American Journal of Physical Medicine & Rehabilitation Articles Ahead of Print
DOI: 10.1097/PHM.0000000000001910

OPEN

Post-acute COVID-19 syndrome negatively impacts physical function, cognitive function, health-related quality of life and participation

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We are submitting original research, and have not currently submitted this data to another journal for consideration. All authors listed have reviewed and approved this manuscript for submission. No authors have conflicts to disclose. No funding was received for this study.

Abstract

Objective: This report describes persistent symptoms associated with post-acute COVID-19 syndrome (PACS), and the impact of these symptoms on physical function, cognitive function, health-related quality of life and participation.

Design: Cross-sectional observational study design. Patients attending Mount Sinai's PACS Clinic completed surveys containing patient-reported outcomes.

Results: A total of 156 patients completed the survey, at a median (range) time of 351 (82 to 457) days post COVID-19 infection. All patients were pre-vaccination. The most common persistent symptoms reported were fatigue (n=128, 82%), brain fog (n=105, 67%) and headache (n=94, 60%). The most common triggers of symptom exacerbation were physical exertion (n=134, 86%), stress (n=107, 69%) and dehydration (n=77, 49%). Increased levels of fatigue (Fatigue Severity Scale) and dyspnea (Medical Research Council) were reported, alongside reductions in levels of regularly completed physical activity. Ninety-eight (63%) patients scored for at least mild cognitive impairment (Neuro-Qol), and the domain of the EQ-5D-5L most impacted was Self-care, Anxiety/Depression and Usual Activities.

Conclusion: Persistent symptoms associated with PACS appear to impact physical and cognitive function, health-related quality of life and participation in society. More research is needed to further clarify the relationship between COVID-19 infection and PACS symptoms, the underlying mechanisms, and treatment options.

Keywords: *Post-acute COVID-19; Fatigue; Cognition; Employment, Quality of life*

What is Known: Post-Acute COVID-19 Syndrome (or LongCOVID) is characterized by persistent and debilitating symptoms that are still present at least 4 weeks after initial infection. Symptoms often occur in the absence of severe acute infection or pre-existing comorbidities. Millions of Americans are at risk of developing PACS. **What is New**: The presence of persistent PACS symptoms negatively impacts physical and cognitive function, health-related quality of life, and participation in society. Physical exertion and dehydration are the major factors causing symptom exacerbation. 63% patients scored for at least mild cognitive impairment.

Introduction

Following the dramatic influx of patients with persistent, debilitating symptoms after acute SARS-CoV-2 (COVID-19) infection, the National Institutes of Health announced an initiative to fully investigate the Post-Acute Sequelae of COVID-19 (PASC). PASC can take many forms, from Post-ICU Syndrome [1] to pulmonary fibrosis secondary to aggressive COVID-19 pneumonia.[2] However, Post-Acute COVID-19 Syndrome (PACS; also known as Long COVID) is one of the most troubling manifestations of PASC that has been reported to date. It is characterized by persistent symptoms that are still present at least 4 weeks after initial infection, and often lasting for several months.[3] Despite the highly debilitating nature of PACS, the long lasting symptoms often occur in the absence of severe acute infection, medically explainable physical symptoms, or pre-existing comorbidities. [4–6]

Several studies have documented the most common persistent symptoms following severe COVID-19 infection. These symptoms include fatigue, dyspnea, "brain fog"/various cognitive symptoms, pain, anxiety, depression, and gastrointestinal issues [3,4,6–9]. In these cohorts, the symptoms arising from COVID-19 increased disability and negatively impacted physical function and quality of life, [7,8] and affected participation in general life activities and the ability to work. [9] There is a critical need to classify the prevalence of specific persistent symptoms that follow acute COVID-19 infection, and the impact of these symptoms on patient-reported outcomes (PRO) that are well-validated in other conditions. This will facilitate the establishment of diagnostic criteria for PACS, and accurate tracking of responses to various prospective therapies.

It has been hypothesized that persistent symptoms after acute COVID-19 infection result from an immune-mediated disruption to the autonomic nervous system. [10,11]. Similar to other post-viral autoimmune conditions (such as Guillain-Barré syndrome), COVID-19 infection appears to act as an immune trigger.[12] This immune response, coupled with a lack of access to acute COVID-19 treatments offered only in a hospital setting, may explain why even those with less severe acute infection are still experiencing persistent symptoms.

It is clear that in the wake of the COVID-19 pandemic, a second, longer term public health emergency has emerged. It is imperative to understand the burden of this novel condition with millions Americans at risk of developing PACS by the end of the pandemic. This study describes the persistent symptoms reported by a cohort of patients with PACS, the majority of whom were infected with COVID-19 in early 2020 and not hospitalized. The impact of these symptoms on physical function, cognitive function, health-related quality of life and participation is also reported.

Methods

This was a retrospective observational study of patients attending Mount Sinai's PACS Clinic. Approval for publication was provided and requirement for patient consent was waived by the Mount Sinai Program for Protection of Human Subjects (IRB 21-01147). This study conforms to all STROBE guidelines and reports the required information accordingly (see Supplementary Checklist, Supplemental Digital Content 1, http://links.lww.com/PHM/B417).

Participants

This was a convenience sample exploring symptom characteristics of patients attending the Mount Sinai PACS clinic. This is an interdisciplinary clinic consisting of physicians, physical therapists and dietitians. Patients were either referred by a physician or self-referred. All patients had confirmed (by PCR and/or antibody test) or probable (diagnosed by a medical doctor in accordance with World Health Organization (WHO) recommendations14) prior COVID-19 infection; and diagnosis of PACS (defined as experiencing symptoms >12 weeks since initial symptom onset). Inclusion criteria for the present study were attending the Mount Sinai Post-Acute COVID-19 Syndrome Clinic between March 2020 and March 2021; and completion of the PRO survey.[15] There were no exclusion criteria.

Data collection and outcomes

Data were collected using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Mount Sinai Health System. REDCap is a secure, web-based application designed to support data capture for research studies. Participants were provided with a link to the survey via email on 14th March 2021 as part of their clinical care

Baseline demographic data included gender, age, body mass index (BMI), race, and comorbidities. COVID-19 clinical data included duration of COVID-19 symptoms (at survey completion), polymerase chain reaction (PCR) (obtained from nasopharyngeal swab) and antibody test completion and results, need for hospitalization at time of COVID-19 infection, and vaccination status.

Patient-reported outcomes included current persistent symptoms and triggers of symptom exacerbation, and screening tools for fatigue (Fatigue Severity Scale [FSS], Fatigue visual analogue scale [VAS]), breathlessness (Medical Research Council [MRC] Breathlessness Scale), completion of regular moderate and vigorous intensity physical activity (author developed), cognitive function (Neuro-QOL), health-related quality of life (HRQoL) (EuroQol EQ-5D-5L), anxiety (GAD-7), depression (PHQ-2), disability (WHODAS) and pre- and post-COVID-19 employment status (author developed).

Statistical analyses

Statistical analyses were undertaken with Stata (StataCorp, Stata Statistical Software Release: V.14). Data were analysed using descriptive statistics and reported using number and percentage, or median and range.

Results

The survey was sent to 386 patients, with 156 (48%) responding. The median (range) time to follow-up time since the onset of COVID-19 infection was 351 (82 to 457) days (Table 1). The most common symptoms reported were fatigue (n=128, 82%), brain fog (n=105, 67%), headache (n=94, 60%), sleep disturbance (n=92, 59%) and dizziness (n=85, 54%) (Figure 1). The most common triggers of symptom exacerbation reported were physical exertion (n=134, 86%), stress (n=107, 69%), dehydration (n=77, 49%), weather changes (n=58, 37%), consuming large meals (n=44, 28%), premenstrual period (n=34, 22%) and alcohol consumption (n=34, 22%).

The median (range) FSS average score was 5.6 (1 to 7) out of 7, with 122 (78%) patients reporting an FSS average score of 4 or greater, indicating problematic fatigue. Sixty-three (40%) patients reported a score of 3 or more (out of 5) on the MRC Breathlessness Scale, suggesting moderate to severe disability due to dyspnea. When compared to pre-COVID-19 infection levels, patients were completing 150 minutes per week of physical activity less frequently post-COVID-19 infection, when asked separately about moderate and vigorous intensities (Figure 2).

Ninety-eight (63%) patients scored for at least mild cognitive impairment on the Neuro-Qol (Figure 3). The domains of the EQ-5D-5L impacted the most (reported as slight problems or greater) were Self-care, Anxiety/depression and Usual activities (Table 2). The median (range) EQ5D5L VAS score was 64 (6 to 99) out of 100, with a higher score indicating greater HRQoL. Twenty-nine (19%) patients scored 10 or greater on the GAD-7, indicating possible anxiety disorder. Forty-three (28%) patients scored 3 or greater on the PHQ-2, indicating possible major depressive disorder. The median (range) WHODAS total score was 14 (0 to 44) out of 100. A total of 134 (86%) patients answered pre- and post-COVID-19 employment questions; the number of patients in full time work reduced from 102 (76)% pre-COVID-19 to 55 (41)% at the time of follow-up (Figure 4).

Discussion

This observational study of a cohort of patients with PACS reported that COVID-19 related symptoms are persistent for at least 2 months, and often longer than 12 months, with fatigue, brain fog, sleep disturbance, dizziness, dyspnea, memory loss, and palpitations being identified as the most common. The most common triggers of symptom exacerbation in this cohort were physical

exertion, stress and dehydration. The negative impact of PACS on a variety of PROs has been demonstrated.

Just under 50% of the patients included in this study had a negative polymerase chain reaction (PCR) test or tested seronegative for antibodies. Issues relating to false negative rates are well-documented with PCR testing.[16–18] Similarly, there is literature to support the idea that antibody levels in patients who experienced less-severe acute infection tend to fade rapidly.[19] In acknowledgement of the potential for health disparities to rapidly arise from an overreliance on COVID-19 tests, the CDC has recently recommended against using seropositive status as the sole diagnostic criteria for any post-acute sequelae of COVID-19. [20] In order to fully understand all of the possible presentations of PACS, studies must incorporate and report data from both seronegative and seropositive patient populations.

The most common symptoms observed in this cohort are consistent with those previously reported.[3,6,21–24] The pattern of PACS symptoms resembles other post-viral syndromes, including dysautonomia[25], postural orthostatic tachycardia syndrome[26] and myalgic encephalomyelitis [27]. It is unsurprising that physical exertion was the most common cause of symptom exacerbation, as this is a feature shared by some of these conditions. The potential for the worsening of symptoms following physical exertion is the most important consideration when prescribing rehabilitation therapies for people with PACS.[28]

The presence of cognitive dysfunction in more than half (63%) of patients, in combination with reduced Usual Activities and Self Care scores on the EQ-5D-5L, highlights that patients with

PACS may have a reduced ability to participate in society. Employment was also impacted in the majority of patients, however it is difficult to determine whether this was specifically due to disability related to COVID-19 infection, or possibly to the broader implications of the pandemic on the ability for workplaces to operate as usual. Levels of self-reported physical activity were greatly reduced, likely coinciding with the potential for symptom exacerbation; this raises concerns given the known longer-term health risks of physical inactivity.[29]

The proportion of participants reporting anxiety (19%) and depression (28%) on the PHQ2 and GAD-7 was slightly higher than reported as part of their medical history, however were similar to what is expected in the normal population, [30] and lower than that observed in chronic individuals with obstructive pulmonary disease [31] and cardiac disease [32]; however, these levels were greater than what participants' reported as part of their pre-COVID-19 medical history. With a lack of pre-COVID-19 PHQ2 and GAD-7 data available, it is difficult to make conclusions about the impact of PACS on anxiety and depression.

Some limitations of the present study include the use of clinical survey data answered in retrospect, a lack of comparison group and/or pre-COVID-19 measures. In addition, the use of non-condition specific PROs can increase the risk of inaccuracy and recall bias.

Conclusion

The presence of persistent symptoms associated with PACS appears to impact physical and cognitive function, health-related quality of life and participation in society. The data reported

contribute to the recognition and research of long-COVID as recommended by the WHO,[33] and will help to inform future rehabilitation strategies.

Acknowledgements

The authors would like to acknowledge the patients in the study, the frontline healthcare workers at Mount Sinai Health System, and the wider research team at the Abilities Research Center and the Center for Post-COVID Care at Mount Sinai. The authors would also like to acknowledge the RTW Charitable Foundation for supporting multiple PACS initiatives in the Abilities Research Center.

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Figure Legends

Figure 1. Most commonly reported persistent symptoms by all patients (n=156).

Figure 2. Levels of moderate (a) and vigorous (b) intensity physical activity regularly completed (150 minutes per week) pre- and post-COVID-19 infection in all patients (n=156).

Figure 3. Neuro-QoL level of impairment according to t-scores in patients who completed the measure (n=155). Neuro-QoL scores have a mean of 50 and standard deviation (SD) of 10 in a referent population. T-scores 40-45 indicate mild dysfunction, t-scores 30-40 indicate moderate dysfunction and t-scores <30 indicate severe dysfunction.

Figure 4. Employment status pre- and post-COVID-19 infection in participants who answered employment questions (n=134).

Figure 1

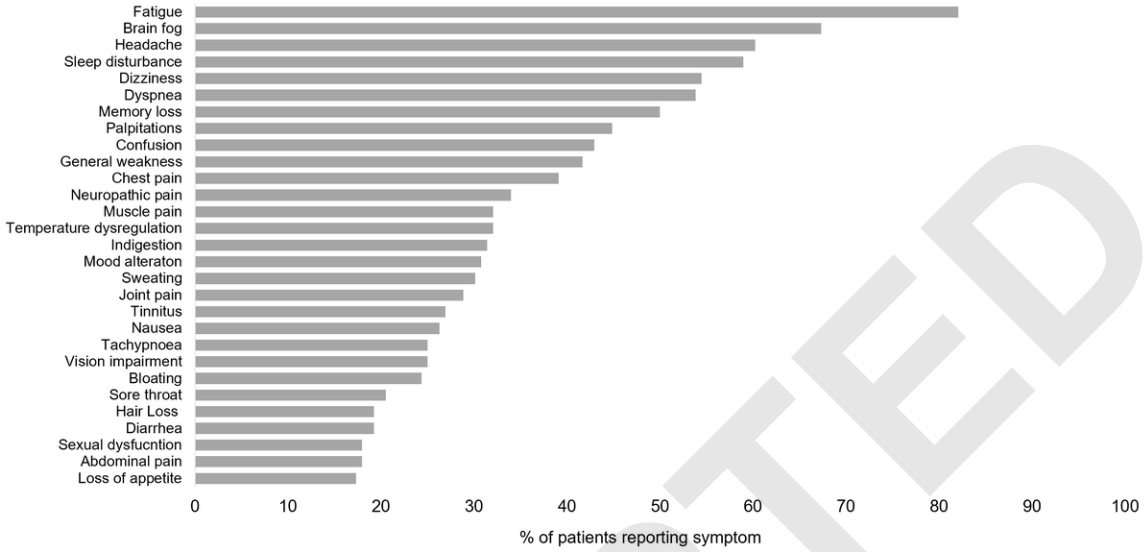

Figure 2

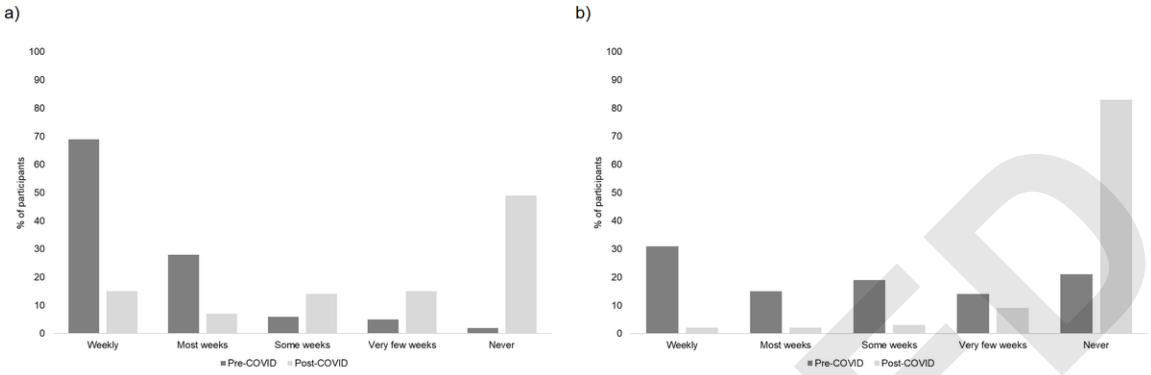

Figure 3

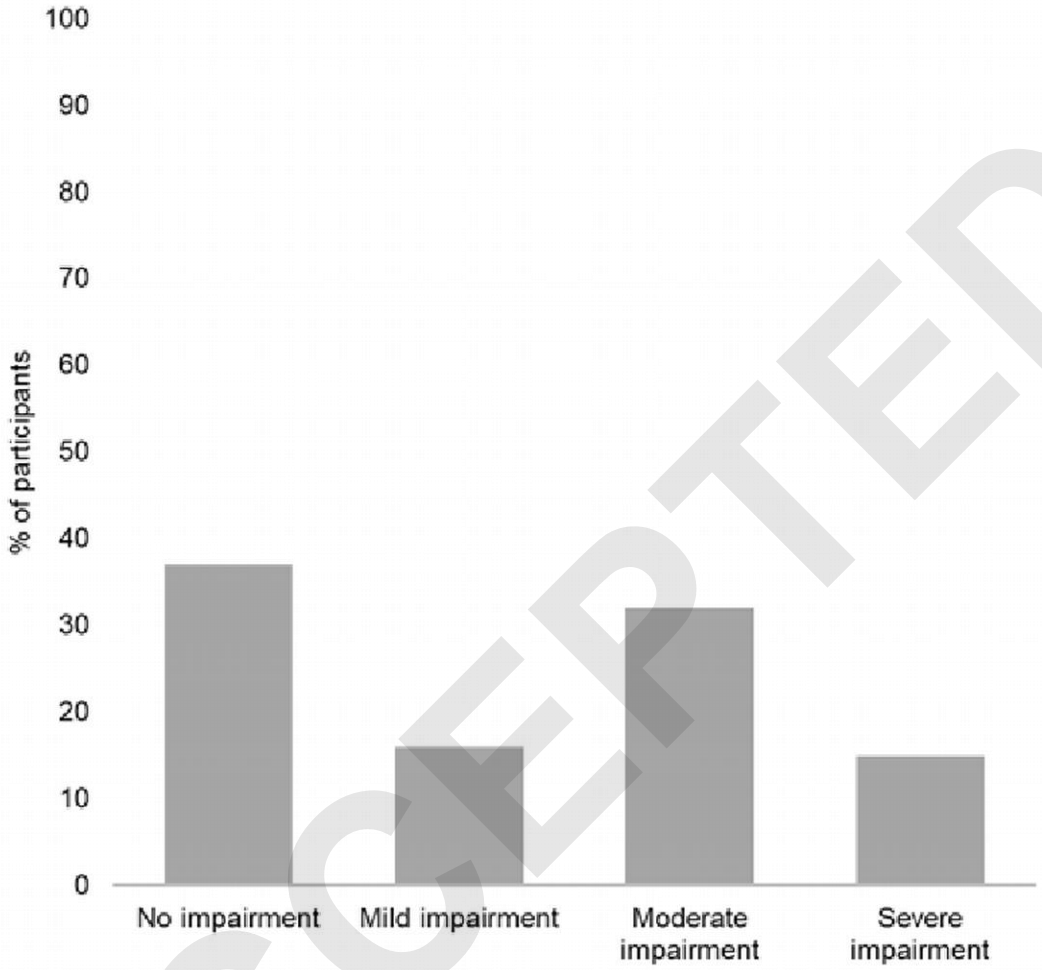

Figure 4

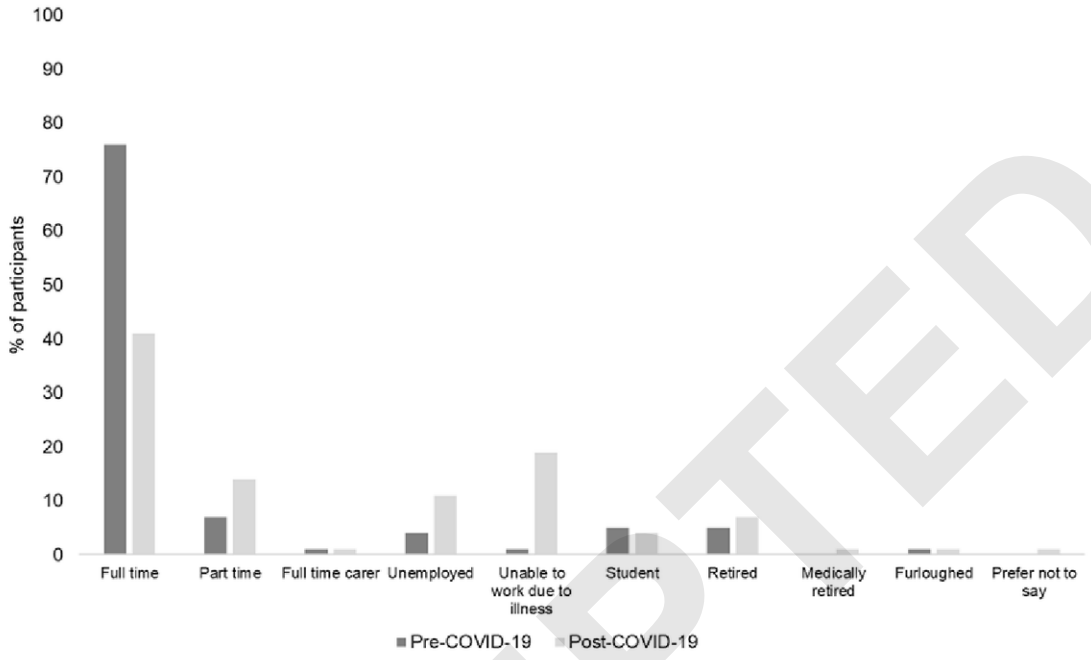

Table 1. Patient (n=156) baseline demographic and COVID-19 related data

	All patients (n = 156)	Confirmed COVID-19 (87)	Presumed COVID-19 (69)
Female	107 (69)	54 (62)	53 (77)
Age y, median (range)	44 (13 to 79)	45 (13 to 79)	44 (14 to 79)
BMI kg/m^2, median (range)	24 (16 to 52)	24 (17 to 52)	24 (16 to 42)
Race			
White	119 (76)	65 (75)	54 (78)
Asian	8 (5)	3 (3)	5 (7)
Black or African American	6 (4)	4 (5)	2 (3)
American Indian or American Native	2 (1)	1 (1)	1 (1)
Native Hawaiian or Pacific Islander	0 (0)	0 (0)	0 (0)
Other	15 (10)	8 (9)	7 (10)
Hispanic or Latinx	10 (7)	3 (4)	7 (10)
Duration of symptoms in days, median (range)	351 (82 to 457)	350 (157 to 424)	355 (82 to 457)
PCR completed	98 (63)	57 (66)	41 (59)
PCR positive	34 (22)	34 (39)	0 (0)
Antibody test completed	149 (96)	86 (99)	63 (91)
Antibody positive	80 (51)	80 (92)	0 (0)
PCR and/or antibody positive	87 (56)	87 (100)	0 (0)
Hospitalized for COVID-19	17 (11)	16 (18)	1 (1)
Received COVID-19 vaccination*	87 (56)	45 (52)	42 (61)
Most prevalent comorbidities			

Cancer (any type)	30 (20)	10 (11)	20 (29)
Asthma	30 (20)	13 (15)	17 (25)
Anxiety	18 (12)	12 (14)	6 (9)
Depression	13 (8)	8 (9)	5 (7)
Hypertension	11 (7)	7 (8)	4 (6)

Data are presented as n (%) unless otherwise indicated. BMI = body mass index, PACS = post-acute COVID-19 syndrome, PCR = polymerase chain reaction. *All COVID-19 vaccination occurred after COVID-19 infection.

Table 2. Patient (n=156) responses to the EQ5D5L.

	No problems	Slight problems	Moderate problems	Severe problems	Extreme problems
Domain					
Mobility	68 (44)	42 (27)	28 (18)	17 (11)	1 (1)
Self-care	23 (15)	48 (31)	39 (25)	35 (22)	11 (7)
Usual activities	29 (19)	64 (41)	45 (29)	11 (7)	7 (4)
Pain discomfort	113 (72)	26 (17)	12 (8)	5 (3)	0 (0)
Anxiety/depression	26 (17)	59 (38)	49 (31)	16 (10)	6 (4)

Data are presented as n (%).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1- 2	"This was a cross-sectional observational study"
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	*Abstract*
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	*Introduction*
Objectives	3	State specific objectives, including any prespecified hypotheses	5	"This study describes the persistent symptoms reported by a cohort of patients with PACS, the majority of whom were infected with COVID-19 in early 2020 and not hospitalized. The impact of these symptoms on physical function, cognitive function, health-related quality of life and participation is also reported. "
Methods				
Study design	4	Present key elements of study design early in the paper	5	"This was a cross-sectional observational study"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	*Methods*
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5	*Participants*

		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants		
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	Data collection and outcomes
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6	
Bias	9	Describe any efforts to address potential sources of bias	n/a	
Study size	10	Explain how the study size was arrived at	6	"This was a convenience sample exploring symptom characteristics of patients with a novel condition. With no prior research on which to base a sample size calculation, the goal was to collect data from as many patients as possible"

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	n/a
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	n/a
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	

		Cross-sectional study—Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	n/a

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.