HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2024 August 29.

Published in final edited form as:

Clin Infect Dis. 2023 May 03; 76(9): 1559–1566. doi:10.1093/cid/ciac966.

Three-month symptom profiles among symptomatic adults with positive and negative SARS-CoV-2 tests: a prospective cohort study from the INSPIRE group

Erica S. Spatz, MD, MHS[*],
Section of Cardiovascular Medicine, Department of Medicine, Yale School of Medicine; Department of Epidemiology, Yale School of Public Health, New Haven, CT, USA

Michael Gottlieb, MD[*],
Department of Emergency Medicine, Rush University Medical Center, Chicago, IL, USA

Lauren E. Wisk, PhD,
Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine at the University of California, Los Angeles (UCLA), Los Angeles, CA; Department of Health Policy and Management, Fielding School of Public Health at UCLA, Los Angeles, CA, USA

Jill Anderson, BSN, RN,
Harborview Center for Prehospital Emergency Care, University of Washington, Seattle, WA, USA

Anna Marie Chang, MD MSCE,
Department of Emergency Medicine, Thomas Jefferson University, Philadelphia, PA, USA

Nicole L. Gentile, MD, PhD,
Departments of Family Medicine and Laboratory Medicine and Pathology, University of Washington, Seattle, WA, USA

Mandy J. Hill, DrPH, MPH,
Department of Emergency Medicine, UTHealth Houston, McGovern Medical School, Houston, TX, USA

Ryan M. Huebinger, MD,
Department of Emergency Medicine, UTHealth Houston, McGovern Medical School, Houston, TX, USA

Corresponding Author: Erica S. Spatz, MD, MHS; Section of Cardiovascular Medicine, Yale School of Medicine. 789 Howard Avenue, Dana 3 Building, New Haven, CT 06519, USA. erica.spatz@yale.edu. **Alternate Corresponding Author:** Arjun Venkatesh, MD, MBA, MHS; Department of Emergency Medicine, Yale School of Medicine, 464 Congress Avenue, New Haven, CT 06519, USA. arjun.venkatesh@yale.edu.

[*]Drs Spatz and Gottlieb contributed equally

[**]Drs Weinstein and Venkatesh contributed equally

TRIALS REGISTRATION: NCT04610515

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Disclosures:

Dr Nichol reports the following: Vapotherm Inc, Exeter, NH- Research funding; ZOLL Medical, Chelmsford, MA- Research funding; Abiomed Inc., Danvers, MA- Consultant; CellPhire Inc., Rockville, MD- Consultant; CPR Therapeutics, Putney, VT- Consultant; ZOLL Circulation, San Jose, CA- Consultant; Patent- Method for non-imaging ultrasound to measure blood flow during CPR; Non-provisional patent- Method for modifying cell injury associated with reduced blood flow; Dr Elmore reports serving as Editor in Chief of Adult Primary Care topics for UpToDate.

Ahamed H. Idris, MD,
Dept. of Emergency Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

Jeremiah Kinsman, MPH,
Department of Emergency Medicine, Yale University School of Medicine, New Haven, CT, USA

Katherine Koo, MS-HSM,
Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA

Shu-Xia Li, PhD,
Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, CT; Center for Outcomes Research and Evaluation, Yale New Haven Hospital, New Haven, CT, USA

Samuel McDonald, MD, MS,
Department of Emergency Medicine, University of Texas Southwestern, Dallas, TX, USA

Ian D. Plumb, MBBS, MSc,
National Center for Immunizations and Respiratory Diseases, Centers for Disease Control & Prevention, Atlanta, GA, USA

Robert Rodriguez, MD,
Department of Emergency Medicine, University of California, San Francisco, CA, USA

Sharon Saydah, PhD MHS,
National Center for Immunizations and Respiratory Diseases, Centers for Disease Control & Prevention, Atlanta, GA, USA

Benjamin Slovis, MD,
Department of Emergency Medicine, Thomas Jefferson University, Philadelphia, PA, USA

Kari A Stephens, PhD,
Departments of Family Medicine, Harborview Center for Prehospital Emergency Care, University of Washington, Seattle, WA, USA

Elizabeth R. Unger, MD PhD,
National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control & Prevention, Atlanta, GA, USA

Ralph C. Wang, MD, MAS,
Department of Emergency Medicine, University of California, San Francisco, CA, USA

Huihui Yu, PhD,
Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, CT; Center for Outcomes Research and Evaluation, Yale New Haven Hospital, New Haven, CT, USA

Bala Hota, MD, MPH, SVP,
Chief Informatics Officer, Tendo Systems, Inc., San Francisco, CA, USA

Joann G. Elmore, MD, MPH,

Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine at the University of California, Los Angeles (UCLA), Los Angeles, CA; Department of Health Policy and Management, Fielding School of Public Health at UCLA, Los Angeles, CA, USA

Robert A. Weinstein, MD[**],
Division of Infectious Diseases, Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA

Arjun Venkatesh, MD, MBA, MHS[**]
Department of Emergency Medicine, Yale School of Medicine, New Haven, CT, Center for Outcomes Research and Evaluation, Yale New Haven Hospital, New Haven, CT, USA

Abstract

BACKGROUND: Long-term symptoms following SARS-CoV-2 infection are a major concern, yet their prevalence is poorly understood.

METHODS: We conducted a prospective cohort study comparing adults with SARS-CoV-2 infection (COVID+) with adults who tested negative (COVID−), enrolled within 28 days of an FDA-approved SARS-CoV2 test result for active symptoms. Sociodemographic characteristics, symptoms of SARS-CoV-2 infection (assessed with the CDC Person Under Investigation Symptom List), and symptoms of post-infectious syndromes (i.e., fatigue, sleep quality, muscle/joint pains, unrefreshing sleep, and dizziness/fainting, assessed with CDC Short Symptom Screener for myalgic encephalomyelitis/chronic fatigue syndrome) were assessed at baseline and 3 months via electronic surveys sent via text or email.

RESULTS: Among the first 1,000 participants, 722 were COVID+ and 278 were COVID−. Mean age was 41.5 (SD 15.2); 66.3% were female, 13.4% were Black, and 15.3% were Hispanic. At baseline, SARS-CoV-2 symptoms were more common in the COVID+ group than the COVID− group. At 3-months, SARS-CoV-2 symptoms declined in both groups although were more prevalent in the COVID+ group: upper respiratory symptoms/head/eyes/ears/nose/throat (HEENT; 37.3% vs 20.9%), constitutional (28.8% vs 19.4%), musculoskeletal (19.5% vs 14.7%), pulmonary (17.6% vs 12.2%), cardiovascular (10.0% vs 7.2%), and gastrointestinal (8.7% vs 8.3%); only 50.2% and 73.3% reported no symptoms at all. Symptoms of post-infectious syndromes were similarly prevalent among the COVID+ and COVID− groups at 3 months.

CONCLUSIONS: Approximately half of COVID+ participants, as compared with one-quarter of COVID− participants, had at least one SARS-CoV-2 symptom at 3 months, highlighting the need for future work to distinguish Long COVID.

Keywords

COVID-19; Long COVID; SARS-CoV-2; coronavirus; registry; outcomes

INTRODUCTION

Infection with SARS-CoV-2 can lead to prolonged or new symptoms or conditions, often referred to as ‘Long COVID.’ Although definitions vary, the Centers for Disease Control and Prevention (CDC) refers to Long COVID as post-COVID conditions that emerge, recur,

or persist beyond 4 weeks following the acute infection.[1] Long COVID encompasses a multitude of symptoms affecting individual's neurocognitive, cardiovascular, pulmonary, musculoskeletal, and psychological health, and impacting people's ability to work and function in their daily lives.

To date, several prior studies estimate the incidence of Long COVID following an acute COVID infection to be 10–30%;[2–8] however, characterization of the epidemiology of Long COVID has been challenging to study given the range of presentations of Long COVID, different sampling and follow-up methods, and the lack of a comparison group.[9] Most prior studies did not systematically and prospectively evaluate participants from the time of SARS-CoV-2 infection through the post-acute period, which may reveal heterogeneity in symptom trajectory and severity. Furthermore, many of these studies were retrospective and relied on convenience sampling at the time of enrollment, thereby introducing risk of selection bias, recall bias, and confounding. Consequently, there is a need to better understand the post-COVID period by systematically investigating the persistence, resolution, and even emergence of new symptoms beyond the acute infectious period in a prospective manner. Moreover, there is a need to systematically evaluate long-term symptoms that may arise from SARS-CoV-2 infection and which may overlap with symptoms that are common among other post-infectious syndromes or medical conditions,[10] or potentially even as a result of the physical and mental toll of a pandemic.

Accordingly, the Innovative Support for Patients with SARS-CoV-2 Infections Registry (INSPIRE) was designed to prospectively assess the longitudinal symptoms and outcomes of adults who test positive for SARS-CoV-2 compared with symptomatic adults who test negative by following them from time of testing for up to 18 months, and to determine whether symptoms and recovery differed by age and care setting when enrolled in the study. This initial interim analysis focuses on the early trajectories of participants at 3-month follow-up with the purpose of describing the prevalence and types of symptoms among persons who had acute SARS-CoV-2 infection compared to a group of persons with COVID-like symptoms who were SARS-CoV-2 negative.

METHODS

Study Design

The INSPIRE study is a multisite study across eight healthcare systems funded by the CDC. The study details were previously published,[11] and a list of study sites is included in the eFigure 1 in the Supplement. In brief, the study aims to enroll 6,000 participants who underwent testing for SARS-CoV-2 infection to diagnose acute symptoms (i.e., not for screening, exposure, or pre-procedural reasons). Participants are recruited through advertisements at testing sites, outreach through the electronic health record, and coordination with testing sites and Departments of Health to identify people who test positive for SARS-CoV-2 infection. We focused on people with symptoms suggestive of SARS-CoV-2 to distinguish them from asymptomatic people being tested for exposure, surveillance, and preprocedural protocols, to enroll a similar baseline population of SARS-CoV-2-positive (COVID+) and SARS-CoV-2-negative (COVID−) persons who may go on to develop long-term symptoms following acute illness.[12]

Participants were enrolled if they met the following eligibility criteria: age ≥ 18 years, English or Spanish fluency, self-reported symptoms suggestive of acute SARS-CoV-2 infection at the time of testing (e.g., fever, cough, shortness of breath; see eFigure 2 in the Supplement for pre-qualification screener) and were tested with an FDA approved or authorized molecular or antigen-based assay within the last 42 days (regardless of test result). Participants needed to provide proof of testing result for inclusion. Participants who previously had SARS-CoV-2 infection more than 42 days before the date of enrollment and those who did not have access to an internet-connected device (e.g., smartphone, tablet, computer) for survey completion were excluded. Participants signed an electronic informed consent and were expected to complete a baseline survey followed by serial surveys every three months for a total of up to 18 months. The study uses a cloud-based platform, Hugo Health (Hugo Health LLC, Guilford, CT) that engages patients as data partners and automates a process that enables them to easily and securely collect and share health information – including surveys, medical records, and pharmacy data. This study was reviewed and approved by the Institutional Review Boards of all eight sites.

Survey invitations were sent via text or email (according to the preference of the participant). If a person's test positivity changed during the duration of the study, we retained them in their initial group for this analysis (2 participants converted to positive during follow-up). Participants received monetary reimbursement for each survey completion. Reminder emails, calls, and texts were sent to encourage participants to complete all surveys. The baseline and 3-month follow-up surveys include questions on sociodemographic characteristics, social determinants of health, baseline health status, testing site, symptoms common for SARS-CoV-2 infection, symptoms of post-infectious syndromes, reinfection or new infection with SARS-CoV-2, patient-reported outcomes on physical, mental, and social well-being, cognitive status, and return to work and daily activities.

COVID Symptom Assessment

The CDC Person Under Investigation symptom list was used to assess symptoms commonly reported with acute SARS-CoV-2 infection. Specifically, we asked participants to identify the presence of each symptom at baseline and again at three months.

Symptoms of post-infectious syndromes

Given the predominance of systemic symptoms such as fatigue, sleep disturbances, cognitive impairment, and muscle and joint pains - symptoms observed in other post-infectious syndromes (e.g., Epstein Barr Virus)[13] - we conducted a detailed assessment of these symptoms using a short symptom screener (eFigure 3 in Supplement). This focused screener, shortened to reduce participant burden, was taken from the CDC Symptom Inventory that was validated for studies of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[14]

Consistent with prior work,[15,16] we calculated a summary score of the 8 symptoms of post-infectious syndromes by multiplying the frequency and severity and then summing across symptoms to understand the potential impact of these symptoms in a person's life. A

symptom score was produced by standardizing the response choices using the scoring tool guidelines; the score ranged from 0 (no symptoms) to 128 (maximum symptoms).[17,18]

Analytic Approach

We restricted this analysis to the first 1,000 participants enrolled in INSPIRE between December 7, 2020 and September 9, 2021 who completed both a baseline and 3-month survey. We compared sociodemographic and clinical characteristics between COVID+ with COVID− individuals included in the study, and with non-responders to the 3-month survey who were excluded from the study. We report the frequency of each SARS-CoV-2 symptom type and each organ system (constitutional, upper respiratory symptoms/head/eyes/ears/nose/throat (HEENT), pulmonary, cardiovascular, gastrointestinal, musculoskeletal, and other) at baseline and at 3 months, and the proportion of these symptoms that were never present, resolved, emerged, and persisted. We assessed for the presence of the 8 symptoms of post-infections syndromes, having ≥ 3 symptoms, symptom severity quartiles, and the proportion of scores ≥ 25, since this represents a previously established threshold for considering ME/CFS.[19] Additionally, we evaluated characteristics of these symptoms, including whether rest improved the symptom and whether the symptom worsened for at least 24 hours after engaging in physical or mental activities that were previously non-taxing. Participants were also asked whether the symptom was present before the acute illness for which they were tested for SARS-CoV-2. Data analyses were conducted using SAS version 9.4. Sociodemographic and clinical characteristics of the COVID+ and COVID− groups were compared using chi-squared and t-tests for categorical and continuous variables, respectively. P values <0.05 were considered significant. We performed stratified analyses by age groups (18 to 34, 35 to 49, and ≥ 50 years) and by care setting at the time of enrollment (outpatient versus acute care setting [either the emergency department or hospital]).

RESULTS

Study Enrollment

At the time of this interim analysis, 4,256 individuals were screened for participation, among whom 1,743 were excluded either due to incomplete enrollment, ineligibility, or withdrawal from the study. In total, 2,513 individuals enrolled in the study and the first 1,000 with complete baseline and 3-month data were selected for this interim analysis (eFigure 4 in the Supplement).

Participant Characteristics

Among the first 1,000 participants, 722 tested positive for SARS-CoV-2 and 278 tested negative for SARS-CoV-2. Baseline sociodemographic and clinical characteristics are presented in Table 1. The mean ages of participants in the COVID+ and COVID− groups were 41.1 and 42.6 years, respectively; 66.0% and 66.9% were female. Among the total cohort, 13.4% were Black and 15.3% were Hispanic. Pre-existing conditions were less common among the COVID+ group compared with the COVID− group, including asthma (12.8% and 19.3%), hypertension (16.4% and 22.3%), and diabetes (5.9% and 10.4%). The following conditions were similarly represented: overweight or obesity; emphysema;

heart conditions; smoking history; kidney disease; and liver disease. Non-responders to the 3-month survey (n=423; excluded from study) were more likely than responders to be older in age, Black race, not of Hispanic ethnicity, earn under $10,000 dollars per year in household income, have private insurance, and have been more likely to have tested at an ambulatory site as opposed to the emergency department or hospital (eTable 1 in Supplement).

COVID Symptoms

Baseline and 3-month symptom prevalence, comparing COVID+ with COVID− participants, is presented in Figures 1a and 1b. The most prevalent baseline symptoms among COVID+ and COVID− groups, respectively, in descending order were: upper respiratory symptoms/HEENT (91.0% and 62.2%), constitutional symptoms (86.7% and 55.4%), pulmonary symptoms (67.9% and 41.0%), musculoskeletal symptoms (64.5% and 38.1%), gastrointestinal symptoms (40.0% and 27.7%) and cardiovascular symptoms (31.0% and 17.6%). At 3-month follow-up, there was a substantial decline in symptoms across all organ systems with most participants in both groups having recovery of symptoms (Figure 2), although symptoms remained more prevalent in the COVID+ group. At 3-month follow-up, 50.2% and 73.3% of participants in the COVID+ and COVID− groups, respectively, did not report any symptoms. Differences by age group and testing site are presented in Table 2.

Symptoms of Post-Infectious Syndromes

Post-infectious symptoms were similar at baseline and 3 months between the COVID+ group and the COVID− group, with the exception that more COVID+ participants had difficulty thinking or concentrating at the time of acute illness, although there was no difference at 3 months (eTable 2 in Supplement, Figure 3). There were some differences by age group and site of enrollment (eTable 2 of the Supplement). The severity of symptoms and the characteristics of the symptoms (e.g., worse post physical or mental exhaustion) were similar between COVID+ and COVID− groups, (eTable 3 and eTable 4 in Supplement). However, in the COVID− group, all post-infectious symptoms were more commonly present before the acute illness than in the COVID+ group.

DISCUSSION

In this prospective cohort study comparing symptomatic adults who test positive for SARS-CoV-2 versus symptomatic adults who test negative, we found that participants in the COVID+ group had more symptoms at baseline as compared to the COVID− group. At 3-month follow-up, most symptoms resolved; however, persistent or emergent symptoms were more common in the COVID+ group with approximately 1-in-2 persons (as compared with 1-in-4 persons in the COVID− group) having at least one symptom. The five most common persistent or emergent symptoms at 3 months in the COVID+ group in descending frequency were: tiredness, loss of smell, muscle aches, loss of taste, and headache. The five most common persistent or emergent symptoms in the COVID− group at 3 months in descending frequency were: tiredness, muscle aches, headache, runny nose, and joint pains.

We also found that the symptoms of post-infectious syndromes, including fatigue/ tiredness/ exhaustion, muscle aches, joint pains, unrefreshing sleep, forgetfulness, difficulty thinking or concentrating, and dizziness or fainting were similarly common in both the COVID+ and COVID− participants at 3 months, with 1-in-6 individuals in both groups reporting severe post-infectious symptoms. The similarity of post-infectious symptoms in the COVID+ and COVID− groups support prior studies that these types of symptoms may follow a variety of viral and non-viral infectious insults.[10] However, it should also be noted that individuals in the COVID− group were more likely to report having these symptoms prior to their acute illness, suggesting that other chronic conditions may explain the high rate of symptoms in the COVID− group. The COVID− group was older and had more comorbidities underscoring the toll of recovery for younger, healthier people with COVID. Additionally, these symptoms may not be a pure response to infection or underlying medical conditions but reflect a general societal effect of the pandemic (with social isolation, disruption of daily lives, financial stress, and grief);[20–22] presumably, this could affect both cases and controls leading to overestimation of the effects of SARS-CoV-2 infection and other acute illnesses. Taken together, the recovery from COVID can be marked by significant fatigue, sleep disturbances, muscle aches, and cognitive impairment, which concerningly, is not unlike other non-COVID illnesses that develop in older, more co-morbid cohorts.

Several prior studies awakened the public and medical community to the prevalence of Long COVID, and there have been calls for a more structured research initiative to better understand the epidemiology, characterization, and treatment of this condition.[6, 7,8] However, some of these studies lacked an adequate control group and may have been subject to selection bias based on recruitment methods.[9] More recent data demonstrate a higher prevalence of Long COVID symptoms among COVID+ as compared with COVID− individuals, although no difference in biomarkers and basic cardiopulmonary testing.[23] The CDC reports that 1-in-5 survivors of COVID-19 between the ages of 18–64 years and 1-in-4 aged ≥65 years experienced at least one condition that may be attributable to SARS-CoV-2 infection.[24] Our data builds on this early and important work, demonstrating not only that COVID+ individuals continue to have a range of symptoms at 3 months, but that COVID− individuals who had symptoms at the time of testing but were negative for SARS-CoV-2 infection, also have a high burden of symptoms at 3 month follow-up. This study and that of Wisk et al (submitted as companion paper; reference to follow) evaluating well-being at 3 months both highlight the importance of discerning the long-term effects of SARS-CoV-2 illness from other viral illnesses and conditions, and in relation to the general effects of a pandemic as well as to individuals' underlying health status and social determinants of health. Future research could build upon this complex and intersecting framework.

LIMITATIONS

There are several important limitations to consider. First, testing is imperfect – with false positive and false negative results – which may have led to misclassification. We did not query participants about the test type at time of enrollment or check antibody status, limiting our capacity to determine test performance and rates of misclassification. Additionally, we cannot determine whether symptoms in the COVID+ group are necessarily because of SARS-CoV-2 infection or due to another virus or condition. Relatedly, a minority of

patients in the COVID− group had loss of taste and smell, which is common for COVID-19 illness; however, it can also be observed with other viral illnesses or may simply reflects the participant's reporting of rhinorrhea as opposed to clinically defined anosmia. Several steps were taken to mitigate misclassification. We restricted the study cohort to those with symptoms that are most specific to COVID, which improves COVID-19 diagnostic test performance (i.e., the sensitivity and specificity of the testing for SAR-CoV-2 is higher compared to if we included an asymptomatic group).[25] Additionally, to be enrolled in the study, participants needed to provide verification of the COVID test result. Third, at each survey timepoint we asked whether participants tested positive for COVID in the interim from the last survey. Therefore, we believe the rate of misclassification to be low. Finally, any misclassification would bias the results to the null. Second, we observed a discordance between the report of symptoms at screening to confirm study eligibility versus upon completion of the baseline survey, particularly among COVID− participants, likely attributable to allowance of up to 42 days for the initial survey completion. COVID− participants completed baseline surveys on average 9 days following enrollment in comparison to COVID+ participants who completed baseline surveys on average 3 days after enrollment, thereby exacerbating known challenges in self-reported symptom recall. Third, this report is limited to three-month outcomes and may not reflect the longer-term impact. Future work will assess symptoms beyond the three-month time period. Fourth, focusing on interim data of the first 1,000 participants enrolled between December 2020 and September 2021 precluded analysis by different SARS-CoV-2 variants. Fifth, stratified analyses by age group were limited by small sample size. For this reason, we lowered the age limit of the older group to 50 and above; future analyses will focus on the 65 and older age group. Sixth, recruitment was based out of eight academic medical centers, which might reduce generalizability. However, sites were intentionally selected for diversity of geography and populations and were not limited to enrolling individuals from their health system; rather, individuals were broadly recruited and represent over 20 different states. Seventh, as the study required participants to have access to an internet-capable device, this may have led to selection bias. The response rate at 3 months was 70.3% with differences in response rates by demographic characteristics.

CONCLUSION

Adults with acute symptoms suggestive of SARS CoV-2 infection, both those COVID+ and those COVID−, experience a range of symptoms, most of which resolve by 3 months. Still, one-in-two persons in the COVID+ group and one-in-four persons in the COVID− group had at least one post-acute symptom at three months with the most common symptoms being fatigue, headache, loss of taste and/or smell, joint pains, and muscle aches. Post-infectious symptoms such as fatigue, sleep disturbance, and cognitive impairments, generally considered a hallmark feature of post-COVID conditions, occurred at similar rates in the COVID+ and COVID− groups. These findings suggest that recovery from COVID is at least as severe as other post-infectious syndromes occurring in an older, more co-morbid COVID- group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Please see eFigure 5 in the Supplement

Funding:

The Innovative Support for Patients with SARS-COV-2 Infections Registry (INSPIRE) is funded by the Centers for Disease Control and Prevention (CDC, www.cdc.gov), National Center of Immunization and Respiratory Diseases (NCIRD) (contract number: 75D30120C08008; PI, Robert A. Weinstein, MD). Partners from the CDC (Ian D Plumb, MBBS, MSc, Sharon Saydah, PhD, MHS, Elizabeth R Unger, MD, PhD) assisted with study design and the preparation of this manuscript.

Abbreviations:

INSPIRE	Innovative Support for Patients with SARS-CoV-2 Infections Registry
CDC	Centers for Disease Control and Prevention

REFERENCE

1. Post-COVID Conditions. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html. Accessed February 23, 2022.
2. Arjun MC, Singh AK, Pal D, et al. Prevalence, characteristics, and predictors of Long COVID among diagnosed cases of COVID-19. medRxiv. 2022:2022.01.04.21268536. doi:10.1101/2022.01.04.21268536
3. Logue JK, Franko NM, McCulloch DJ, et al. Sequelae in Adults at 6 Months After COVID-19 Infection. JAMA Netw Open. Feb 1 2021;4(2):e210830. doi:10.1001/jamanetworkopen.2021.0830 [PubMed: 33606031]
4. Havervall S, Rosell A, Phillipson M, et al. Symptoms and Functional Impairment Assessed 8 Months After Mild COVID-19 Among Health Care Workers. JAMA. May 18 2021;325(19):2015–2016. doi:10.1001/jama.2021.5612 [PubMed: 33825846]
5. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med Apr 2021;27(4):601–615. doi:10.1038/s41591-021-01283-z [PubMed: 33753937]
6. Whitaker M, Elliott J, Chadeau-Hyam M, et al. Persistent symptoms following SARS-CoV-2 infection in a random community sample of 508,707 people. medRxiv. 2021:2021.06.28.21259452. doi:10.1101/2021.06.28.21259452
7. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. Aug 2021;38:101019. doi:10.1016/j.eclinm.2021.101019 [PubMed: 34308300]
8. Lambert N, Corps S, El-Azab S, et al. COVID-19 Survivors' Reports of the Timing, Duration, and Health Impacts of Post-Acute Sequelae of SARS-CoV-2 (PASC) Infection. 2021:
9. Wisk LE, Nichol G, Elmore JG. Toward Unbiased Evaluation of Postacute Sequelae of SARS-CoV-2 Infection: Challenges and Solutions for the Long Haul Ahead. Ann Intern Med Mar 8 2022;doi:10.7326/M21-4664
10. Choutka J, Jansari V, Hornig M, Iwasaki A. Unexplained post-acute infection syndromes. Nat Med May 2022;28(5):911–923. doi:10.1038/s41591-022-01810-6 [PubMed: 35585196]
11. O'Laughlin KN, Thompson M, Hota B, et al. Study protocol for the Innovative Support for Patients with SARS-COV-2 Infections Registry (INSPIRE): a longitudinal study of the medium and long-term sequelae of SARS-CoV-2 infection. medRxiv. 2022:2021.08.01.21261397. doi:10.1101/2021.08.01.21261397

12. OL'aughlin KN, Thompson M, Hota B, et al. Study protocol for the Innovative Support for Patients with SARS-COV-2 Infections Registry (INSPIRE): A longitudinal study of the medium and long-term sequelae of SARS-CoV-2 infection. PLoS One. 2022;17(3):e0264260. doi:10.1371/journal.pone.0264260 [PubMed: 35239680]

13. Sandler CX, Wyller VBB, Moss-Morris R, et al. Long COVID and Post-infective Fatigue Syndrome: A Review. Open Forum Infect Dis 2021;8(10):ofab440–ofab440. doi:10.1093/ofid/ofab440 [PubMed: 34631916]

14. Wagner D, Nisenbaum R, Heim C, Jones JF, Unger ER, Reeves WC. Psychometric properties of the CDC Symptom Inventory for assessment of Chronic Fatigue Syndrome. Population Health Metrics. 2005/07/22 2005;3(1):8. doi:10.1186/1478-7954-3-8 [PubMed: 16042777]

15. Ghali A, Lacout C, Ghali M, et al. Warning Signals of Post-Exertional Malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Retrospective Analysis of 197 Patients. J Clin Med 2021;10(11):2517. doi:10.3390/jcm10112517 [PubMed: 34200126]

16. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol Oct 1989;46(10):1121–3. doi:10.1001/archneur.1989.00520460115022 [PubMed: 2803071]

17. Wagner D, Nisenbaum R, Heim C, Jones JF, Unger ER, Reeves WC. Psychometric properties of the CDC Symptom Inventory for assessment of chronic fatigue syndrome. Popul Health Metr 2005;3:8–8. doi:10.1186/1478-7954-3-8 [PubMed: 16042777]

18. Scoring Algorithm of CDC Symptom Inventory. https://www.cdc.gov/me-cfs/pdfs/wichita-data-access/si-scoring-algorithm.pdf. Accessed February 18, 2022.

19. Reeves WC, Wagner D, Nisenbaum R, et al. Chronic fatigue syndrome--a clinically empirical approach to its definition and study. BMC Med Dec 15 2005;3:19. doi:10.1186/1741-7015-3-19 [PubMed: 16356178]

20. Ueda M, Nordström R, Matsubayashi T. Suicide and mental health during the COVID-19 pandemic in Japan. J Public Health (Oxf). 2021:fdab113. doi:10.1093/pubmed/fdab113

21. Kwong ASF, Pearson RM, Adams MJ, et al. Mental health before and during the COVID-19 pandemic in two longitudinal UK population cohorts. Br J Psychiatry. 2021;218(6):334–343. doi:10.1192/bjp.2020.242 [PubMed: 33228822]

22. Ping W, Zheng J, Niu X, et al. Evaluation of health-related quality of life using EQ-5D in China during the COVID-19 pandemic. PLoS One. 2020;15(6):e0234850. doi:10.1371/journal.pone.0234850 [PubMed: 32555642]

23. Sneller MC, Liang CJ, Marques AR, et al. A Longitudinal Study of COVID-19 Sequelae and Immunity: Baseline Findings. Ann Intern Med May 24 2022;doi:10.7326/M21-4905

24. Bull-Otterson L, Baca S, Saydah S, et al. Post–COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years — United States, March 2020–November 2021. MMWR Morb Mortal Wkly Rep ePub: 24 May 2022. DOI: 10.15585/mmwr.mm7121e1external icon.

25. Pray IW, Ford L, Cole D, et al. Performance of an Antigen-Based Test for Asymptomatic and Symptomatic SARS-CoV-2 Testing at Two University Campuses — Wisconsin, September–October 2020. MMWR Morb Mortal Wkly Rep 2021;69:1642–1647. DOI: 10.15585/mmwr.mm695152a3external. [PubMed: 33382679]

Key Points:

Among persons testing for acute viral symptoms suggestive of SARS-CoV2, emergent/persistent symptoms at 3 months were common, reported by approximately half of COVID+ participants and one-quarter of COVID- participants. Post-infectious syndromes were equally common in both groups at 3 months, highlighting the challenges in identifying symptoms specific for Long COVID and the importance of longitudinal studies including comparison groups.

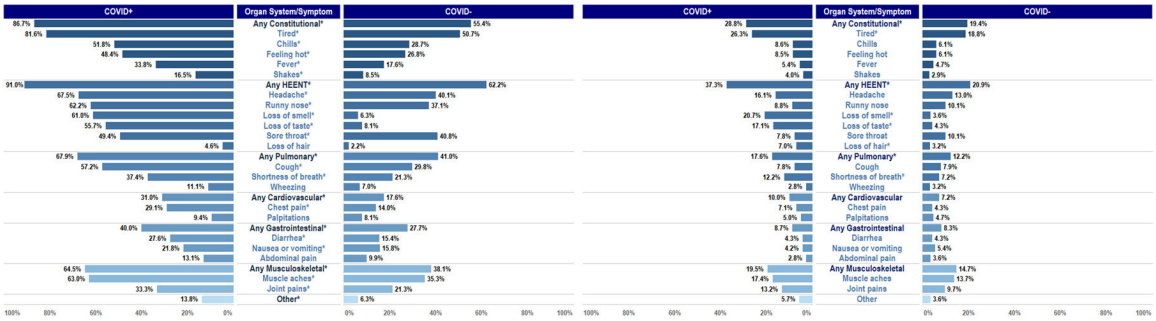

Figure 1 Footnotes:

A, Baseline COVID symptoms prevalence among 722 COVID+ and 278 COVID− participants in the INSPIRE study enrolled between December 2020 and September 2021. B, Three-month follow-up COVID symptom prevalence among 722 COVID+ and 278 COVID− participants in the INSPIRE study enrolled between December 2020 and September 2021. Abbreviations: COVID, coronavirus disease; INSPIRE, Innovative Support for Patients with SARS-CoV-2 Infections Registry; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

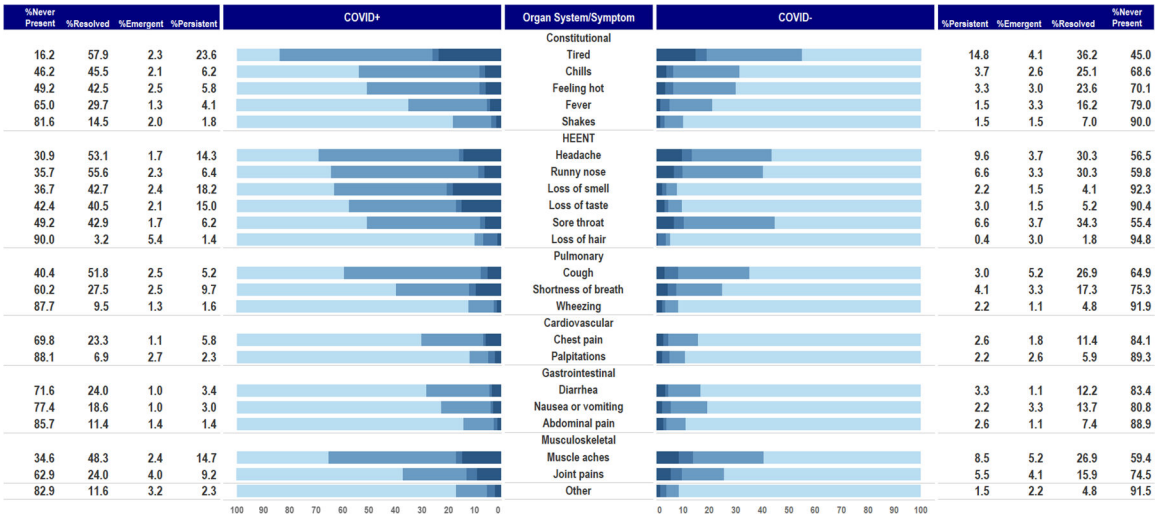

Figure 2 Footnotes:

COVID symptom course comparing baseline to 3-mo follow-up among 722 COVID+ and 278 COVID− participants in the INSPIRE study enrolled between December 2020 and September 2021: proportion which never occurred, resolved, persisted, and emerged. Abbreviations: COVID, coronavirus disease; INSPIRE, Innovative Support for Patients with SARS-CoV-2 Infections Registry; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

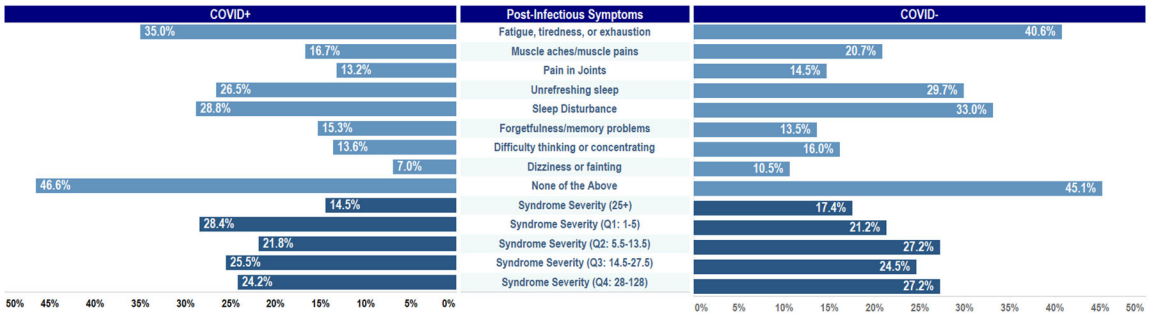

Figure 3 Footnotes:

Symptoms of post-infectious syndromes at 3-mo follow-up, comparison of 722 COVID+ and 278 COVID− participants in the INSPIRE study enrolled between December 2020 and September 2021. Abbreviations: COVID, coronavirus disease; INSPIRE, Innovative Support for Patients with SARS-CoV-2 Infections Registry; SARSCoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1.

Baseline characteristics of COVID+ compared with COVID− participants who presented for testing of SARS-CoV-2 infection

	Total		COVID+		COVID−		
Total n	**1000**		**722**		**278**		
Sociodemographic Characteristics	**N**	%	**N**	%	**N**	%	P value
Age (at enrollment)							0.005
18 to 34	406	40.7	288	39.9	118	42.6	
35 to 49	286	28.7	220	30.5	66	23.8	
50 to 64	215	21.5	160	22.2	55	19.9	
65+	91	9.1	53	7.4	38	13.7	
Gender							0.072 *
Female	644	66.3	464	66.0	180	66.9	
Male	313	32.2	232	33.0	81	30.1	
Transgender/Non-binary/Other	15	1.5	7	1.0	8	3.0	
Ethnicity							0.884
Hispanic	151	15.3	110	15.4	41	15.1	
Not Hispanic	833	84.7	602	84.6	231	84.9	
Race							0.007
Asian	89	9.1	52	7.4	37	13.8	
Black or African American	131	13.4	91	12.9	40	14.9	
Other/Multiple	69	7.1	55	7.8	14	5.2	
White	685	70.3	508	72.0	177	66.0	
Educational Attainment							0.699 *
Less than high school diploma	17	1.8	13	1.9	4	1.5	
High school graduate or GED	106	11.0	78	11.1	28	10.5	
Some college but did not complete degree	149	15.4	106	15.1	43	16.2	
2-year college degree	87	9.0	65	9.3	22	8.3	
4-year college degree	290	30.0	218	31.1	72	27.1	
More than 4-year college degree	317	32.8	220	31.4	97	36.5	
Marital Status							0.008
Married/Living with a partner	503	51.5	383	54.2	120	44.3	
Divorced/Widowed/Separated	126	12.9	80	11.3	46	17.0	
Never married	348	35.6	243	34.4	105	38.7	
Household Income (pre-pandemic)							<.001
Less than $10,000	70	7.2	44	6.2	26	9.6	
$10,000 to $35,000	132	13.5	91	12.9	41	15.1	
$35,000 to $50,000	124	12.7	76	10.7	48	17.6	

	Total		COVID+		COVID−		
Total n	**1000**		**722**		**278**		
$50,000 to $75,000	126	12.9	100	14.1	26	9.6	
$75,000 or more	483	49.3	369	52.2	114	41.9	
Prefer not to answer	44	4.5	27	3.8	17	6.3	
Health Insurance							0.001
Private only	663	67.6	499	70.4	164	60.3	
Public only	240	24.5	155	21.9	85	31.3	
Private & Public	42	4.3	25	3.5	17	6.3	
None	36	3.7	30	4.2	6	2.2	
Employment (pre-pandemic)							0.031
Employed, essential or health care worker	409	41.8	309	43.7	100	36.9	
Employed, not essential or health care worker	373	38.1	270	38.2	103	38.0	
Not employed	196	20.0	128	18.1	68	25.1	
Clinical Characteristics							
Pre-existing conditions							
Asthma (moderate or severe)	137	14.7	85	12.8	52	19.3	0.010
Hypertension or high blood pressure	169	18.1	109	16.4	60	22.3	0.034
Diabetes	67	7.2	39	5.9	28	10.4	0.015
Overweight or obesity	280	30.0	194	29.2	86	32.0	0.398
Emphysema or COPD	22	2.4	12	1.8	10	3.7	0.081
Heart conditions	42	4.5	25	3.8	17	6.3	0.087
Smoking	49	5.2	38	5.7	11	4.1	0.313
Kidney disease	14	1.5	8	1.2	6	2.2	0.245 *
Liver disease	17	1.8	11	1.7	6	2.2	0.591 *
Tobacco use, past 12 months							0.045 *
Daily or near daily	54	5.5	36	5.1	18	6.7	
Weekly	26	2.7	24	3.4	2	0.7	
Monthly	13	1.3	11	1.6	2	0.7	
Less than monthly	44	4.5	36	5.1	8	3.0	
Not at all	841	86.0	601	84.9	240	88.9	
COVID testing site							<.001 *
Nonacute Care Settings							
At home testing kit	15	1.5	10	1.4	5	1.8	
Clinic including an Urgent Care Clinic	143	14.4	104	14.5	39	14.0	
Tent/Drive-up testing site	526	53.0	403	56.4	123	44.2	
Acute Care Settings							
Hospital	144	14.5	101	14.1	43	15.5	
Emergency Department	90	9.1	46	6.4	44	15.8	

	Total		COVID+		COVID−		
Total n	**1000**		**722**		**278**		
Other	75	7.6	51	7.1	24	8.6	
Hospitalization							
Hospitalized for COVID+	76	8.1	72	10.8	4	1.5	<.001
ICU Hospitalization for COVID+	29	3.1	27	4.1	2	0.7	0.008

Note: Percentages are calculated among non-missing responses.

Abbreviations: GED (general educational development); COPD (chronic obstructive pulmonary disease); ICU (intensive care unit)

* For variables with cell expected values < 5, p-values were estimated using Fisher exact method; chi-square tests were used to derive other p values.

Table 2.

Prevalence of symptoms at 3-month follow-up, comparing COVID+ vs COVID− participants by age group

	3-Month Follow-up*						
	Total		COVID+		COVID−		
	n	Col. %	n	Col. %	n	Col. %	p-value
Total Participants (Any Symptoms)							
Yes	433	43.3	359	49.7	74	26.6	<.001
No	567	56.7	363	50.2	204	73.3	
Age Group: 18 to 34 n	**406**		**288**		**118**		
Symptom Category							
Constitutional (at least one)	92	22.7	68	23.6	24	20.3	0.475
HEENT (at least one)	117	28.8	89	30.9	28	23.7	0.147
Pulmonary (at least one)	59	14.5	46	16.0	13	11.0	0.198
Musculoskeletal (at least one)	53	13.1	37	12.8	16	13.6	0.847
Gastrointestinal (at least one)	33	8.1	22	7.6	11	9.3	0.573
Cardiovascular (at least one)	35	8.6	28	9.7	7	5.9	0.217
Other Symptoms	6	1.5	5	1.7	1	0.8	0.676*
3+ Symptoms	88	21.7	64	22.2	24	20.3	0.676
No Symptoms selected	252	62.2	169	58.9	83	70.3	0.031
Age Group: 35 to 49 n	**286**		**220**		**66**		
Symptom Category							
Constitutional (at least one)	85	29.7	72	32.7	13	19.7	0.042
HEENT (at least one)	113	39.5	99	45.0	14	21.2	<.001
Pulmonary (at least one)	45	15.7	34	15.5	11	16.7	0.813
Musculoskeletal (at least one)	65	22.7	54	24.5	11	16.7	0.18
Gastrointestinal (at least one)	23	8.0	20	9.1	3	4.5	0.234
Cardiovascular (at least one)	28	9.8	23	10.5	5	7.6	0.49
Other Symptoms	23	8.0	17	7.7	6	9.1	0.721
3+ Symptoms	82	28.7	68	30.9	14	21.2	0.127
No symptoms selected	141	49.3	94	42.7	47	71.2	<.001
Age Group: 50+	**306**		**213**		**93**		
Symptom Category							
Constitutional (at least one)	84	27.5	67	31.5	17	18.3	0.018
HEENT (at least one)	96	31.4	81	38.0	15	16.1	<.001
Pulmonary (at least one)	57	18.6	47	22.1	10	10.8	0.019
Musculoskeletal (at least one)	63	20.6	50	23.5	13	14.0	0.059
Gastrointestinal (at least one)	30	9.8	21	9.9	9	9.7	0.961

	3-Month Follow-up*						
	Total		COVID+		COVID−		
	n	Col. %	n	Col. %	n	Col. %	p-value
Cardiovascular (at least one)	29	9.5	21	9.9	8	8.6	0.73
Other Symptom	22	7.3	19	9.0	3	3.3	0.076
3+ Symptoms	80	26.1	65	30.5	15	16.1	0.008
No symptoms selected	171	56.4	98	46.4	73	79.3	<.001

Note: Percentages are calculated among non-missing responses.

Abbreviations: HEENT (head/ears/eyes/nose/throat)

* For variables with cell expected values < 5, p-values were estimated using Fisher exact method; chi-square tests were used to derive other p values.