symptoms at a short follow-up interval of one month or less. The final study reports a high proportion of abnormal cardiac findings among both hospitalized and non-hospitalized individuals.

- A study led by the CDC COVID-19 Response Team surveyed symptomatic adults who had a positive outpatient test for SARS-CoV-2 (n=274) at 14-21 days after their positive test and found that 35% of participants had not returned to their usual state of health. The proportion of participants still reporting symptoms at this short-term assessment by age group was 26% among participants aged 18-34 years, 32% among those aged 35-49 years, and 47% among participants at least 50 years old.^{9*}
- Non-hospitalized participants with confirmed COVID-19 (n=273) reported that their most common symptoms at 30 days following diagnosis were cough (7%), loss of smell or taste (5%), body aches (5%), nasal congestion (5%), shortness of breath with exertion (5%), and joint pain (5%). Initial severity of symptoms was a significant predictor of symptom duration, but age and comorbidities were not.¹⁰
- A highly-cited study performed cardiac MRI on adults who had recovered from COVID-19 (n=100), the majority of whom had recovered at home (n=67) versus requiring hospitalization (n=33) at a median of 71 days (IQR 64-92) following symptom onset. They found that patients recently recovered from COVID-19 had lower measures of cardiac function than a comparison group of individuals without COVID-19. Seventy-eight patients (78%) had abnormal cardiac imaging findings and 60 (60%) had evidence of ongoing myocardial inflammation. These outcomes were independent of preexisting conditions, severity and overall course of the acute illness, and time from the original diagnosis. Additionally, 36% of participants reported ongoing shortness of breath and general exhaustion at the time of the follow-up assessment. A correction to this manuscript followed publication, but the primary findings were unchanged.^{11,12*}

A promising study using an app-based, big data approach is The COVID Symptom Study, which currently reports more than 4 million participants across many countries and stated a goal to report on the long-term sequelae of COVID-19.¹³

Community advocacy regarding long-term effects of COVID-19

COVID-19 survivors experiencing long-term symptoms have organized membership groups – often through social media – for support, education, and advocacy. Some have become a venue for research into COVID-19 sequelae.

Some of the more than 90,000 members of the group Survivor Corps who identified as “Long Haulers” due to long-term symptoms of COVID-19 participated in a social media survey about COVID-19 symptoms developed by researchers at the Indiana University School of Medicine. The most commonly reported symptoms among the survey participants (n=1,567) were fatigue (100%), muscle or body aches (67%), shortness of breath (65%), inability to exercise or be active (58%), and headache (58%).¹⁴

Additionally, members of the LongCOVIDsos campaign organized by COVID-19 survivors in the UK spoke with WHO Director General Dr. Tedros Adhanom Ghebreyesus and featured in his remarks on August 21, 2020.

Although we have learned so much about this disease, we only have less than 8 months of experience to draw on. We still know relatively little about the long-term effects. My message to these patients was: we hear you loud and clear, and we are committed to working with countries to ensure you receive the services you need, and to advancing research to serve you better.¹⁵

Ongoing Studies of COVID-19 Clinical Outcomes and Sequelae

The Infectious Disease Society of America maintains a table of open COVID-19 registries that includes 40 entries at the time of this report. Some registries focus on specific populations including:

- Children
- People living with HIV
- People who have received transplanted organs
- Pregnant women

There are many ongoing epidemiological studies investigating sequelae of COVID-19 catalogued at clinicaltrials.gov or in the World Health Organization International Clinical Trials Registry Platform. A selection of the COVID-19 epidemiological studies from these sites or reported on other media sites are listed in the table below.

Table: Epidemiological studies of the sequelae of COVID-19 that are currently in enrolling or reporting phases

Study Name	Population	Exposures	Outcomes	Enrollment Goal	Duration	Institutions	Link
USA Pediatric COVID-19 Registry	Children (< 21 years)	Laboratory-confirmed COVID-19	Severity of illness, hospitalization, death	Open	unknown	Multi-site children's hospitals in US	https://www.pedscovid19registry.com/
Long-term Impact of Infection with Novel Coronavirus	Adults	Laboratory-confirmed COVID-19	Clinical outcomes, including development of medical conditions, measures of immune activation and inflammation, changes in immunologic function, and variability in host responses.	800	unknown	UCSF	ClinicalTrials.gov Identifier: NCT04362150
A longitudinal Study of COVID-19 Sequelae and Immunity	Adults	Documented COVID-19 infection	Medical sequelae, persistent symptoms, risk factors for sequelae, antibody and cell-mediated immune response to SARS-CoV-2 over time, incidence of re-infection, incidence of clinically silent infection, mental health status	900	unknown	NIH	ClinicalTrials.gov Identifier: NCT04411147
Longitudinal COVID-19 Cohort Study	Hospitalized patients with acute respiratory failure	Hospitalized patients with acute respiratory failure (new oxygen requirement) due to COVID-19	Exercise capacity (six-minute walk distance, four-meter timed walk), anxiety, depression, health status, mental and cognitive functioning, health care utilization, death, pulmonary function, immune and inflammation responses	225	12 months	Johns Hopkins University	ClinicalTrials.gov Identifier: NCT04393155
Long Term Outcomes of Patients with COVID-19	Patients hospitalized in ICU	COVID-19+ ICU patients and COVID-19-comparison group	Quality of life, cognitive function, physical ability, psychological sequelae	500	unknown	University of Chicago	ClinicalTrials.gov Identifier: NCT04360538
Epidemiology, Immunology, and Clinical Characteristics of COVID-19 (EPIC ³)	Inpatients and outpatients cared for at Veteran Health	COVID-19+ and COVID-19-negative comparison group	Clinical course and outcomes, duration of viral shedding, development of immune markers, and re-infection	3000	24 months	Veterans Affairs Cooperative Studies Program	https://www.seattle.eric.research.va.gov/research/CS P-2028-EPIC3/home.asp

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Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EpiCC-EID)	Inpatients and outpatients cared for at military treatment facilities	COVID-19+ and COVID-19-negative comparison group	Clinical course and outcomes, duration of viral shedding, development of immune markers	unknown	unknown	Uniformed Services University, Department of Defense	
COVID-19 Brain Study	Adults, outpatients	Confirmed COVID-19	Cognitive function	50,000	unknown	Western University, University of Toronto, Sunnybrook Health Sciences	https://www.cambridgebrainsciences.com/studies/covid-brain-study
Post-Hospitalisation COVID-19 Study	Adults hospitalized in the UK	Patients hospitalized with COVID-19	Long term effects	10,000	12 months	NIHR Leicester Biomedical Research Centre	https://www.phosp.org/
RED CORAL: PETAL Repository of Electronic Data COVID-19 Observational Study	Acute and critically-ill adults with COVID-19	Confirmed COVID-19 patients at participating sites between March 1 and April 1, 2020	Data from hospitalization	unknown	unknown		https://petalnet.org/studies/public/redcoral
The Severe Acute Respiratory and emerging Infection Consortium (ISARIC) COVID-19 follow up study	Hospitalized patients over 16 at global sites, discharged at least 28 days	Lab-confirmed COVID-19	All-cause and cause specific mortality, specific consequences including: deep vein thrombosis, pulmonary embolism, recent febrile illness, new and persistent symptoms, quality of life, dyspnea, difficulties in functioning (UN/Washington disability score), lifestyle and socioeconomic data	unknown	unknown	Universities in Europe, Africa, Asia, and North America	https://media.tghn.org/media-library/2020/08/ISARIC_Global_Covid-19_Follow_Up_Protocol_FINAL_3_Aug2020.pdf
The COVID-19 Symptom Study ¹³	Adults globally (app-based recruitment)	Not specified	COVID-19 associated symptoms by geographic area	Open, >4 million participants	unknown	ZOE, King's College London, Massachusetts General Hospital	https://covid.joinzoe.com/us-2

Recommended Resources

Infectious Disease Society of America COVID-19 Expanded Resource Center

See section on “Post-Acute Care and Issues”

See section on “Clinical Trials”

<https://www.idsociety.org/public-health/COVID-19-Resource-Center/covid19-expanded-resource-center/>

Annotated Bibliography

1. COVID-19 Expanded Resource Center. <https://www.idsociety.org/public-health/COVID-19-Resource-Center/covid19-expanded-resource-center/>.
2. Wang, X. *et al.* The Clinical Features and Outcomes of Discharged Coronavirus Disease 2019 Patients: A Prospective Cohort Study. *QJM* (2020) doi:10.1093/qjmed/hcaa178.
3. Carfi, A., Bernabei, R., Landi, F. & Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. *JAMA* (2020) doi:10.1001/jama.2020.12603.
4. Garrigues, E. *et al.* Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J. Infect.* (2020) doi:10.1016/j.jinf.2020.08.029.
 - In a single-center study assessing post-discharge persistent symptoms and health-related quality of life of COVID-19 patients (n=279), most patients still had persistent symptoms 110 days after being discharged, especially fatigue (55%) and shortness of breath (42%). Twenty percent of patients, primarily women, reported significant hair loss. Among the participants who were actively working prior to infection (n=56), 69% had gone back to work. Among the patients who engaged in regular sports activities prior to hospitalization (n=39), 72% were able to resume physical activity, but at a lower level for 46% of them.
5. Halpin, S. J. *et al.* Post-discharge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J. Med. Virol.* jmv.26368 (2020) doi:10.1002/jmv.26368.
 - Halpin et al. evaluated 100 COVID-19 survivors between 29 and 71 days after hospital discharge, including 32 people who had required ICU admission. Commonly reported symptoms among recovered patients included new illness-related fatigue (72% of the ICU group and 60% of the general admission group), breathlessness (66% of ICU group, 43% of general admission), and psychological distress (47% of ICU group, 24% of general admission).
 - Survivors were also assessed using the EQ-5D-5L scale, which measures mobility, self-care, usual activities, pain/discomfort, and anxiety/depression in patients. A clinically significant decline in scale scores was reported in 69% of ICU patients and 46% of general admissions.
6. Weerahandi, H. *et al.* Post-discharge health status and symptoms in patients with severe COVID-19. *medRxiv* (2020) doi:10.1101/2020.08.11.20172742.
7. Arnold, D. T. *et al.* Patient outcomes after hospitalisation with COVID-19 and implications for follow-up; results from a prospective UK cohort. *medRxiv* 2020.08.12.20173526 (2020)

doi:10.1101/2020.08.12.20173526.

8. Liu, D. *et al.* Risk factors associated with mental illness in hospital discharged patients infected with COVID-19 in Wuhan, China. *Psychiatry Res.* **292**, 113297 (2020).
10.1016/j.psychres.2020.113297
9. Tenforde, M. W. *et al.* Characteristics of Adult Outpatients and Inpatients with COVID-19 — 11 Academic Medical Centers, United States, March–May 2020. *MMWR. Morb. Mortal. Wkly. Rep.* **69**, (2020). <https://doi.org/10.15585/mmwr.mm6930e1>
 - A telephone survey of non-hospitalized symptomatic COVID-19 patients found that illness can be prolonged, even among young adults without underlying chronic medical conditions. Among 274 symptomatic COVID-19 patients interviewed 14-21 days after diagnosis, 65% percent had returned to their usual state of health a median of 7 days (IQR 5-12 days) after testing, while the 35% had not yet returned to their usual state of health. Older age and presence of chronic medical conditions were associated with a higher risk of not having returned to normal health. Among those with no chronic medical conditions and in the youngest age group (18-34 years), 19% had not returned to normal health by 14-21 days after diagnosis.
10. Keefe, J. B., Tong, E. J., Datto O;Keefe, G. A. & Tong, D. C. Predictors of disease duration and symptom course of outpatients with acute covid-19: a retrospective cohort study. *medRxiv* 2020.06.05.20123471 (2020) doi:10.1101/2020.06.05.20123471.
11. Puntmann, V. O. *et al.* Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* (2020) doi:10.1001/jamacardio.2020.3557. (Correction below)
 - In a cohort study of German patients recently recovered from COVID-19 infection (n=100), cardiovascular magnetic resonance (CMR) imaging revealed cardiac involvement in 78 patients and ongoing myocardial inflammation in 60 patients, independent of preexisting conditions, severity and overall course of the acute illness, and time from the original diagnosis. Compared with healthy controls and risk factor-matched controls, patients recently recovered from COVID-19 had lower left ventricular ejection fraction, higher left ventricle volumes, higher left ventricle mass, and raised native T1 and T2 signals.
12. Nagel, E. & Puntmann, V. O. Errors in Statistical Numbers and Data in Study of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From COVID-19. *JAMA Cardiol.* (2020) doi:10.1001/jamacardio.2020.4661.
 - Correction to: “Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19),” published in *JAMA Cardiology* on July 27, 2020 and summarized in the Lit Rep on July 30, 2020. The authors provided missing data from the original cardiovascular magnetic resonance images and corrected data entry errors, resulting in minor changes in the area under the receiver operating characteristic curve values in Table 2 and a change in the comparison of left ventricular mass index between participants with COVID-19 and healthy controls from a significant to non-significant association. In addition, the authors clarified in the Methods section that the cutoff values for abnormal native T1 and T2 values were based on

previously derived sequence-specific standard deviations above the respective means in a healthy population and not based on the current healthy control group.

13. Drew, D. A. *et al.* Rapid implementation of mobile technology for real-time epidemiology of COVID-19. *Science* eabc0473 (2020) doi:10.1126/science.abc0473.
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