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RESEARCH ARTICLE

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Post-sequelae symptoms and comorbidities after COVID-19

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Abstract

The frequency, severity, and forms of symptoms months after coronavirus 2019 (COVID-19) are poorly understood, especially in community settings. To better understand and characterize symptoms months after community-based COVID-19, a retrospective cohort analysis was conducted. Three hundred and twenty-eight consecutive persons with a positive test for SARS-CoV-2 in the Johns Hopkins Health System, Maryland, March–May 2020, were selected for the study. Symptom occurrence and severity were measured through questionnaires. Of 328 persons evaluated, a median of 242 days (109–478 days) from the initial positive SARS-CoV-2 test, 33.2% reported not being fully recovered and 4.9% reported symptoms that constrained daily activities. Compared to those who reported being fully recovered, those with post-acute sequelae were more likely to report a prior history of heart attack ($p < 0.01$). Among those reporting long-term symptoms, men and women were equally represented (men = 34.8%, women = 34.6%), but only women reported symptoms that constrained daily activities, and 56% of them were caregivers. The types of new or persistent symptoms varied, and for many, included a deviation from prior COVID-19 health, such as being less able to exercise, walk, concentrate, or breathe. A limitation is that self-report of symptoms might be biased and/or caused by factors other than COVID-19. Overall, even in a community setting, symptoms may persist months after COVID-19 reducing daily activities including caring for dependents.

KEYWORDS

long-haul, post-COVID-19, SARS-CoV-2, sequela

1 | INTRODUCTION

Although more than 90% of those with coronavirus 2019 (COVID-19) survive, the proportion who are fully recovered 3–12 months after the initial infection is varied, as are the types and frequencies of residual sequelae. As initial infection severity might alter symptom persistence and most SARS-CoV-2 infected persons are never hospitalized, the paucity of long-term outpatient data is especially salient.

2 | METHODS AND STUDY DESIGN

We contacted consecutive adults with SARS-CoV-2 infection confirmed at Johns Hopkins Medical Institutions from March–May 2020 ($n = 328$). Additional participants were sampled from the Johns Hopkins HOPE Registry, which includes persons who tested positive for SARS-CoV-2 from April–November 2020 and indicated an interest in research studies ($n = 179$). Consented participants were administered a

TABLE 1 Clinical and demographic characteristics of consecutive case series and HOPE Registry participants by recovery status

Characteristics	Johns Hopkins consecutive case series, *N* (%)				Johns Hopkins HOPE Registry, *N* (%)			
	Fully recovered (*n* = 203)	Symptomatic but functional (*n* = 109)	Symptomatic and limited (*n* = 16)	X^2, *p* value*	Fully recovered (*n* = 103)	Symptomatic but functional (*n* = 58)	Symptomatic and limited (*n* = 18)	X^2, *p* value*
Race								
White	134 (66)	73 (67)	8 (50)	0.40	87 (85)	49 (85)	16 (89)	0.55
Black/African American	51 (25)	22 (20)	6 (37.5)	0.27	6 (6)	8 (14)	0 (0)	0.16
Asian	8 (4)	4 (5.5)	2 (12.5)	0.25	5 (5)	3 (5)	0 (0)	0.06
Other/mixed race	14 (7)	14 (13)	1 (6)	0.20	6 (6)	2 (3)	2 (11)	0.64
Median age (range), years	43 (19–87)	47 (21–78)	45 (25–63)		44 (18–87)	40.5 (20–67)	41 (21–67)	
Ethnicity								
Hispanic	44 (22)	28 (26)	2 (12.5)	0.44	11 (11)	4 (7)	1 (6)	0.71
Gender								
Male	87 (43)	46 (42)	0 (0)	0.10	37 (38)	15 (28)	4 (19)	0.38
Female	113 (56)	62 (57)	16 (100)		60 (61)	39 (72)	14 (82)	
Nonbinary	3 (2)	1 (1)	0 (0)		1 (1)	0	0	
Education								
No/primary school	14 (7)	7 (7)	2 (12.5)	0.81	2 (2)	0 (0)	0 (0)	0.67
Any high school	28 (14)	21 (19)	1 (6)	0.26	1 (1)	2 (3)	2 (11)	0.11
Any college	89 (43)	45 (41)	9 (56)	0.53	45 (44)	35 (60)	9 50)	0.18
Any graduate school	72 (35)	36 (33)	4 (25)	0.67	54 (53)	21 (36)	7 (39)	0.14
Higher risk occupations								
Health care worker in hospital	46 (23)	23 (21)	5 (31)	0.66	20 (19)	9 (17)	5 (29)	0.46
Health care worker in community	16 (8)	11 (10)	1 (6)	0.76	5 (5)	7 (12)	1 (6)	0.37
Nursing home staff	3 (1)	3 (3)	1 (6)	0.38	1 (1)	0 (0)	0 (0)	0.86
Teacher K-12	5 (2)	3 (3)	0 (0)	0.80	3 (3)	2 (3)	0 (0)	0.88
Cleaning (office/home)	6 (3)	6 (5.5)	2 (12.5)	0.14	-	-	-	-
Fire/police/EMT	4 (2)	5 (5)	0 (0)	0.32	1 (1)	1 (3)	2 (11)	0.11
Transportation worker	3 (1)	3 (3)	0 (0)	0.62	-	-	-	-
Caregiver for a dependent in your home	69 (34)	43 (41)	9 (56)	0.15	26 (26)	18 (33)	7 (44)	0.58

(Continues)

TABLE 1 (Continued)

Characteristics	Johns Hopkins consecutive case series, *N* (%)				Johns Hopkins HOPE Registry, *N* (%)			
	Fully recovered (*n* = 203)	Symptomatic but functional (*n* = 109)	Symptomatic and limited (*n* = 16)	X^2, *p* value*	Fully recovered (*n* = 103)	Symptomatic but functional (*n* = 58)	Symptomatic and limited (*n* = 18)	X^2, *p* value*
Time since infection								
0–3 months	5 (2)	5 (5)	0 (0)	0.85	33 (32)	14 (24)	3 (17)	0.49
3–6 months	21 (10)	10 (9)	2 (12.5)		26 (25)	18 (31)	3 (17)	
6–9 months	109 (54)	55 (50)	7 (44)		24 (23)	13 (22)	8 (44)	
9–11 months	68 (33.5)	39 (36)	7 (44)		20 (19)	13 (22)	4 (22)	
Medical care during acute COVID-19								
Hospitalized	21 (10)	27 (25)	5 (31)	0.001	3 (3)	4 (7)	5 (28)	0.002
Outpatient	180 (90)	82 (75)	11 (69)		100 (97)	54 (93)	13 (72)	
Baseline comorbidities								
Diabetes	14 (7)	16 (15)	2 (12.5)	0.08	4 (4)	4 (7)	0 (0)	0.70
Chronic heart disease	5 (2.5)	8 (61)	0 (0)	0.08	4 (4)	1 (2)	1 (6)	0.86
History of heart attack	0 (0)	5 (5)	0 (0)	<0.01	0 (0)	1 (2)	0 (0)	0.69
High blood pressure	48 (24)	29 (27)	1 (6)	0.20	25 (25)	12 (22)	2 (6)	0.10
High cholesterol	43 (21)	22 (20)	1 (6)	0.36	21 (21)	9 (17)	0 (0)	0.30
History of stroke	1 (0.5)	1 (1)	1 (6)	0.07	3 (3)	0 (0)	1 (6)	0.58
Autoimmune disorder	14 (7)	8 (7)	0 (0)	0.54	7 (7)	6 (11)	2 (12)	0.72
Asthma/reactive airway	28 (14)	20 (18)	5 (31)	0.14	11 (11)	7 (13)	2 (12)	0.96
Chronic lung disease	4 (2)	2 (2)	0 (0)	0.85	3 (3)	0 (0)	1 (6)	0.58
Chronic kidney disease	3 (1)	3 (3)	0 (0)	0.62	3 (3)	0 (0)	0 (0)	0.63
Cancer	9 (4)	5 (5)	1 (6)	0.94	4 (4)	0 (0)	0 (0)	0.48
Depression	23 (11)	16 (15)	3 (19)	0.54	14 (14)	12 (22)	8 (47)	0.009
Anxiety	27 (13)	20 (18)	5 (31)	0.11	21 (21)	19 (35)	9 (53)	0.003
Pregnant	4 (2)	3 (3)	0 (0)	0.75	2 (2)	0 (0)	0 (0)	0.79
Overweight/obese	60 (30)	35 (32)	9 (56)	0.09	27 (27)	27 (50)	7 (41)	0.08

*p values refer to the probability that there is no difference in the factors shown across the comparison groups.

questionnaire by phone which queried the severity of initial and current symptoms and asked persons to rate their overall functional ability. Data were recorded electronically with the secure, web-based software platform RedCap (Research Electronic Data Capture)[1,2] and analyzed in STATA/MP 16.1 (StataCorp). Study procedures were approved by the Institutional Review Board of the Johns Hopkins Medical Institutions and all participants provided consent.

3 | RESULTS

The 328 cases (59% women) had a mean age of 47.6 years (range, 19–87 years) (Table 1). Seven women were pregnant. The median time between testing reverse transcriptase polymerase chain reaction positive and completing the interview was 242 days (range, 109–478 days). The majority of case participants remained outpatients (84%), but some individuals required hospitalization (16%). Overall, 61.9% of participants reported being fully recovered, 33.2% reported persistent symptoms but were able to perform daily activities (symptomatic but functional), and 4.9% reported symptoms that constrained daily activities (symptomatic and limited). The distribution of recovery status did not vary significantly by time since symptom onset up to 15.9 months ($p = 0.85$). This lack of correlation between the percentage who reported symptom persistence and time from symptom onset was true both for those with symptoms but were functional (3–6 months = 9%, 6–9 months = 50%, 9+ months = 36%) and for those with symptoms that limited daily activities, (3–6 months = 12.5%, 6–9 months = 44%, 9+ months = 44%).

The types of new or persistent symptoms reported varied considerably in form and severity post-infection, and no single symptom was present in the majority of those recovering.

The principal differences before the diagnosis of COVID-19 across the three groups were that those with persistent symptoms were more likely to report an antecedent heart attack ($p < 0.01$). Contemporaneous with the diagnosis of COVID-19, those individuals reporting persistent symptoms were more likely to have shortness of breath, pressure in the chest or tightness, lack of energy, dizziness, hallucinations, joint aches, loss of taste, loss of smell, nausea/vomiting, and diarrhea compared to those fully recovered ($p < 0.05$) (Table 2a). There was no variability in recovery status by age, and too few persons

TABLE 2a Frequency of initial symptoms (2 weeks pre-/post-testing) by recovery status in the consecutive case series

	Fully recovered ($n = 203$), n (%)	Symptomatic but functional ($n = 109$), n (%)	Symptomatic and limited ($n = 16$), n (%)	X^2, p value*
Respiratory				
Sore throat	52 (26)	33 (30)	7 (44)	0.24
Runny nose	27 (13)	21 (19)	4 (25)	0.22
Shortness of breath	59 (29)	61 (56)	12 (75)	<0.0001
Pressure in chest/tightness	40 (20)	42 (38)	9 (56)	<0.0001
Persistent cough	99 (49)	65 (60)	10 (62)	0.14
Systemic				
Any fever	129 (60)	75 (68)	11 (73)	0.71
Headache	96 (48)	64 (58)	11 (69)	0.06
Joint aches	52 (26)	29 (27)	9 (56)	0.03
Muscle aches	111 (55)	58 (53)	10 (62)	0.78
Lack of energy	132 (65)	94 (86)	16 (100)	<0.0001
Chills	85 (42)	53 (49)	10 (62)	0.19
Gastrointestinal				
Loss of appetite	63 (31)	42 (38)	7 (44)	0.29
Nausea/vomiting	34 (17)	30 (27)	8 (50)	0.002
Diarrhea	44 (22)	37 (34)	8 (50)	0.007
Neurologic				
Dizziness	15 (7)	12 (11)	7 (44)	<0.0001
Hallucinations	5 (2.5)	6 (5.5)	4 (25)	<0.0001
Loss of smell	86 (43)	61 (56)	11 (68)	0.02
Loss of taste	55 (27)	46 (42)	7 (44)	0.02

*p values refer to probability that there is no difference in the factors shown across the comparison groups.

TABLE 2b Frequency of initial symptoms (2 weeks pre-/post-testing) by recovery status in the HOPE registry

	Fully recovered (n = 103), n (%)	Symptomatic, functional (n = 58), n (%)	Symptomatic, limited (n = 18), n (%)	X^2, p value
Respiratory				
Sore throat	29 (28)	24 (41)	11 (61)	0.03
Runny nose	18 (17)	17 (29)	2 (11)	0.21
Shortness of breath	25 (24)	21 (36)	14 (78)	<0.0001
Pressure in chest/tightness	17 (38)	14 (31)	14 (31)	<0.0001
Persistent cough	51 (50)	38 (65)	14 (78)	0.04
Systemic				
Any fever	82 (52)	43 (31)	13 (72)	0.47
Headache	51 (50)	43 (74)	11 (61)	0.01
Joint aches	16 (15)	19 (33)	8 (44)	0.004
Muscle aches	49 (48)	36 (62)	13 (72)	0.09
Lack of energy	75 (73)	51 (88)	17 (94)	0.04
Chills	37 (36)	25 (43)	8 (44)	0.46
Gastrointestinal				
Loss of appetite	21 (39)	21 (39)	10 (19)	0.003
Nausea/vomiting	15 (15)	16 (28)	4 (22)	0.23
Diarrhea	17 (17)	14 (24)	7 (39)	0.15
Neurologic				
Dizziness	4 (4)	10 (17)	4 (22)	<0.0001
Hallucinations	1 (1)	5 (9)	2 (11)	0.06
Loss of smell	45 (44)	40 (69)	15 (83)	0.001
Loss of taste	38 (37)	38 (65)	12 (67)	0.001

received COVID-19 specific treatments (i.e., convalescent plasma, remdesivir) (n < 5) to evaluate recovery impact. Interestingly, all of those with significantly limiting symptoms were women (n = 16) and 56% were responsible for the care of another person (Table 1).

Some additional differences were evident among those with persistent symptoms. Compared to the 109 who were symptomatic but still able to perform daily roles (functional), the 16 individuals with post-acute symptoms that were limiting were more likely to report an inability to walk long distances (25% vs. 5.5%, p = 0.007) or walk-upstairs (31% vs. 6%, p = 0.002) and to report new heart problems (12.5% vs. 2% p = 0.02) (Table 3a).

As they self-selected COVID-19 research instead of being contacted consecutively from a list testing SARS-CoV-2 positive, we separately analyzed an additional 179 individuals who participated in the Johns Hopkins HOPE Registry. Those in the HOPE Registry who continued to experience symptoms reported initially experiencing nearly all the presenting symptoms more often than those whose symptoms had resolved (Tables 2b and 3b). Shortness of breath and pressure/tightness in the chest was a presenting symptom across both studies in those that reported symptoms but limited function.

4 | DISCUSSION

In this study, persistent symptoms were reported by 40% of the study participants a median of 8 months (242 days) after SARS-CoV-2 infection, a majority of whom remained outpatients. No single organ system was uniformly affected, with symptoms ranging from neurocognitive to respiratory and musculoskeletal. However, many reported a clear, persistent decline from their pre-COVID-19 health condition with 4.9% reporting severe limitations in performing daily activities. Interestingly, the prevalence of persistent symptoms did not appreciably decline with time from infection onset, even for those whose symptoms were so severe as to limit their daily activities. This finding underscores the importance of efforts to prevent SARS-CoV-2 infections and research to understand and combat the long-term morbidity.

Our findings are consistent with another study that has systematically characterized the spectrum of symptoms in an ambulatory setting.[3] A median of 169 days after illness, Logue and coworkers reported that at least one symptom persisted in 49 (32.7%) of 150 Seattle, WA outpatients and 5 (31.3%) of 16 hospitalized patients. Other reports from primarily severe, and in some cases hospitalized, patients found a higher estimated prevalence of persistent

TABLE 3a Frequency and type of persistent or new symptoms post-SARS-CoV-2 infection in those who have not fully recovered[a]

Continued or new symptoms	Symptomatic but functional (n = 109), n (%)	Symptomatic and limited (n = 16), n (%)	X^2, p value
Muscle or joint aches	14 (13)	4 (25)	0.20
Shortness of breath	16 (15)	4 (25)	0.29
Persistent cough	2 (2)	1 (6)	0.28
Lower energy/increased tiredness	30 (27)	3 (19)	0.46
Cannot walk long distances	6 (5.5)	4 (25)	0.007
Cannot walk upstairs	7 (6)	5 (31)	0.002
Cannot exercise like I did before	15 (14)	5 (31)	0.07
New heart problems	2 (2)	2 (12.5)	0.02
Loss of smell	15 (14)	1 (6)	0.40
Loss of taste	16 (15)	2 (12.5)	0.82
Brain fog/inability to concentrate	14 (13)	4 (25)	0.20
Anxiety	5 (5)	0 (0)	0.38
Stress	5 (5)	0 (0)	0.38

[a]Data are self-reported by participants at the time of interview, which occurred a median of 8 months after positive SARS-CoV-2 RNA test.

TABLE 3b Frequency and type of persistent or new symptoms post-SARS-CoV-2 infection in those who have not fully recovered as part of the HOPE registry[a]

Continued or new symptoms	Symptomatic but functional (n = 58), n (%)	Symptomatic and limited (n = 18), n (%)	X^2, p value
Muscle or joint aches	8 (15)	6 (33)	<0.0001
Shortness of breath	3 (6)	11 (61)	<0.0001
Persistent cough	3 (6)	2 (12)	<0.0001
Lower energy/increased tiredness	12 (22)	17 (94)	<0.0001
Cannot walk long distances	2 (4)	8 (44)	<0.0001
Cannot walk upstairs	3 (6)	8 (44)	<0.0001
Cannot exercise like I did before	5 (9)	10 (55)	<0.0001
New heart problems	5 (9)	5 (28)	<0.0001
Loss of smell	20 (37)	5 (28)	<0.0001
Loss of taste	12 (22)	2 (11)	<0.0001
Brain fog/inability to concentrate	7 (13)	10 (55)	<0.0001
Anxiety	1 (2)	4 (22)	<0.0001
Stress	0 (0)	3 (17)	<0.0001

[a]Data are self-reported by participants at the time of interview, which occurred a median of 5.9 months after positive SARS-CoV-2 RNA test.

symptoms. For example, Carfi and coworkers reported on 143 individuals in Italy a mean of 60.3 days after initial symptom onset and only 18 persons (12.6%) were completely free of SARS-CoV-2 related symptoms.[4] Similarly, Huang and colleagues evaluated 1733 patients 6 months after COVID-19 hospitalization and 76% of these patients reported at least one symptom.[5] Additional community-based efforts are needed to determine the burden of long-term COVID-19 symptoms at the population level.

Interestingly, we did not detect differences in post-SARS-CoV-2 sequalae by age. However, there was a distinct sex difference, with women having more severe post-acute symptom persistence than men. Other sex differences have been described with SARS-CoV-2, including

lower anti-SARS-CoV-2 antibody titers[6] or loss of antibodies.[7] The significance of this finding is underscored in view of the disproportionate burden of dependent care born by women, as reported by half of those with significant functional limitations in our study.

In this study, there were two sources of patients: those we consecutively called from a list of persons testing positive and the other persons who on their own initiative signed up for a COVID-19 registry and volunteered to participate in research. Although a greater proportion reporting severe limitations would be expected in the voluntary registry, the proportions were not markedly different. Instead, we noticed that those in the registry with limitations from symptoms were more likely to report nearly all symptoms on infection onset. They recalled being sicker when they were first diagnosed. In addition, those who volunteered to participate reported more depression and anxiety as pre-existing comorbidities. These differences underscore the importance of appreciating the source of persons recruited for studies of the post-COVID-19 sequelae, which might contribute to some of the differences in studies mentioned above.

One limitation of this and existing studies is the absence of detailed health examinations before and during the course of SARS-CoV-2 infection. It is possible that the recall of symptoms and their attribution to the SARS-CoV-2 infection is biased. Public awareness of the potential for symptom persistence might also affect reporting months later. However, the inclusion of all individuals who tested positive for SARS-CoV-2 may have reduced some of the bias from self-report. These consecutive case series participants reported fewer overall presenting and persistent symptoms as compared to those who entered our study by contacting the Johns Hopkins HOPE Registry. It's likely that those who experience persistent symptoms and limitations on their daily function may be more motivated to seek out related research and report their symptoms. It is also notable that other studies have used different instruments to assess symptoms after COVID-19. For example, O'Connor and coworkers used accepted psychometric measures to characterize the COVID-19 Yorkshire Rehabilitation Scale.[8] The apparent types and severity of post-COVID-19 symptoms might differ based on the instruments used. That used in the present study is available online (Supporting Information Data).

In summary, up to 15 months after SARS-CoV-2 infection, persistent symptoms are common in ambulatory and hospitalized patients. More research is needed to understand why only some persons fully recover and to promote more rapid recovery among others.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

All authors reviewed and approved the manuscript. Priya Duggal, Shruti H. Mehta, and David L. Thomas designed the study, primarily wrote the paper, and managed institutional, financial, and ethical reviews, and performed the analyses. Priya Duggal, Tristan Penson, Hannah N. Manley, Candelaria Vergara, Rebecca M. Munday, Dylan Duchen, Elizabeth A. Linton, Amber Zurn, and Jeanne C. Keruly participated in the study design, pilot-tested instruments, obtained informed consent, and conducted the surveys.

DATA AVAILABILITY STATEMENT

The instrument used to produce these data is available in the Online Supporting Information Data. In addition, de-identified summary data can be obtained by email to one of the communicating authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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