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MAJOR ARTICLE

Persistence, Magnitude, and Patterns of Postacute Symptoms and Quality of Life Following Onset of SARS-CoV-2 Infection: Cohort Description and Approaches for Measurement

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Background. There is mounting evidence for the presence of postacute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (PASC), but there is limited information on the spectrum, magnitude, duration, and patterns of these sequelae as well as their influence on quality of life.

Methods. We assembled a cohort of adults with a documented history of SARS-CoV-2 RNA positivity at ≥2 weeks past onset of coronavirus disease 2019 (COVID-19) symptoms or, if asymptomatic, first positive test. At 4-month intervals, we queried physical and mental health symptoms and quality of life.

Results. Of the first 179 participants enrolled, 10 were asymptomatic during the acute phase of SARS-CoV-2 infection, 125 were symptomatic but not hospitalized, and 44 were symptomatic and hospitalized. During the postacute phase, fatigue, shortness of breath, concentration problems, headaches, trouble sleeping, and anosmia/dysgeusia were most common through 8 months of observation. Symptoms were typically at least somewhat bothersome and sometimes exhibited a waxing-and-waning course. Some participants experienced symptoms of depression, anxiety, and post-traumatic stress, as well as difficulties with performance of usual activities. The median visual analogue scale rating of general health was lower at 4 and 8 months compared with pre-COVID-19. Two clusters of symptom domains were identified.

Conclusions. Many participants report bothersome symptoms following onset of COVID-19 with variable patterns of persistence and impact on quality of life. The substantial variability suggests the existence of multiple subphenotypes of PASC. A rigorous approach to the prospective measurement of symptoms and functional manifestations sets the stage for the next phase of research focusing on the pathophysiologic causes of the various subgroups of PASC.

Keywords. COVID-19; long COVID; post-acute sequelae of SARS-CoV-2 (PASC); quality of life; SARS-CoV-2.

Coronavirus disease 2019 (COVID-19), the condition caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was initially characterized as a time-limited illness [1–3]. Patients were believed to either succumb to COVID-19 or return to their usual health. Subsequently, anecdotal reports emerged stating that while recovery from the symptoms typically associated with an acute infection (eg, fever and chills) is near uniform, some individuals complain of persistent symptoms (eg, fatigue and pain) well after the period of acute SARS-CoV-2 infection [4–6]. These patients gave rise to the colloquial terms "long haulers" and "long COVID" [7, 8]. Formal scientific investigation of what is clinically known as postacute sequelae of SARS-CoV-2 infection (PASC) has just begun and has been useful to establish the frequency of the condition beyond anecdote and to demonstrate its geographic and sociodemographic diversity. Early investigations

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were limited by studying populations who had not all been confirmed to have SARS-CoV-2 [9], were enriched with patients who were hospitalized and may thus be more indicative of the effects of hospitalization than COVID-19 [10, 11], or had short follow-up [12]. Furthermore, there is little systematic information on the magnitude or severity, longitudinal within-person persistence, or co-occurrence of PASC symptoms. As millions of individuals worldwide continue to become infected with SARS-CoV-2, the public health implications of PASC and the need to uncover interventions to prevent or treat it are self-evident.

To rapidly gain insights into PASC, we established a cohort dedicated to the study of PASC. We intentionally sought to enroll patients with RNA-confirmed SARS-CoV-2 infection recovering from a wide spectrum of acute disease manifestations. Herein, we describe the assembly of this cohort along with some key methodologic approaches to study design, measurement of self-reported aspects of PASC, and portrayal of findings that could inform this nascent field of research. As a demonstration of these approaches, we also describe our preliminary findings in cohort participants regarding the spectrum, magnitude, duration, and co-occurrence of physical and mental health symptoms, as well as their influence on quality of life through 8 months of observation following acute SARS-CoV-2 infection.

METHODS

Patient Consent

The institutional review board of the University of California, San Francisco, approved this study. All participants provided written informed consent.

Overall Design

We enrolled consecutive adults at ≥2 weeks past onset of COVID-19 symptoms or, if asymptomatic, first positive diagnostic test for SARS-CoV-2 and who responded to notification and advertisements regarding the study. Participants underwent comprehensive questionnaire-based evaluation and biological specimen collection at an initial visit and every 4 months thereafter.

Participants

Any individual age ≥18 years with documentation of SARS-CoV-2 RNA detected on a prior nucleic acid amplification test and ability to travel to our research site in San Francisco was eligible to participate. Minimal duration of time following symptom onset (or first positive RNA detection) depended on local infection control guidelines, starting with 28 days and subsequently shortening to 14 days. Participants were recruited through clinician referral, mailings to consecutive patients testing positive at University of California, San Francisco–affiliated testing sites, and response to medical center paper postings, websites, and advertisements. Although quotas were not set for distribution of acute SARS-CoV-2 disease manifestations, most recruitment resources were dedicated to attracting persons who had not been hospitalized, including asymptomatic individuals.

Processes

Once identified, participants deemed eligible by a phone interview were examined in person at the research center. Participants were administered structured questionnaires, asked to provide whole unstimulated saliva and/or a swab of gingival crevice fluid, and had peripheral blood collected, which was stored as serum, plasma, and cryopreserved peripheral blood mononuclear cells (PBMCs). Following the initial visit, participants were invited to complete additional visits every 4 months.

Measurements

A battery of instruments was assembled by a team of infectious disease clinicians and epidemiologists, aided by consultation with content specialists from pulmonology, cardiology, neurology, and mental health. Development of the instruments was an iterative process as information emerged regarding SARS-CoV-2 infection and recovery. These instruments queried about sociodemographic characteristics, medical history and concomitant medications, SARS-CoV-2 exposure, physical symptoms, quality of life, mental health, and substance use. With the exception of the mental health questions, which were self-administered, all questionnaires were interviewer-administered. Interviews were conducted in English or Spanish by bilingual research staff according to participant preference. Study instruments were available in both English and Spanish.

The Patient Health Questionnaire (PHQ) somatic symptom scale [13] was used to ascertain presence and magnitude of physical symptoms. Participants were specifically asked to describe symptoms only if they were new or worse compared with the period before COVID-19. In addition to this predetermined list of symptoms, participants were asked about any other symptoms they were experiencing. At the initial visit, participants were asked about symptoms experienced during the acute phase of their SARS-CoV-2 infection (the first 3 weeks after initial symptom onset) as well as the prior 2 days (ie, current moment). At all subsequent visits, participants were asked about any symptoms experienced since their last visit, with separate ascertainment regarding the prior 2 days (ie, current moment). Quality of life was measured using the EuroQol metrics [14], and mental health symptoms were measured using a combination of the General Anxiety Disorder–7 (GAD-7) [15], PHQ-8 [16], and an adaptive 4-item version of the Posttraumatic Stress Disorder (PTSD) Checklist (PCL) 5 [17–19]. In contrast to physical symptoms, questions about quality of life and mental health symptoms were not limited to new perceptions or feelings that occurred since onset of COVID-19; instead, they were answered from the perspective of the time of the interview, regardless of whether their presence predated the SARS-CoV-2 diagnosis.

Statistical Analysis

Participants were described according to severity of COVID-19 during the first 21 days following onset of symptoms, which was classified as asymptomatic, symptomatic but not hospitalized, and hospitalized for the purposes of management of severe COVID-19. There were no hospitalizations solely for infection control or nonacute care. For each of the domains of physical symptoms, mental health symptoms, and quality of life, we characterized 4 time periods: (1) acute illness (0–3 weeks), (2) early recovery (centered at 6 weeks, range 3–10 weeks), (3) late recovery 1 (centered at 16 weeks, range 12–20 weeks), and (4) late recovery 2 (centered at 32 weeks, range 28–36 weeks).

To explore the extent to which patients cluster according to their symptoms, we implemented a model-based approach and focused on participants reporting at least 1 symptom present during the first late recovery period. To decrease multidimensionality, we first reduced 32 symptoms into 7 of domains of complaints (fatigue, upper respiratory, cardiopulmonary, gastrointestinal, musculoskeletal, neurological, or sleep), each containing between 1 and 8 symptoms. Participants were considered to possess the domain if they reported at least 1 symptom. The model-based approach attempted to cluster participants with similar patterns of symptom domains into k groups, where the number of groups and their associated distribution of domains are estimated via a modified expectation–maximization algorithm with model selection automatically performed via the Bayesian Information Criterion (BIC) [20]. Given the limited sample size, we performed a grid search between 2 and 6 clusters ($k = 2, \ldots, 6$). For a given k clusters, participants were assigned to the estimated latent distribution most likely to generate their observed symptom domains. Cluster performance was evaluated using the average silhouette score, a measure quantifying the internal validity of estimated cluster assignments within and across a sample.

We used Stata (version 16.1; StataCorp, College Station, TX, USA) throughout, with the exception of R for the alluvial plots (alluvial) and clustering (VarSelLCM [21]).

RESULTS

Characteristics of Participants at Enrollment

From April 21, 2020, to January 4, 2021, we enrolled 179 adult participants; most (60%) were enrolled between April and July 2020. At the time of enrollment, participants were a median (interquartile range [IQR]) of 1.8 (1.2–2.7) days past the date of symptom onset/first positive RNA detection. The cohort represented the full spectrum of illness severity during the acute phase of SARS-CoV-2 infection (Table 1); 10 were asymptomatic, 125 were symptomatic but not hospitalized, and 44 were symptomatic and hospitalized. Among those who had been hospitalized, 37 (88%) required supplemental oxygen, but only 6 (14%) required mechanical ventilation. Few participants had received therapeutic interventions during acute SARS-CoV-2 infection; 6% received remdesivir, 10% glucocorticoids, and 2% convalescent plasma.

Follow-up of Cohort

Longitudinal observation was scheduled every 4 months following onset of symptoms/date of first detected SARS-CoV-2 RNA. At 4 months, of the 165 participants who were evaluable (ie, whose duration since symptom onset was at least 20.5 weeks, the outer boundary of the window for this visit), 143 (87%) completed the study visit. At 8 months, of the 111 participants who were evaluable (ie, whose duration since symptom onset was at least 36.5 weeks), 68 (61%) completed the study visit. Twenty-five individuals (23%) missed their 8-month visit but had a subsequent visit and thus were not lost to follow-up. Reasons for such visit delays included reduced availability during the winter holidays, re-implementation of local stay-at-home orders, reduced staffing density due to medical center guidelines before the SARS-CoV-2 vaccine rollout, and participant concerns related to the winter 2020 COVID-19 surge. Of the remaining 18 individuals (16% of the 111 who are theoretically evaluable), 13 have formally withdrawn from the study (no time because of family obligations related to dependent care [n = 3], inability to tolerate blood draws [n = 3], moved out of region [n = 2], and declined to provide a reason [n = 5]), 3 were withdrawn by study investigators because of behavioral issues, and 2 remain in contact with the study but have not decided whether they wish to resume. No participant is known to have died. No participants were vaccinated against SARS-CoV-2 during the study period.

Physical and Mental Health Symptoms

The most common physical symptoms during the acute phase of SARS-CoV-2 infection were fatigue, fever, myalgia, cough, and anosmia/dysgeusia (Figure 1). In the postacute phase, fatigue, shortness of breath, concentration problems, headaches, trouble sleeping, and anosmia/dysgeusia were the most commonly reported, but a variety of other symptoms were endorsed by at least some participants at each time point. Not all participants, however, complained of symptoms. At early recovery (3–10 weeks), 61 of 126 participants reported no current symptoms. At the late recovery time points, 54 of 143 reported no current symptoms at the first late follow-up time point (12–20 weeks), and 16 of 68 reported no symptoms at the second late follow-up time point (28–36 weeks). When symptoms were present, very few participants stated that the symptom did not bother them (Table 2). For some symptoms (eg, "trouble concentrating, trouble with thinking, or trouble with memory"), >50% of the participants in the 2 late recovery periods who endorsed the symptom reported that it bothered them "a lot." Among the subset of participants with complete data at all 3 time periods (n = 38), there was substantial within-individual variation in the

Table 1. Characteristics at Time of SARS-CoV-2 Infection Among Participants Enrolled in a Study of Postacute Sequelae of SARS-CoV-2 Infection

Characteristic	Asymptomatic (n = 10)	Symptomatic Not Hospitalized (n = 125)	Symptomatic Hospitalized (n = 44)	All (n = 179)
Age, y	45.5 (38–55)[a]	46 (46–57)	49 (37–57)	48 (37–57)
	(29–70)[b]	(19–76)	(19–85)	(19–85)
Female birth sex	2 (20)	62 (50)	15 (34)	79 (44)
Gender identity				
Female	2 (20)	61 (49)	15 (34)	78 (44)
Male	8 (80)	52 (50)	28 (64)	98 (55)
Transgender male	0 (0)	1 (0.8)	1 (2)	2 (1.0)
Transgender female	0 (0)	0 (0)	0 (0)	0 (0)
Prefer not to answer	0 (0)	1 (0.8)	0 (0)	1 (0.5)
Race/ethnicity[c]				
Hispanic/Latino	3 (30)	29 (24)	24 (55)	56 (32)
Hawaiian/Pacific Islander	0 (0)	2 (1.7)	2 (4.6)	4 (2.3)
White	5 (50)	75 (62)	9 (20)	89 (51)
Black/African American	1 (10)	6 (5.0)	2 (4.6)	9 (5.1)
Asian	1 (10)	9 (7.4)	7 (16)	17 (9.7)
Native American/Alaska Native	0 (0)	0 (0)	0 (0)	0 (0)
Education				
Any HS or less	1 (10)	16 (13)	26 (59)	43 (24)
Any college	5 (50)	53 (42)	12 (27)	70 (39)
Any graduate school	4 (40)	56 (45)	6 (14)	66 (37)
Sexual orientation[c]				
Asexual	0 (0)	0 (0)	1 (4.2)	1 (1.0)
Bisexual	0 (0)	2 (1.9)	0 (0)	2 (1.5)
Gay/lesbian	3 (33)	28 (27)	4 (17)	35 (25)
Straight/heterosexual	5 (56)	71 (68)	19 (79)	95 (69)
Other	1 (11)	3 (2.9)	0 (0)	4 (2.9)
Annual household income[c]				
≤$50 000	4 (40)	25 (23)	16 (52)	45 (30)
$50 001–$100 000	1 (10)	15 (14)	7 (23)	23 (15)
$100 001–$300 000	4 (40)	36 (33)	6 (19)	46 (31)
>$300 000	1 (10)	32 (30)	2 (6.5)	35 (23)
Body mass index, kg/m^2[c]				
≤24.9	3 (30)	49 (39)	4 (9.1)	56 (31)
25–29.9	3 (30)	35 (28)	17 (39)	55 (31)
≥30	4 (40)	41 (33)	23 (52)	68 (38)
Self-reported comorbid conditions				
Autoimmune	2 (20)	3 (2.4)	6 (14)	11 (6.2)
Cancer[d,c]	2 (20)	4 (3.2)	1 (2.3)	7 (3.9)
Diabetes[c]	0 (0)	7 (5.7)	14 (32)	21 (12)
HIV[c]	4 (40)	25 (20)	3 (7.0)	32 (18)
Heart attack or heart failure	1 (10)	2 (1.6)	1 (2.3)	4 (2.2)
Hypertension[c]	3 (30)	19 (15)	15 (32)	36 (20)
Lung problems[e,c]	0 (0)	17 (14)	11 (25)	28 (16)
Kidney disease	0 (0)	1 (0.8)	1 (2.3)	2 (1.1)
Ever used tobacco[f]	5 (50)	36 (39)	13 (30)	54 (30)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Median (interquartile range).

[b]Absolute range.

[c]Missing and nonresponse. Race/ethnicity: 3 missing, 1 prefer not to answer; sexual orientation: 41 missing, 1 prefer not to answer; income: 1 missing, 29 prefer not to answer; BMI: 6 missing; cancer: 1 missing; diabetes: 3 missing; HIV: 1 missing; hypertension: 1 missing; lung problems: 1 missing.

[d]Cancer requiring treatment within the 2 years before COVID-19.

[e]Asthma, COPD, emphysema, or bronchitis experienced in the 5 years before COVID-19.

[f]Cigarettes, cigars, or any product containing tobacco in a hookah.

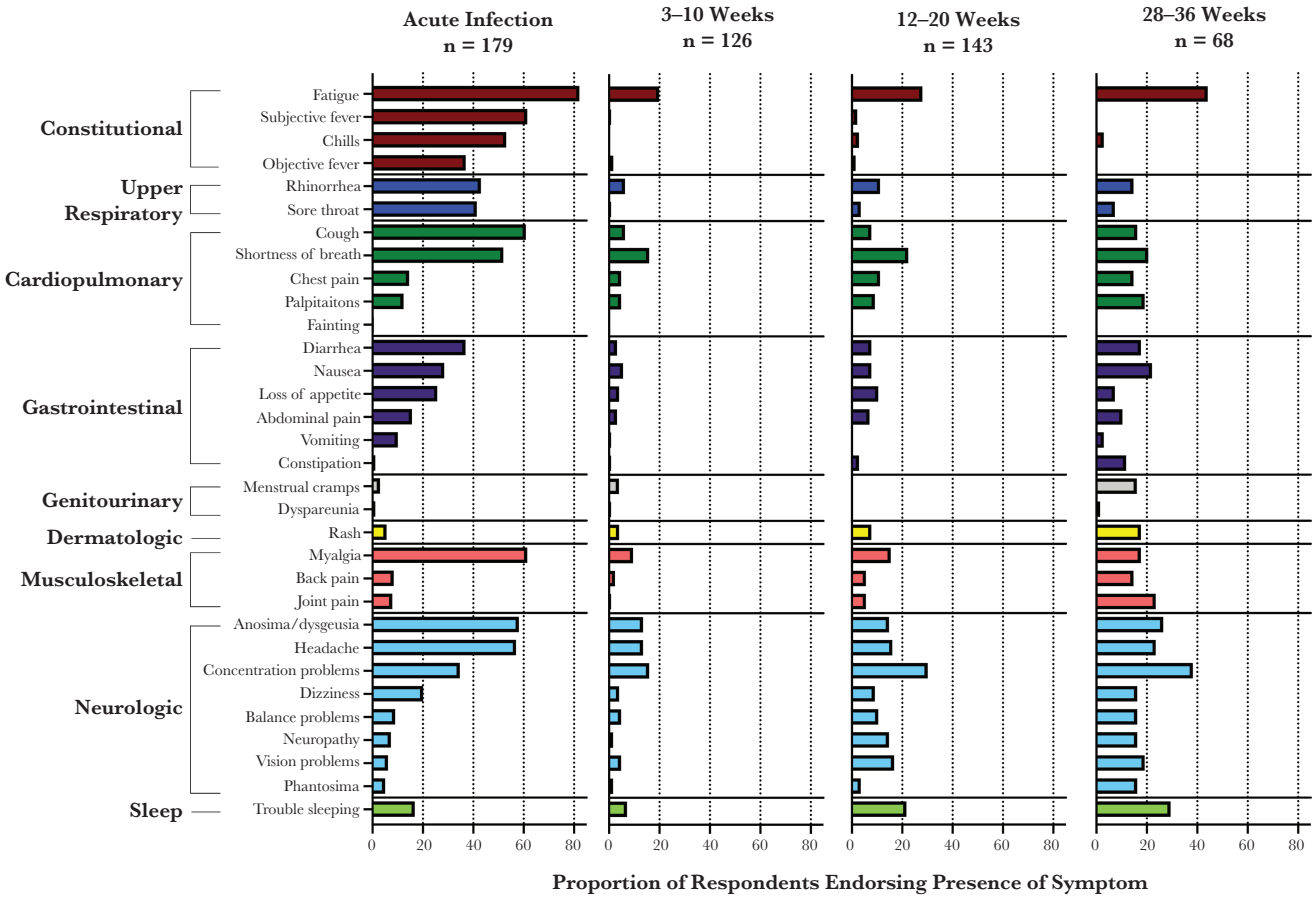

Figure 1. Prevalence of symptoms reported by participants in a study of individuals with SARS-CoV-2 infection during acute infection and 3 time points in the postacute phase. Endorsement is defined as presence of a symptom that either started or worsened at or after initial COVID-19 symptoms. Concentration problems refers to "trouble concentrating, trouble with your thinking, or trouble with your memory." Vision problems refers to "trouble with vision, for example double vision, blurry vision, or other visual issues." Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

presence of many symptoms over the study period (Figure 2). While most participants reported consistency in the presence or absence of each symptom over time, some participants reported the resolution of previously present symptoms, some reported the onset of previously absent symptoms, and some reported variability in the presence of symptoms.

Regarding mental health, some participants experienced symptoms of depression, anxiety, and post-traumatic stress during the late recovery phase (Table 3). Most of these symptoms were described as minimal or mild, but a small number of individuals experienced moderate or severe symptoms.

Clustering of Symptoms

Among 82 participants experiencing at least 1 physical symptom in the late recovery period, model-based clustering identified 2 groups of participants (Cluster 1 = 40 participants and Cluster 2 = 42 participants) in whom presence of symptoms within group members was more similar to each other than to those in the other group. The clusters are characterized by the proportion of participants experiencing each of the 7 domains of symptoms (Table 4). Silhouette scores suggest that the cluster configuration for the first cluster is strong while the second cluster is poorly configured. Participants in Cluster 1 have higher prevalence of all symptom domains except for respiratory, indicating that symptom presence across the 7 domains is, in general, positively correlated. Cluster 1 is particularly distinguished from Cluster 2 in its greater absolute difference in prevalence of fatigue, cardiopulmonary symptoms, and gastrointestinal symptoms.

Quality of Life

Measures of quality of life, which integrate across physical and mental health symptoms to depict functional impairments, showed expected high frequencies of inability to ambulate, perform self-care, and perform usual activities during the worst point of acute SARS-CoV-2 infection (Table 5). These frequencies were substantially higher than what participants reported before COVID-19. During the 2 late recovery periods, very few participants expressed moderate or more severe problems in self-care, but some reported difficulties with ambulation and performance of usual activities. Participant-rated health on a visual analogue scale of 0 to 100 was, again,

Table 2. Magnitude of Symptom Burden Among Participants who Reported Presence of Symptoms at 6, 16, and 32 Weeks After Onset of COVID-19 Symptoms; Only Symptoms That Were Endorsed by >5 Participants Are Shown

Characteristic	Week 6, No. (%)	Week 16, No. (%)	Week 32, No. (%)
Feeling tired or having low energy			
Not bothered at all[a]	1 (5.0)	1 (5.0)	1 (3.3)
Bothered a little	7 (35)	6 (30)	16 (53)
Bothered a lot	12 (60)	13 (65)	13 (43)
Cough			
Not bothered at all	1 (17)	2 (29)	2 (18)
Bothered a little	1 (17)	3 (43)	6 (55)
Bothered a lot	4 (67)	2 (29)	3 (27)
Shortness of breath			
Not bothered at all	1 (8.3)	0 (0)	0 (0)
Bothered a little	4 (33)	7 (44)	8 (62)
Bothered a lot	7 (58)	9 (56)	5 (38)
Chest pain			
Not bothered at all	0 (0)	2 (14)	2 (20)
Bothered a little	3 (38)	5 (36)	4 (40)
Bothered a lot	5 (63)	7 (50)	4 (40)
Feeling heart pound or race			
Not bothered at all	0 (0)	3 (25)	1 (9.1)
Bothered a little	4 (57)	6 (50)	5 (45)
Bothered a lot	3 (43)	3 (25)	5 (45)
Runny nose or congestion			
Not bothered at all	-	2 (25)	1 (10)
Bothered a little	-	3 (38)	6 (60)
Bothered a lot	-	3 (38)	3 (30)
Muscle aches			
Not bothered at all	0 (0)	0 (0)	0 (0)
Bothered a little	2 (25)	5 (71)	5 (42)
Bothered a lot	6 (75)	2 (29)	7 (58)
Loss of appetite			
Not bothered at all	-	7 (78)	-
Bothered a little	-	2 (22)	-
Bothered a lot	-	0 (0)	-
Nausea, gas, indigestion			
Not bothered at all	-	2 (25)	2 (13)
Bothered a little	-	3 (38)	6 (40)
Bothered a lot	-	3 (38)	7 (47)
Stomach pain			
Not bothered at all	-	-	0 (0)
Bothered a little	-	-	2 (29)
Bothered a lot	-	-	5 (71)
Constipation			
Not bothered at all	-	-	3 (38)
Bothered a little	-	-	3 (38)
Bothered a lot	-	-	2 (25)
Diarrhea or loose bowels			
Not bothered at all	-	1 (17)	3 (25)
Bothered a little	-	2 (33)	8 (67)
Bothered a lot	-	3 (50)	1 (8.3)
New spots or rash on skin			
Not bothered at all	-	3 (43)	3 (25)
Bothered a little	-	0 (0)	1 (8.3)
Bothered a lot	-	4 (57)	8 (67)
Trouble with smell or taste			
Not bothered at all	2 (25)	5 (50)	5 (29)
Bothered a little	2 (25)	3 (30)	4 (24)
Bothered a lot	4 (50)	2 (20)	8 (47)

Table 2. Continued

Characteristic	Week 6, No. (%)	Week 16, No. (%)	Week 32, No. (%)
Smelling an odor that is not actually there			
Not bothered at all	-	-	4 (36)
Bothered a little	-	-	3 (27)
Bothered a lot	-	-	4 (36)
Trouble concentrating, trouble with thinking, or trouble with memory			
Not bothered at all	1 (7.1)	1 (4)	0 (0)
Bothered a little	7 (50)	10 (40)	9 (35)
Bothered a lot	6 (43)	14 (56)	17 (65)
Headache			
Not bothered at all	0 (0)	8 (47)	0 (0)
Bothered a little	4 (40)	8 (47)	4 (27)
Bothered a lot	6 (60)	1 (5.9)	11 (73)
Trouble with vision, for example double vision, blurry vision, or other visual issues			
Not bothered at all	-	0 (0)	1 (9.1)
Bothered a little	-	4 (33)	1 (9.1)
Bothered a lot	-	8 (67)	9 (82)
Dizziness			
Not bothered at all	-	0 (0)	1 (9.1)
Bothered a little	-	4 (33)	1 (9.1)
Bothered a lot	-	8 (67)	9 (82)
Trouble with balance or feeling unsteady			
Not bothered at all	0 (0)	1 (9.1)	0 (0)
Bothered a little	4 (67)	6 (55)	4 (36)
Bothered a lot	2 (33)	4 (36)	7 (64)
Numbness, tingling, or pins and needles in arms or legs			
Not bothered at all	-	1 (10)	0 (0)
Bothered a little	-	7 (70)	3 (23)
Bothered a lot	-	2 (20)	10 (76)
Pain in arms, legs, or joints such as knees and hips			
Not bothered at all	-	0 (0)	0 (0)
Bothered a little	-	1 (17)	6 (38)
Bothered a lot	-	5 (83)	10 (63)
Back pain			
Not bothered at all	-	-	1 (11)
Bothered a little	-	-	3 (33)
Bothered a lot	-	-	5 (56)
Trouble sleeping			
Not bothered at all	1 (11)	3 (19)	1 (5.6)
Bothered a little	2 (22)	3 (19)	7 (39)
Bothered a lot	6 (66)	10 (63)	10 (56)

Abbreviation: COVID-19, coronavirus disease 2019.

[a]Responses to "When the symptom was at its worst, how much did it/does it bother you? Would you say you were not bothered at all, bothered a little, or bothered a lot?" Note: the total number of individuals experiencing each symptom at the time point can be calculated by adding the numbers of each response for the symptom at that time point.

much lower during the worst point of acute infection compared with before COVID-19 (Table 5). In the 2 late recovery periods, the median visual analogue scale value was lower than before COVID-19.

DISCUSSION

Within 2 months of the first documented case of community transmission of SARS-CoV-2 in the United States, we initiated a research cohort dedicated to studying the long-term impact of the infection. Overcoming some of the limitations of earlier work, we limited our population to participants with RNA-confirmed SARS-CoV-2 infection, included a large fraction of participants who had not been hospitalized, and extended observation to 8 months post–COVID-19 onset. We found that in the postacute phase of infection, there is a large spectrum of symptoms, ranging from generalized complaints such as fatigue to organ system–specific manifestations such as cardiopulmonary and neurocognitive symptoms to mental health symptoms of anxiety and depression. While few participants endorsed major alterations in quality of life, some individuals have not resumed normal function. Our data support emerging clinical anecdotes regarding the severity of symptoms

Figure 2. Alluvial plots representing within-person changes in symptoms over time for a subset of individuals with complete data for all 3 recovery periods (n = 38). Y refers to the endorsement of the symptom at the respective time point, and N refers to absence. Endorsement is defined as presence of a symptom that either started or worsened at or after initial COVID-19 symptoms. Symptoms showing no variability among participants are not shown. Concentration problems refers to "trouble concentrating, trouble with your thinking, or trouble with your memory." Vision problems refers to "trouble with vision, for example double vision, blurry vision, or other visual issues." Abbreviation: COVID-19, coronavirus disease 2019.

and their variability over time by providing evidence that these symptoms are of significant magnitude for many individuals, are not uniformly improving or worsening, and may cluster into distinct phenotypes. We believe that our approach to the self-reported aspects of phenotypic characterization of individuals with PASC will be critical to designing studies regarding the underlying pathogenesis of this complex condition.

Requiring an RNA-positive confirmed SARS-CoV-2 diagnosis for participation in PASC research is controversial. At certain times and places, access to testing has been limited and has disproportionately affected certain populations. Thus, excluding persons without a documented diagnosis could result in nonrepresentative study samples. On the other hand, recent work found that persistent physical symptoms were more commonly reported by persons with self-reported SARS-CoV-2 infection than those with objectively confirmed infection [22], suggesting that self-report may be misclassified. We contend that requiring a documented diagnosis depends upon the research objective. For research aimed at unraveling etiopathogenesis, like our study, we believe that specificity in eligibility criteria is paramount in order to optimize validity in the ultimate inferences. In treatment studies, more flexibility is encouraged, especially to give affected populations access to experimental therapy. In any case, any study enrolling both persons with and without documented SARS-CoV-2 infection should report findings stratified by diagnosis documentation status.

Several aspects of our symptom measurement provide greater context regarding their meaning, relevance, and utility. Throughout our interviews, we focus participants on limiting report of symptoms to those that started (or worsened) since COVID-19 onset. Interviewer-administered questionnaires allow us to achieve this emphasis. By limiting to symptoms starting (or worsening) after COVID-19 onset, we subtract the non-0 prevalence of symptoms present in any population.

Table 3. Responses Regarding Symptoms of Anxiety, Depression, and Post-traumatic Stress at 16 and 32 Weeks Following Onset of COVID-19 Among Participants Enrolled in a Study of Postacute Sequelae of SARS-CoV-2 Infection

Mental Health Symptoms and Severity	Week 16 (n = 119),[a] No. (%)	Week 32 (n = 65),[a] No. (%)
Symptoms of anxiety (GAD-7 total score)[b]		
Minimal (0–4)	68 (44)	33 (51)
Mild (5–9)	86 (56)	32 (49)
Moderate (10–14)	0 (0)	0 (0)
Severe (15–21)	0 (0)	0 (0)
Symptoms of depression (PHQ-8 total score)[b]		
None (0–4)	70 (54)	39 (54)
Mild (5–9)	19 (17)	12 (20)
Moderate (10–14)	13 (12)	5 (8.0)
Moderately severe (15–19)	4 (3.5)	3 (5.0)
Severe (20–24)	4 (3.5)	2 (3.0)
Symptoms of post-traumatic stress disorder (PCL-5 total score)[b,c]		
Score ≥10	6 (6.0)	7 (11)

Abbreviations: COVID-19, coronavirus disease 2019; GAD-7, General Anxiety Disorder–7; PCL-5, Post-traumatic Stress Disorder Checklist; PHQ-8, patient health questionnaire-8; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Twenty-four responses at week 16 and 3 responses at week 32 are not expected due to differences in form versions used at the time of participant visit.

[b]Missing and nonresponse. GAD-7: 2 missing at week 16; PHQ-8: 3 responses missing at week 16, 5 missing at week 32; PCL-5: 8 missing at week 16, 1 missing at week 32.

[c]Four-item version of Post-Traumatic Stress Disorder Checklist 5; cutoff of 10 has 76% sensitivity and 52% specificity for meeting the diagnostic criteria for post-traumatic stress disorder.

Measuring self-reported magnitude of bother caused by symptoms is more informative than a simple present vs absent. Specifically, symptoms are inherently subjective, and what, for example, "presence of fatigue" means varies by person. Degree of bother, in contrast, provides better characterization and may, when focusing only on those with the highest level of bother, sharpen analyses seeking causes of symptoms. We also evaluated within-participant variability in symptoms over time and found some participants to have a waxing and waning course. This suggests that symptom course is not merely persistent or monotonically improving or worsening. Finally, quality of life is the ultimate integral of symptoms and, usually, what matters most to patients. We expect that quality-of-life measurements will become requisite in PASC research, and its importance means that electronic medical record–based ascertainment based on routine clinical care will typically not be sufficient.

Similar to findings about symptom clustering during acute SARS-CoV-2 infection [23], we found in a preliminary analysis that domains of symptoms clustered among those who reported symptoms during the postacute phase. While our sample size precluded an analysis of clustering of more granular symptoms or the identification of specific organ system–based phenotypes, we found that participants either tended to report many symptom domains (particularly fatigue, cardiopulmonary symptoms, and gastrointestinal symptoms) or just a few. This finding provides further support to the anecdotal observation that some patients are experiencing an extensive magnitude of symptom burden. Despite the limitations of our

Table 4. Proportion of Participants Endorsing Presence of at Least 1 Symptom in the Symptom Domain, According to Cluster Status[a]

Symptom Domain	Specific Symptoms in Domain	Cluster 1 (n = 40), % (95% CI)	Cluster 2 (n = 42), % (95% CI)
Fatigue	Fatigue	90 (75–97)[b]	0 (0–10)
Upper respiratory	Runny nose and sore throat	20 (10–36)	21 (11–37)
Cardiopulmonary	Cough, chest pain, palpitation, and shortness of breath	80 (64–90)	31 (18–47)
Gastrointestinal	Abdominal pain, diarrhea, loss of appetite, and nausea	52 (36–68)	12 (4–26)
Musculoskeletal	Back pain, myalgia, and pain in the arms, legs, and joints	40 (25–57)	14 (6–29)
Neurologic	Anosmia, difficulty with concentration or memory, dizziness, dysgeusia headache, numbness, trouble with balance, and trouble with vision	92 (79–98)	69 (53–82)
Sleep	Trouble with sleep	42 (27–59)	26 (14–42)

[a]Clusters (or groups) derived from model-based clustering using the method of Marbac and Sedki [21]. Average silhouette score was 0.22; cluster-specific silhouette scores were 0.39 and 0.05 for Clusters 1 and 2, respectively.

[b]Proportion (95% CI) endorsing at least 1 symptom in the symptom domain.

Table 5. Responses Regarding Quality of Life Before COVID-19, at the Self-Described Worst Point of COVID-19, and at Weeks 16 and 32 Following Onset of COVID-19 Among Participants Enrolled in a Study of Postacute Sequelae of SARS-CoV-2 Infection

Quality of Life Domain	Response	Before Illness (n = 92)	Worst Point (n = 179)	Week 16 (n = 117)	Week 32 (n = 66)
Mobility *"Which of the following best describes your ability to walk about?"*	No problems, %	91	39	85	77
	Slight problems, %	6.0	10	9.0	11
	Moderate problems, %	2.0	29	4.0	8.0
	Severe problems, %	0	4.0	1.0	4.0
	Unable to walk, %	1.0	18	0.0	0.0
Self-care *"Which of the following describes your ability to wash and dress yourself?"*	No problems, %	95	60	96	90
	Slight problems, %	1.0	6.5	1.0	6.0
	Moderate problems, %	4.0	17	2.0	4.0
	Severe problems, %	0	1.5	1.0	0
	Unable to wash or dress, %	0	15	0	0
Usual activities *"Which of the following describes your ability to perform your usual activities?"*	No problems, %	95	31	81	77
	Slight problems, %	2.0	11	11	14
	Moderate problems, %	1.0	23	6.0	1.0
	Severe problems, %	2.0	7.0	2.0	5.0
	Unable to do usual activities, %	0	28	0	3.0
Pain/discomfort[a] *"Which of the following describes how much pain or discomfort you felt?"*	No pain or discomfort, %	70	27	65	52
	Slight pain or discomfort, %	20	13	14	26
	Moderate pain or discomfort, %	7.0	26	17	15
	Severe pain or discomfort, %	3.0	24	3.0	2.0
	Extreme pain or discomfort, %	0	10	1.0	5.0
	Unable to wash or dress, %	0	15	0	0
Anxiety/depression[a] *"Which of the following describes how anxious or depressed you felt?"*	No anxiety or depression, %	51	18	48	43
	Slight anxiety or depression, %	27	23	31	32
	Moderate anxiety or depression, %	17	24	15	14
	Severe anxiety or depression, %	2.0	17	4.0	6.0
	Extreme anxiety or depression, %	3.0	18	2.0	5.0
Visual analogue scale					
"On a scale of 0 to 100, we would like to know how good or bad your health was…"		85 (75–90)	50 (25–65)	80 (70–90)	80 (75–90)

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Not administered due to differences in form versions used at the time of participant visit: pain/discomfort: 22 from week 16 and 1 from week 32; anxiety/depression: 29 from week 16 and 1 from week 32.

sample size, we believe that this is a first step in defining different subphenotypes of PASC, which is important not only for a comprehensive clinical description of the disorder but also for investigation of pathogenesis. That is, PASC may represent several different pathophysiologic conditions. Greater specificity in outcome classification using detailed measurements as outlined here will greatly increase the efficiency and accuracy of translational research that seeks to determine biochemical causes of the various subphenotypes [24]. As a practical example, our cluster analysis supports a strategy of grouping individuals based on the number of reported symptoms for pathophysiologic studies, at least until larger data sets can be used to identify more granular phenotypic clusters.

There are multiple mechanisms that might contribute to PASC. While SARS-CoV-2 infection definitionally initiates the pathogenesis of PASC, it is unclear whether viral antigen persists beyond the acute period, either in the form of persistent virus replication [25] or persistence of noninfectious genetic material or protein in the tissues [26]. Regardless of whether the virus persists, several mechanisms that are active in the recovery phase could explain PASC. First, systemic immune activation with alterations in B- and T-cell phenotypes and elevations in plasma cytokines and inflammatory markers could underlie at least some postacute sequelae [27–29]. Second, even in the absence of systemic inflammation, local tissue inflammation or ongoing immune cell infiltration into the tissues could result in tissue injury and remodeling, which could drive PASC through processes like microbial translocation in the gut [30] or tissue fibrosis in the heart or lungs [31, 32]. Third, multiple studies, including autopsy studies, have demonstrated endotheliitis and microvascular thrombosis in acute COVID-19, with neutrophil extracellular traps as one contributing mechanism [33–38]; in addition to explaining severe disease, ongoing microvascular dysfunction may contribute to the pathobiology of PASC. Fourth, autoreactive immunity may be a significant contributor, as immunoglobulin G autoantibodies are highly prevalent in

acute infection, including those associated with clinical disease entities similar to PASC [33, 39–42]. Importantly, some mechanisms may contribute to certain organ-specific morbidity, whereas others might cause other PASC phenotypes.

Our approach has several potential limitations that we believe will be of interest to investigators seeking to study PASC. One concern is the retrospective nature of the questioning about the acute phase of illness. It is our experience that participants who received formal RNA-confirmed diagnoses of SARS-CoV-2 infection claim no difficulty in remembering what symptoms they felt during the acute period. We believe this is the case because the sociocultural context associated with SARS-CoV-2 makes it different from other common infections (eg, influenza or rhinovirus). We concede, however, that recall may be imperfect. Yet, if memory is faulty, it is not obvious that symptoms reported a few months in retrospect would be systematically over- or underestimated or that current symptom status would influence recall. Because many studies of PASC will face this same issue, the field would benefit from formal investigation of retrospective patient reports compared with clinical notes made at the time of diagnosis.

More importantly, the nature of our participant sampling process limits what we can infer about PASC. It is axiomatic that our predominantly self-referred study population might be enriched for persons experiencing persistent symptoms because they were seeking answers for this condition. This may overestimate the parameter that all patients, clinicians, and scientists wish to know, which is the prevalence (at, eg, 4 or 8 months) of persistent symptoms among all persons infected with SARS-CoV-2. Alternatively, but less likely, it may be that persons who are most severely affected may be so debilitated that they were unable to travel to our research site. Relatedly, losses during longitudinal follow-up also pose a threat to artifactually enrich the study population for those with persistent symptoms. While most of our participants who missed their 32-week window did ultimately return to the study, it remains possible that the presence or absence of persistent symptoms systematically influenced who was able to attend an on-time visit. Therefore, it will only be through population-based probability samples and high longitudinal retention that researchers can be confident that their study populations are representative of the relevant targets for descriptive research, such as the prevalence of various sequelae. For these reasons, we are not emphasizing absolute percentages of the symptoms in this report. Likewise, the percentage of study participants with persistent symptoms that others [43–45] calculate cannot be interpreted as meaningful population-level prevalence. More recent reports have studied more representative populations [46–48], but there are far too few to form a consensus on true prevalence. While our sampling approach precludes estimation of population-level prevalence of symptoms, it will support biologically oriented research on the causes of PASC, which has already begun [29, 45, 49–54].

In summary, we have established a cohort of participants enrolled in the postacute phase of SARS-CoV-2 infection and have described our approach to research-level characterization of PASC symptoms and quality of life. We found that a large array of physical and mental health symptoms are reported up to 8 months following COVID-19 onset, many patients report these symptoms to be at least somewhat bothersome, and some report these symptoms intermittently over time. In a preliminary evaluation of symptom clustering, we found at least 2 groups. Collectively, these findings suggest that PASC is not monolithic and that multiple subphenotypes may exist. The convenience nature of our sampling—like many other nascent cohorts of PASC—precludes estimation of the population-level prevalence of these persistent symptoms, but it will allow for analytic work to study the pathogenesis of PASC. Larger population-based samples will be needed for unbiased estimates of prevalence of symptoms and quality of life, robust inferences regarding symptom clustering, and comprehensive assessment of the socio-behavioral determinants of PASC.

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References

1. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med **2020**; 382:1708–20.
2. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med **2020**; 382:2372–4.
3. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA **2020**; 323:2052–9.
4. Harding L. "Weird as hell": the Covid-19 patients who have symptoms for months. Guardian. 15 May **2020**. Available at: http://www.theguardian.com/world/2020/may/15/weird-hell-professor-advent-calendar-covid-19-symptoms-paul-garner. Accessed 7 March 2021.
5. Chuck E, Edwards E. Doctors couldn't help these COVID-19 patients with their endless symptoms. So they turned to one another. NBC News. 17 May **2020**. Available at: https://www.nbcnews.com/health/health-news/doctors-couldn-t-help-these-covid-19-patients-their-endless-n1208116. Accessed 7 March 2021.
6. Horowitz J. Surviving Covid-19 may not feel like recovery for some. New York Times. 10 May **2020**. Available at: https://www.nytimes.com/2020/05/10/world/europe/coronavirus-italy-recovery.html. Accessed 7 March 2021.
7. Yong E. COVID-19 can last for several months. The Atlantic. 4 June **2020**. Available at: https://www.theatlantic.com/health/archive/2020/06/covid-19-coronavirus-longterm-symptoms-months/612679/. Accessed 7 March 2021.
8. Yong E. Long-haulers are redefining COVID-19. The Atlantic. 19 August **2020**. Available at: https://www.theatlantic.com/health/archive/2020/08/long-haulers-covid-19-recognition-support-groups-symptoms/615382/. Accessed 7 March 2021.
9. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine **2021**; 38:101019.
10. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA **2020**; 324:603–5.
11. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet **2021**; 397:220–32.
12. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network - United States, March-June 2020. MMWR Morb Mortal Wkly Rep **2020**; 69:993–8.
13. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med **2002**; 64:258–66.
14. Rabin R, Charro F de. EQ-SD: a measure of health status from the EuroQol group. Ann Med **2001**; 33:337–43.
15. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med **2006**; 166:1092–7.
16. Kroenke K, Strine TW, Spitzer RL, Williams JBW, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord **2009**; 114:163–73.
17. Cameron RP, Gusman D. The Primary Care PTSD Screen (PC-PTSD): development and operating characteristics. Primary Care Psychiatr **2003**; 9:9–14.
18. Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5): development and initial psychometric evaluation: Posttraumatic Stress Disorder Checklist for DSM-5. J Trauma Stress **2015**; 28:489–98.
19. Price M, Szafranski DD, van Stolk-Cooke K, Gros DF. Investigation of abbreviated 4 and 8 item versions of the PTSD Checklist 5. Psychiatry Res **2016**; 239:124–30.
20. Matthieu M, Mohammed S. Variable selection for model-based clustering using the integrated complete-data likelihood. Stat Comput **2015**; 27:1049–63.
21. Marbac M, Sedki M. VarSelLCM: an R/C++ package for variable selection in model-based clustering of mixed-data with missing values. Bioinformatics **2019**; 35:1255–7.
22. Matta J, Wiernik E, Robineau O, et al. Association of self-reported COVID-19 infection and SARS-CoV-2 serology test results with persistent physical symptoms among French adults during the COVID-19 pandemic. JAMA Intern Med **2022**; 182:19–25.
23. Sudre CH, Lee KA, Lochlainn MN, et al. Symptom clusters in COVID-19: a potential clinical prediction tool from the COVID symptom study app. Sci Adv. **In press**.
24. Webster AJ, Gaitskell K, Turnbull I, et al. Characterisation, identification, clustering, and classification of disease. Sci Rep **2021**; 11:5405.
25. Zheng S, Fan J, Yu F, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. BMJ **2020**; 369:m1443.
26. Gaebler C, Wang Z, Lorenzi JCC, et al. Evolution of antibody immunity to SARS-CoV-2. Nature **2021**; 591:639–44.
27. Lucas C, Wong P, Klein J, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature **2020**; 584:463–9.
28. Laing AG, Lorenc A, del Molino del Barrio I, et al. A dynamic COVID-19 immune signature includes associations with poor prognosis. Nat Med **2020**; 26:1623–35.
29. Peluso MJ, Lu S, Tang AF, et al. Markers of immune activation and inflammation in individuals with postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection. J Infect Dis. **In press**.
30. Giron LB, Dweep H, Yin X, et al. Severe COVID-19 is fueled by disrupted gut barrier integrity. bioRxiv 2020.11.13.20231209 [Preprint]. 16 November **2020**. Available at: https://doi.org/10.1101/2020.11.13.20231209. Accessed 1 September 2021.
31. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol **2020**; 5:1265–73.
32. Huang L, Zhao P, Tang D, et al. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. JACC Cardiovasc Imaging **2020**; 13:2330–9.
33. Zuo Y, Estes SK, Ali RA, et al. Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. Sci Transl Med **2020**; 12:eabd3876.
34. Gu SX, Tyagi T, Jain K, et al. Thrombocytopathy and endotheliopathy: crucial contributors to COVID-19 thromboinflammation. Nat Rev **2021**; 18:194–209.
35. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol **2020**; 7:e575–82.
36. Rauch A, Dupont A, Goutay J, et al. Endotheliopathy is induced by plasma from critically ill patients and associated with organ failure in severe COVID-19. Circulation **2020**; 142:1881–4.
37. Maccio U, Zinkernagel AS, Shambat SM, et al. SARS-CoV-2 leads to a small vessel endotheliitis in the heart. EBioMedicine **2021**; 63:103182.
38. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet **2020**; 395:1417–8.
39. Chang SE, Feng A, Meng W, et al. New-onset IgG autoantibodies in hospitalized patients with COVID-19. Nat Commun **2021**; 12:5417.
40. Zhou Y, Han T, Chen J, et al. Clinical and autoimmune characteristics of severe and critical cases of COVID-19. Clin Transl Sci **2020**; 13:1077–86.
41. Bhadelia N, Belkina AC, Olson A, et al. Distinct autoimmune antibody signatures between hospitalized acute COVID-19 patients, SARS-CoV-2 convalescent individuals, and unexposed pre-pandemic controls. bioRxiv 2021.01.21.21249176 [Preprint]. 25 January **2021**. Available at: https://doi.org/10.1101/2021.01.21.21249176. Accessed 1 September 2021.
42. Song E, Bartley CM, Chow RD, et al. Divergent and self-reactive immune responses in the CNS of COVID-19 patients with neurological symptoms. Cell Rep Med **2021**; 2:100288.
43. Logue JK, Franko NM, McCulloch DJ, et al. Sequelae in adults at 6 months after COVID-19 infection. JAMA Netw Open **2021**; 4:e210830.
44. Jacobson KB, Rao M, Bonilla H, et al. Patients with uncomplicated COVID-19 have long-term persistent symptoms and functional impairment similar to patients with severe COVID-19: a cautionary tale during a global pandemic. Clin Infect Dis **2021**; 73:e826–9.
45. Hellmuth J, Barnett TA, Asken BM, et al. Persistent COVID-19-associated neurocognitive symptoms in non-hospitalized patients. J Neurovirol **2021**; 27:191–5.
46. Blomberg B, Mohn KG-I, Brokstad KA, et al. Long COVID in a prospective cohort of home-isolated patients. Nat Med **2021**; 27:1607–13.
47. Ayoubkhani D. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK - Office for National Statistics. **2021**. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/1april2021. Accessed 7 April 2021.
48. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature **2021**; 594:259–64.

49. Peluso MJ, Deitchman AN, Torres L, et al. Long-term SARS-CoV-2-specific immune and inflammatory responses in individuals recovering from COVID-19 with and without post-acute symptoms. Cell Rep **2021**; 36:109518.
50. Peluso MJ, Takahashi S, Hakim J, et al. SARS-CoV-2 antibody magnitude and detectability are driven by disease severity, timing, and assay. Sci Adv **2021**; 7:eabh3409.
51. Peluso MJ, Thomas IJ, Munter SE, Deeks SG, Henrich TJ. Lack of antinuclear antibodies in convalescent COVID-19 patients with persistent symptoms. Clin Infect Dis **2021**;ciab890.
52. Peluso MJ, Munter SE, Lynch KL, et al. Discordant virus-specific antibody levels, antibody neutralization capacity, and T-cell responses following 3 doses of SARS-CoV-2 vaccination in a patient with connective tissue disease. Open Forum Infect Dis **2021**; 8:XXX–XX.
53. Peluso MJ, Sans HM, Forman CA, et al. Plasma markers of neurologic injury and systemic inflammation in individuals with self-reported neurologic post-acute sequelae of SARS-CoV-2 infection (PASC). bioRxiv 2021.11.02.21265778 [Preprint]. 4 November **2021**. Available at: https://doi.org/10.1101/2021.11.02.21265778. Accessed 15 November 2021.
54. Durstenfeld MS, Peluso MJ, Daniel Kelly J, et al. Role of antibodies, inflammatory markers, and echocardiographic findings in post-acute cardiopulmonary symptoms after SARS-CoV-2 infection. medRxiv 2021.11.24.21266834 [Preprint]. 26 November **2021**. Available at: https://doi.org/10.1101/2021.11.24.21266834. Accessed 1 December 2021.