Prevalence and predictors of persistent post-COVID-19 symptoms

Jose Estrada-Codecido MSc[1], Adrienne K Chan MD, MPH[2,3], Nisha Andany MD, MPH[2,3], Philip W Lam MD, BScPhm[2,3], Melody Nguyen MD[4], Ruxandra Pinto PhD[1], Andrew Simor MD[2,3], Nick Daneman MD, MSc[2,3]

BACKGROUND: The pandemic has affected hundreds of millions of people; early reports suggesting high rates of prolonged symptoms may be prone to selection bias. **METHODS:** In a program caring for all SARS-CoV-2 positive inpatients and outpatients between March to October 2020, and offering universal 90-day follow-up, we compared those who died prior to 90 days, not responding to follow-up, declining, or accepting follow-up. Among those seen or declining follow-up, we determined the prevalence and predictors of persistent symptoms. **RESULTS:** Among 993 patients, 21 (2.1%) died prior to 90 days, 506 (50.9%) did not respond, 260 (26.1%) declined follow-up because they were well, and 206 (20.7%) were fully assessed. Of 466 who responded to follow-up inquiry, 133 (28.5%) reported ≥1 persistent symptom, including constitutional (15.5%), psychiatric (14.2%), rheumatologic (13.1%), neurologic (13.1%), cardiorespiratory (12.0%), and gastrointestinal (1.7%). Predictors differed for each symptom type. Any persistent symptom was more common in older patients (adjusted odds ratio [aOR] 1.11, 95% CI 1.04 to 1.18/5 years), those diagnosed in hospital (aOR 2.03, 95% CI 1.24 to 3.33) and those with initial constitutional and rheumatologic symptoms. Patients not responding to follow-up were younger and healthier at baseline. **CONCLUSION:** Persistent symptoms are common and diverse 3 months post-COVID-19 but are likely over-estimated by most reports.

KEYWORDS: COVID-19, outpatients, persistent symptoms, post-COVID-19, prevalence

HISTORIQUE : La pandémie touche des centaines de millions de gens. Les rapports précoces laissant croire à des symptômes prolongés pourraient être assujettis à un biais de sélection. **MÉTHODOLOGIE :** Dans un programme de soins auprès de tous les patients ambulatoires et hospitalisés ayant reçu un résultat positif au SRAS-CoV-2 entre mars et octobre 2020, assorti d'un suivi universel de 90 jours, les chercheurs ont comparé les personnes qui ont succombé avant 90 jours, n'ont pas répondu au suivi ou ont décliné ou accepté le suivi. Chez celles qui ont été vues ou ont décliné le suivi, ils ont déterminé la prévalence et les prédicteurs de symptômes persistants. **RÉSULTATS :** Chez les 993 patients, 21 (2,1 %) sont décédés avant les 90 jours, 506 (50,9 %) n'ont pas répondu, 260 (26,1 %) ont décliné le suivi parce qu'ils se sentaient bien et 206 (20,7 %) se sont soumis à une évaluation complète. Des 466 qui ont répondu à l'offre de suivi, 133 (28,5 %) ont signalé ressentir au moins un symptôme persistant, y compris d'ordre constitutionnel (15,5 %), psychiatrique (14,2 %), rhumatologique (13,1 %), neurologique (13,1 %), cardiorespiratoire (12,0 %) et gastro-intestinal (1,7 %). Les prédicteurs différaient en fonction de chaque type de symptômes. Les symptômes persistants étaient courants chez les personnes âgées (rapport de cotes corrigé [RCc] 1,11, IC à 95 %, 1,04 à 1,18/cinq ans), les personnes diagnostiquées à l'hôpital (RCc 2,03, IC à 95 %, 1,24 à 3,33) et celles dont les manifestations initiales comportaient des symptômes constitutionnels et rhumatologiques. Les patients qui ne répondaient pas au suivi étaient plus jeunes et en meilleure santé au départ. **CONCLUSION :** Les symptômes persistants sont courants et diversifiés trois mois après la COVID-19, mais sont probablement surestimés dans la plupart des rapports.

MOTS-CLÉS : COVID-19, patients ambulatoires, post-COVID-19, prévalence, symptômes persistants

[1]Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; [2]Department of Medicine, University of Toronto, Toronto, Ontario, Canada; [3]Division of Infectious Diseases, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; [4]Division of Physical Medicine & Rehabilitation, Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Correspondence: Nick Daneman, Sunnybrook Health Sciences Centre, Department of Medicine, Infectious Diseases Division, 2075 Bayview Avenue, Room H259, Toronto, Ontario M4N 3M5 Canada. Telephone: 416-480-6100 ext.3862. E-mail: nick.daneman@sunnybrook.ca

COVID-19 has affected more than 200 million people and resulted in more than 4 million deaths worldwide ([1]). In addition, COVID-19 has had a profound impact on health care systems and economies globally. In Canada, the first case of COVID-19 occurred in January 2020 ([2]), and since then there have been more than 2 million confirmed cases and over 30,000 deaths across the country ([3]).

Initial reports from China, where the pandemic originated, indicate that the vast majority of individuals affected by COVID-19 (81%) will experience mild symptoms. Approximately 14% develop a severe infection and 5% will experience critical illness ([23]). The predictors of severe outcomes during initial infection have been extensively studied, and include older age, medical comorbidities, obesity, and certain laboratory parameters such as lymphopenia and elevated inflammatory markers ([4]–[6]).

Although the manifestations and spectrum of acute COVID-19 have been well described, ([7]–[10]) very little is known about the intermediate and long-term sequela of COVID-19. Most studies of long-term follow-up and outcomes have focused on patients requiring hospitalization for severe COVID-19 and suggest that the majority of those individuals are still experiencing residual symptoms up to 6 months post-illness onset ([8],[11]). However, less is known about the long-term prognosis across the full spectrum of acute COVID-19 illness, particularly those with mild-moderate infection who do not require hospitalization. As these individuals account for more than 80% of those affected by COVID-19, it is important to assess the longer-term effect of COVID-19 infection in this population.

Therefore, we conducted a cohort study to describe the prevalence and nature of COVID-19 symptoms 90 days post-infection, across the full spectrum of illness severity and to evaluate predictors of persistent constitutional, upper respiratory, lower respiratory, rheumatologic, neurologic, gastrointestinal, and psychiatric symptoms.

METHODS

Study design and participants

This is a retrospective cohort study of all consecutive patients included in the COVID-19 Expansion to Outpatients (COVIDEO) program at Sunnybrook Health Science Centre (SHSC), from March 2020 to October 2020. SHSC is a 678-bed tertiary-care teaching hospital in Toronto, Ontario, Canada.

COVIDEO is an inter-disciplinary collaboration between Infectious Diseases, Microbiology, Infection Prevention and Control, and Public Health. A full description of the program has been previously published ([12]). Testing could have been performed at the COVID-19 assessment centre (CAC), emergency department (ED), occupational health and safety (OHS), inpatient ward, or any SHSC-affiliated outpatient clinic. Occasionally, patients and/or health care workers who were tested at a different facility were enrolled into the program based on referral by a SHSC-based physician or the OHS department. Assessments were conducted virtually (either by telephone or video). All patients were offered an initial baseline assessment by either a physician or nurse practitioner. Further follow-up during the acute phase of illness was at the discretion of the clinician doing the initial assessment, but 90-day in-person follow-up was offered to all patients. First, all COVIDEO patients were contacted after 90 days via email survey inquiring about ongoing complications requiring a clinical follow-up, current symptoms and return to functional baseline. Then, patients who replied that they were having symptoms or those who wanted a follow-up were contacted individually via phone call to schedule an appointment.

Data collection

We reviewed patients' electronic medical records to collect data from baseline COVIDEO assessments and 90-day follow-up assessments, which includes information on demographics, exposure, household contacts, past medical history, laboratory tests, and physical examination. This initial assessment was essential to accurately determine the prevalence of persistent symptoms among the overall population of patients with COVID-19 (to avoid selection bias related to only capturing those requiring or requesting clinical follow-up).

Data analysis

Baseline characteristics for the cohort were described with medians and interquartile ranges (for continuous variable) or frequencies and percentages (for categorical variables). The prevalence of

individual symptoms was described for both initial illness and 90-day follow-up. We then grouped individual symptoms into different systems to facilitate more detailed analyses, including: constitutional symptoms (fever, chills, lymphadenopathy, fatigue), upper respiratory (pharyngitis, rhinorrhea, otalgia, conjunctivitis), cardiorespiratory (chest pain, cough, sputum, hemoptysis, dyspnea), gastrointestinal (abdominal pain, nausea, vomiting, diarrhea), rheumatologic (myalgia, arthralgia, rash, hair loss), neurologic (anosmia, dysgeusia, headache, confusion), and psychiatric symptoms (depression, anxiety, insomnia, anorexia). For this analysis, patients were stratified as outpatients (patients tested at the CAC, OHS, dialysis, clinic, or Toronto Public Health) and in-hospital (tested in the ward or ED). We used medians and inter-quartile range for continuous variables, and frequency and percentages for categorical variables.

Bivariate analyses (chi-square test and unadjusted logistic regression) were used to assess potential predictors of persistent symptoms at 90-day follow-up. Predictors of interest included age, sex, presence of a cardiorespiratory comorbidity (asthma, cardiovascular diseases, or chronic lung disease), presence/absence of each symptom group at baseline assessment, location at time of test (outpatient versus in-hospital), and requirement for hospital admission at any time during the course of illness. These analyses were performed separately for the presence of any persistent individual symptom, and then again for the presence of persistent constitutional, upper respiratory, cardiovascular, gastrointestinal, rheumatologic, neurologic, and psychiatric symptoms.

We then performed multivariable logistic regression, incorporating these same pre-specified predictor variables. One multivariable logistic regression model was performed for the outcome of any persistent symptom at 90-day follow-up. Separate multivariable models were then carried out for the presence of persistent constitutional, upper respiratory, cardiovascular, gastrointestinal, rheumatologic, neurologic, and psychiatric symptoms. However, regression models were not conducted for outcomes with insufficient events. Models were exploratory across multiple symptom group outcomes and so we did not perform correction for multiple hypothesis testing. All analyses were performed in SAS Studio Version 5.2 (Cary, NC).

RESULTS

Patients assessed by COVIDEO

Between March 2020 and October 2020, 993 patients were assessed by the COVIDEO program (Table 1). Approximately half of the patients were female (n = 514, 51.7%), and the median age was 38 years (IQR 27–57). Most of the patients assessed by COVIDEO were tested at the outpatient CAC (707, 71.1%). At initial presentation, the most commonly reported symptoms were constitutional symptoms in 629 (63.2%) of patients. 145 patients (14.5%) were hospitalized within 30 days of diagnosis, of which most (140, 96.6%) were already hospitalized at time of testing, 44 (4.4%) required ICU admission, and 34 (3.4%) required mechanical ventilation.

Availability for follow-up assessment at 90 days

Among the cohort of patients, 21 (2.1%) died prior to 90 day follow up assessment, 506 (50.9%) did not respond to the offer for follow-up visit, 260 (26.1%) declined follow-up because they were feeling well, and 206 (20.7%) participated in a complete 90-day follow-up assessment. Therefore, information on follow-up symptoms was available for 466 (46.8%) of patients (Table 1). Notably, the patients that did not respond to the offer for follow-up assessment were younger, had fewer comorbidities, and were more likely to have been diagnosed in the outpatient setting (Table 1). Among the 206 patients seen in clinic for a complete 90-day assessment, 133 patients (64.5%) reported at least one residual symptom. Even though more than half of the patients reported at least one symptom, the vast majority (191/206, 93.2%) reported feeling 'back to baseline' during the 90-day assessment.

Baseline symptoms by test location

Baseline characteristics and outcomes of patients are described and categorized by test location in Table 2; overall rates of persistent symptoms are described in Figure 1. The total number of patients tested at the outpatient CAC and in-hospital (ED or ward) reporting at least one symptom at initial assessment was 246 (56.6%) and 133 (95%), respectively. Furthermore, the most common reported group of symptoms among those tested as outpatients or in-hospital were constitutional in 178 (40.9%) and 109 (77.9%) patients, respectively.

Prevalence of symptoms after 90 days

Long-term and persistent symptoms among patients with a 90-day assessment are summarized in Figure 1. Just under a third of patients reported persistent symptoms after 90 days from diagnosis (133/466, 28.5%). Constitutional, psychiatric, rheumatologic, and neurological symptoms were the most prevalent symptom groups after 90 days in 72/466 (15.5%), 66/466 (14.2%), 61/466 (13.1%), and 61/466 (13.1%) of patients, respectively. Among individual symptoms, the most common were fatigue (58/466, 12.5%), hair loss (38/466, 8.2%), insomnia (34/466, 7.3%), confusion (31/466, 6.7%), and anosmia (28/466, 6.0%) (Figure 1).

Associations with clinical outcomes after 90 days

Univariate predictors of persistent symptoms at 90 days are summarized in Table 3. Baseline cardiorespiratory comorbidity

Table 1: Baseline characteristics of patients with COVID-19 including those responding and not responding to follow-up invitation

Demographics	No. (%) of patients*				
	All patients; *n* = 993	Seen at 90-day follow-up; *n* = 206	Declined follow-up invitation; *n* = 260	Never responded to follow-up; *n* = 506	Died prior to 90 days; *n* = 21
Age (median, IQR)	38 (27-57)	51 (35–61)	37 (26–54)	34 (25–53)	79 (71–88)
Sex (female)	514 (51.7)	122 (59.2)	136 (52.3)	246 (48.6)	10 (43.5)
Pregnant	20 (2.0)	7 (3.4)	5 (1.9)	8 (1.6)	0 (0)
Health care worker	206 (20.7)	66 (32.0)	57 (21.9)	83 (16.4)	0 (0)
International travel (within 14 days of symptom onset)	73 (7.3)	21 (10.2)	15 (5.7)	36 (7.1)	1 (4.4)
Known exposure to case with COVID-19	524 (52.7)	96 (46.6)	140 (53.8)	272 (53.8)	16 (69.6)
Household contacts (average per case)	0.9	0.9	0.9	0.9	0.8
Number of days from symptom onset to COVID-19 test	4.2 (-5 to 42)	4.4 (-3 to 37)	4 (-1 to 31)	4.4 (-4 to 42)	3.1 (-5 to 11)
Location of COVID-19 test					
Assessment centre	707 (71.1)	106 (51.4)	189 (72.7)	411 (81.2)	1 (4.4)
In-hospital	219 (22.0)	80 (38.8)	60 (23.0)	62 (12.3)	17 (73.9)
Number of days from symptom onset to initial COVIDEO assessment	6.5 (-2 to 48)	7 (-2 to 48)	6.5 (1 to 46)	6.3 (-2 to 44)	5.2 (2 to 17)
Initial symptoms grouped by system					
Constitutional	629 (63.2)	151 (73.3)	159 (61.2)	302 (59.7)	17 (73.1)
Cardiorespiratory	557 (56.0)	134 (65.1)	148 (57.0)	257 (50.8)	18 (78.3)
Upper respiratory	468 (47.0)	103 (50.0)	112 (43.1)	250 (49.4)	3 (13.0)
Neurological	527 (53.0)	121 (58.7)	141 (54.2)	255 (50.4)	10 (43.5)
Gastrointestinal	296 (29.8)	80 (38.8)	77 (29.6)	134 (26.5)	5 (21.7)
Rheumatologic	373 (37.5)	96 (46.6)	103 (39.6)	173 (34.2)	1 (4.4)
Psychiatric	290 (29.2)	79 (38.4)	76 (29.2)	133 (25.3)	7 (30.4)
Comorbidities					
Cardiac disease	66 (6.6)	14 (6.8)	19 (7.3)	25 (4.9)	8 (34.8)
Hypertension	176 (17.6)	57 (27.7)	45 (17.3)	61 (12.1)	13 (56.5)
Diabetes	93 (9.3)	22 (10.7)	21 (8.1)	42 (8.3)	8 (34.8)
Chronic lung disease	29 (2.9)	8 (3.9)	4 (1.5)	10 (2.0)	7 (30.4)
Asthma	89 (8.9)	27 (13.1)	22 (8.4)	38 (7.5)	2 (8.7)
Chronic kidney disease	29 (2.9)	5 (2.4)	9 (3.5)	11 (2.2)	4 (17.4)
Chronic liver disease	11 (1.1)	2 (0.9)	4 (1.5)	4 (0.8)	1 (4.4)
Malignancy	62 (6.2)	14 (6.8)	19 (7.3)	20 (4.0)	9 (39.1)
Chronic hematologic disease	23 (2.3)	6 (2.9)	4 (1.5)	11 (2.2)	2 (8.7)
Rheumatic disease	17 (1.7)	7 (3.4)	5 (1.9)	3 (0.6)	2 (8.7)
HIV	4 (0.4)	0 (0)	2 (0.8)	1 (0.2)	1 (4.6)
Chronic neurological disease	60 (6.0)	9 (4.3)	16 (6.2)	21 (4.2)	14 (60.9)

(*Continued*)

Table 1: Continued

	No. (%) of patients*				
Demographics	All patients; n = 993	Seen at 90-day follow-up; n = 206	Declined follow-up invitation; n = 260	Never responded to follow-up; n = 506	Died prior to 90 days; n = 21
Obesity	49 (4.9)	22 (10.7)	15 (5.8)	12 (2.4)	0 (0)
Smoker	66 (6.6)	13 (6.3)	22 (8.4)	29 (5.7)	2 (8.7)
Malnutrition	8 (0.8)	0 (0)	1 (0.4)	3 (0.6)	4 (17.4)
Antibiotic therapy					
Beta-lactam	96 (9.7)	28 (13.6)	31 (11.9)	24 (4.7)	13 (56.5)
Macrolides	55 (5.5)	17 (8.3)	19 (7.3)	14 (2.8)	5 (21.7)
Additional household cases	0.8 (0–6)	0.8 (0–6)	-	-	-
Lymphocyte count	1.2 (0.5)	1.2 (0.2–3.3)	1.1 (0–2.4)	1.3 (0.3–5.0)	1.2 (0.4–4.3)
Abnormal chest X-ray	171 (17.1)	59 (28.6)	45 (17.3)	49 (9.7)	18 (78.3)
Hospitalization at or within 30 days of diagnosis	145 (14.5)	44 (21.4)	46 (17.7)	35 (6.9)	20 (87.0)
Days from diagnosis to hospital admission	1.4 (-61 to 74)	2 (-3 to 11)	3 (-31 to 74)	0.9 (-61 to 70)	-2.5 (-34 to 6)
ICU admission within 30 days of diagnosis	44 (4.4)	15 (7.3)	13 (5.0)	9 (1.8)	7 (30.4)
Mechanical ventilation within 30 days of diagnosis	34 (3.4)	11 (5.3)	9 (3.5)	7 (1.4)	7 (30.4)
Duration of hospitalization, d	1.7 (0–164)	1.7 (0–23)	1.6 (0–125)	1.0 (0–164)	17.8 (0–61)
Duration of mechanical ventilation, d	6.7 (0–60)	4.8 (0–21)	5.8 (0–60)	8.5 (0–36)	9.5 (0–52)

*Unless otherwise specified

Table 2: Initial symptoms and persistent symptoms at 90 days among patients diagnosed with COVID-19 in outpatient and inpatient settings

	Outpatients, no. (%); n = 326		Inpatients, no. (%); n = 140	
	Initial assessment	90-day assessment	Initial assessment	90-day assessment
	n (%)	n (%)	n (%)	n (%)
Any symptom	276 (84.7)	74 (22.7)	133 (95)	59 (42.1)
Constitutional	201 (61.7)	38 (11.7)	109 (77.9)	34 (24.3)
Cardiorespiratory	177 (54.3)	27 (8.3)	105 (75.0)	29 (20.7)
Upper respiratory	164 (50.3)	10 (3.1)	51 (36.4)	11 (7.9)
Neurological	189 (58.0)	32 (9.8)	73 (52.1)	29 (20.7)
Gastrointestinal	86 (26.4)	3 (0.9)	71 (50.7)	5 (3.6)

(*Continued*)

Table 2: Continued

|	Outpatients, no. (%); *n* = 326		Inpatients, no. (%); *n* = 140	
	Initial assessment	90-day assessment	Initial assessment	90-day assessment
	n (%)	*n* (%)	*n* (%)	*n* (%)
Rheumatologic	134 (41.1)	28 (8.6)	65 (46.4)	33 (23.6)
Psychiatric	92 (28.2)	37 (11.4)	63 (45.0)	29 (20.7)
Fever	101 (31.0)	0 (0)	76 (54.3)	1 (0.7)
Pharyngitis	95 (29.1)	2 (0.6)	22 (15.7)	3 (2.1)
Rhinorrhea	104 (31.9)	6 (1.8)	31 (22.1)	6 (4.3)
Cough	151 (46.3)	13 (4.0)	85 (60.7)	7 (5.0)
Sputum	24 (7.4)	2 (0.6)	25 (5.7)	5 (3.6)
Hemoptysis	1 (0.3)	0 (0)	3 (3.6)	0 (0)
Dyspnea	33 (10.1)	10 (3.1)	49 (35.0)	16 (11.4)
Dyspnea at rest	5 (1.5)	2 (0.6)	9 (6.4)	3 (2.1)
Tachypnea	9 (2.8)	1 (0.3)	12 (8.6)	0 (0)
Breathless today	11 (3.4)	2 (0.6)	12 (8.6)	3 (2.1)
Chills	76 (23.3)	1 (0.3)	44 (31.4)	1 (0.7)
Chest pain	43 (13.2)	7 (2.2)	28 (20.0)	8 (5.7)
Wheezing	7 (2.2)	5 (1.5)	8 (5.7)	1 (0.7)
Otalgia	15 (4.6)	0 (0)	7 (5.0)	3 (2.1)
Conjunctivitis	15 (4.6)	4 (1.2)	8 (5.7)	0 (0)
Anosmia	93 (28.5)	18 (5.5)	25 (17.9)	10 (7.1)
Dysguesia	107 (32.8)	12 (3.7)	22 (15.7)	4 (2.9)
Myalgia	123 (37.7)	7 (2.2)	62 (44.3)	6 (4.3)
Arthralgia	42 (12.9)	5 (1.5)	22 (15.7)	7 (5.0)
Abdominal pain	21 (6.4)	3 (0.9)	27 (19.3)	2 (1.4)
Nausea/vomiting	44 (13.5)	0 (0)	38 (27.1)	2 (1.4)
Diarrhea	46 (14.1)	1 (0.3)	39 (27.9)	2 (1.4)
Lymphadenopathy	4 (1.2)	0 (0)	0 (0)	1 (0.7)
Rash	6 (1.8)	5 (1.5)	2 (1.4)	7 (5.0)
Fatigue	165 (50.6)	33 (10.1)	88 (62.9)	25 (17.9)
Headache	134 (41.1)	8 (2.5)	55 (39.3)	12 (8.6)
Confusion	5 (1.5)	17 (5.2)	12 (8.6)	14 (10.0)
Depression	2 (0.6)	12 (3.7)	1 (0.7)	9 (6.4)
Insomnia	28 (8.6)	17 (5.2)	26 (18.6)	17 (12.1)
Anorexia	77 (23.6)	2 (0.6)	52 (37.1)	5 (3.6)
Weight loss	-	7 (2.2)	-	14 (10.0)
Hair loss	-	16 (4.9)	-	22 (15.7)
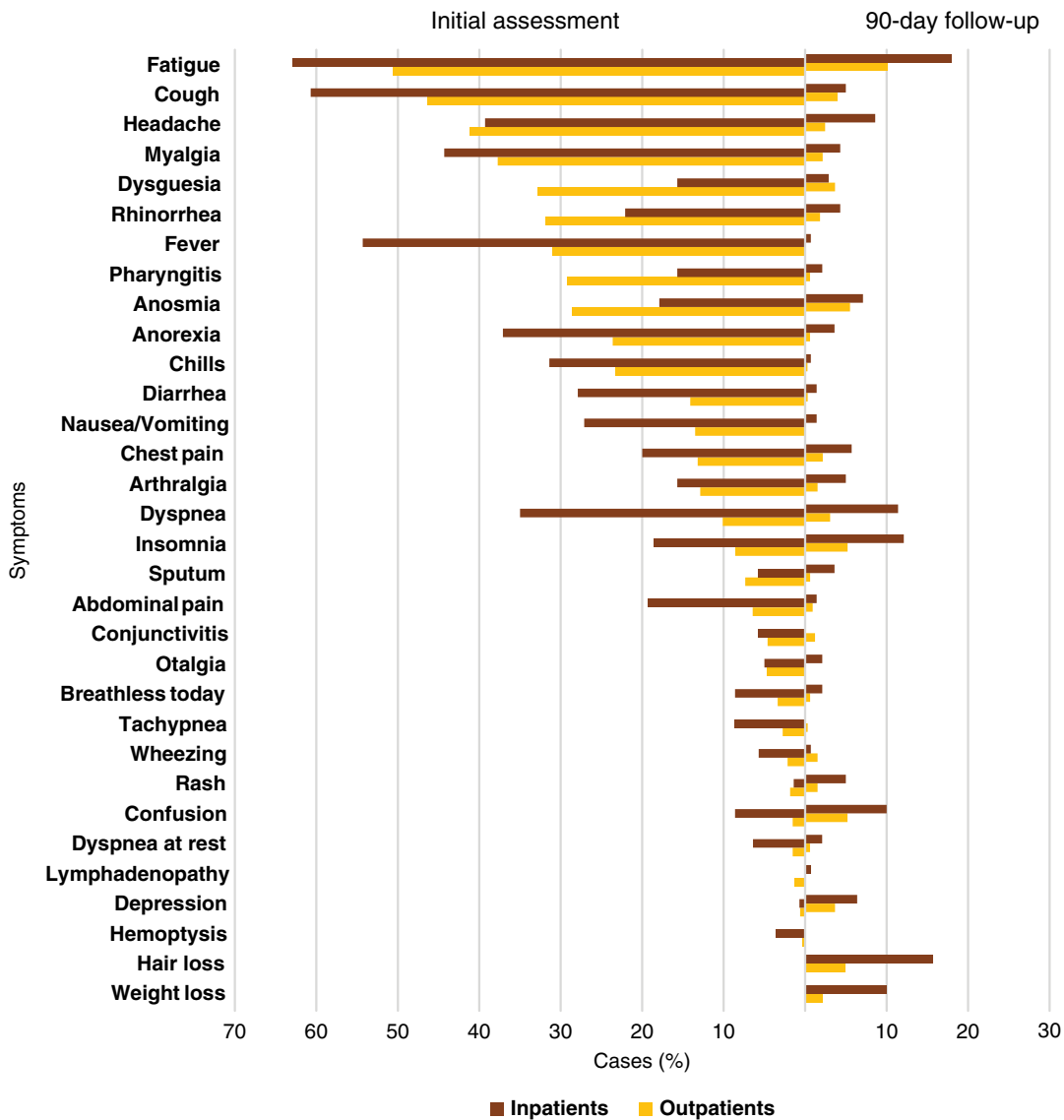
Figure 1: Symptom prevalence at initial assessment and 90-day follow-up among those diagnosed in the inpatient (red) and outpatient (yellow) settings

(asthma, cardiovascular diseases, or chronic lung disease) was significantly more common among those with any symptom than those without any persistent symptoms (25.6% versus 14.4%, *p* = 0.004). Cardiorespiratory comorbidities were also more common among people with persistent cardiorespiratory symptoms (33.9% versus 15.4%, *p* = 0.0006) and upper respiratory symptoms (52.4% versus 16.0%, *p* <0.0001) after 90 days of diagnosis. Similarly, reporting two or more comorbidities at baseline was significantly associated with any persistent symptoms (17.3% versus 9.3%, *p* = 0.015), as well as persistent constitutional (19.4% versus 10.2%, *p* = 0.02), gastrointestinal (37.5% versus 11.1% *p* = 0.02), and rheumatologic symptoms (23.0% versus 9.9%, *p* = 0.002) at 90-day follow-up.

In hospital testing, as compared to outpatient testing, was associated with nearly all types of persistent symptoms at 90 days (Table 2). Initial constitutional symptoms were strongly associated with persistent symptoms at 90 days, including any symptoms (23.6%, *p* = <0.0001), constitutional (12.6%, *p* = 0.002), cardiorespiratory (10.3%, *p* = 0.001), neurological (10.5%, *p* = 0.01), rheumatologic (10.5%, *p* = 0.01), and psychiatric symptoms (11.5%, *p* = 0.004) (Table 3).

Multivariable predictors of clinical outcomes after 90 days

Among patients with a 90-day assessment, those reporting constitutional symptoms at initial assessment (OR 2.24, 95% CI 1.23 to 4.08), rheumatologic symptoms at initial

Table 3: Univariate predictors of persistent symptoms at 90 days, by symptom group

	Any symptoms at 90 d			Constitutional symptoms at 90 d			Cardiorespiratory symptoms at 90 d			Upper respiratory symptoms at 90 d			Neurological symptoms at 90 d			Gastrointestinal symptoms at 90 d			Rheumatologic symptoms at 90 d			Psychiatric symptoms at 90 d		
	No (%)	Yes (%)	p-value	No (%)	Yes (%)	p-value	No (%)	Yes (%)	p-value	No (%)	Yes (%)	p-value	No (%)	Yes (%)	p-value	No (%)	Yes (%)	p-value	No (%)	Yes (%)	p-value	No (%)	Yes (%)	p-value
Mean age, y	42.2	50.0	<0.0001	43.0	52.3	<0.0001	43.9	47.9	0.13	44.1	51.7	0.06	43.6	49.7	0.01	44.4	45.6	0.85	42.9	54.6	<0.0001	43.7	48.6	0.04
Sex																								
Female	53.2	60.9	0.12	54.3	61.1	0.28	54.4	62.5	0.25	54.2	81.0	0.01	52.8	72.1	0.004	55.2	62.5	0.68	54.6	60.7	0.37	54.3	62.1	0.23
Comorbidities																								
Cardiorespiratory	14.4	25.6	0.004	16.5	23.6	0.14	15.4	33.9	0.0006	16.0	52.4	<0.0001	16.3	26.2	0.05	17.3	37.5	0.13	16.3	26.3	0.05	16.8	22.7	0.23
1 comorbidity	28.2	35.3	0.13	29.2	36.1	0.23	29.8	33.9	0.52	30.1	33.3	0.75	29.6	34.4	0.44	30.6	12.5	0.27	29.1	37.7	0.17	30.0	31.8	0.76
2 comorbidities	9.3	17.3	0.015	10.2	19.4	0.02	11.0	16.1	0.26	11.2	19.1	0.27	11.1	14.8	0.4	11.1	37.5	0.02	9.9	23.0	0.002	10.8	16.7	0.16
3+ comorbidities	9.3	11.3	0.51	9.4	12.5	0.41	9.3	14.3	0.23	9.2	23.8	0.02	9.6	11.5	0.65	9.8	12.5	0.8	9.4	13.1	0.36	9.8	10.6	0.82
Test location																								
CAC	69.7	47.4	<0.0001	66.0	48.6	0.004	66.6	39.3	<0.0001	64.3	42.9	0.04	66.2	44.3	0.0009	63.8	37.5	0.12	67.2	37.7	<0.0001	66.3	45.5	0.001
In-hospital	24.3	44.4	<0.0001	26.9	47.2	0.0005	27.1	51.8	0.0002	29.0	52.4	0.02	27.4	47.5	0.0014	29.5	62.5	0.04	26.4	54.1	<0.0001	27.8	43.9	0.007
Hospital admission	17.6	27.9	0.01	18.6	30.4	0.02	18.7	34.0	0.01	20.1	27.8	0.43	18.5	33.3	0.009	20.4	25.0	0.74	16.5	46.6	<0.0001	18.8	30.2	0.03
ICU admission	7.0	14.4	0.03	7.9	15.7	0.07	7.4	24.2	0.001	8.2	30.8	0.005	8.2	14.3	0.17	9.4	0.0	0.43	6.5	25.0	<0.0001	7.3	20.0	0.006
Symptomatic initial	85.0	94.7	0.003	86.8	93.1	0.13	86.6	96.4	0.03	87.2	100	0.08	86.4	96.7	0.02	87.6	100	0.28	86.7	95.1	0.06	87.0	92.4	0.21
Constitutional	60.1	82.7	<0.0001	63.7	81.9	0.002	63.9	85.7	0.001	65.9	81.0	0.15	64.4	80.3	0.01	66.2	87.5	0.2	64.4	80.3	0.01	64.0	81.8	0.004
Cardiorespiratory	57.1	69.2	0.01	59.1	68.1	0.15	58.1	78.6	0.003	59.3	85.7	0.015	58.3	75.4	0.01	60.5	62.5	0.9	59.0	70.5	0.08	59.3	68.2	0.16
Upper respiratory	43.5	52.6	0.07	45.2	51.4	0.33	45.1	53.6	0.23	45.8	52.4	0.55	43.7	62.3	0.006	45.9	62.5	0.34	46.4	44.3	0.75	45.0	53.0	0.22
Neurological	53.2	63.9	0.03	55.1	62.5	0.24	54.9	66.1	0.11	55.7	66.7	0.32	53.8	72.1	0.007	56.1	62.5	0.71	55.6	60.7	0.45	55.0	63.4	0.19
Gastrointestinal	30.7	41.4	0.02	33.3	36.1	0.63	32.2	44.6	0.06	32.8	52.4	0.06	32.1	44.3	0.06	33.4	50.0	0.32	31.6	47.5	0.01	32.0	43.9	0.05
Rheumatologic	37.5	55.6	0.0004	40.9	52.8	0.06	40.2	60.7	0.003	42.3	52.4	0.35	39.8	62.3	0.0009	42.4	62.5	0.25	41.2	52.5	0.09	40.0	59.1	0.003
Psychiatric	29.4	42.9	0.005	31.2	44.4	0.02	30.2	55.4	0.0002	32.4	52.4	0.05	30.9	49.2	0.004	33.0	50.0	0.31	31.9	42.6	0.09	31.3	45.5	0.02

assessment (OR 1.64, 95% CI 1.01 to 2.64), and those diagnosed in-hospital (OR 2.03, 95% CI 1.24 to 3.33) had increased odds of experiencing at least one persistent symptom (See Table 4).

Experiencing initial constitutional symptoms (OR 2.12, 95% CI 1.01 to 4.44) was associated with increases odds of constitutional symptoms after 90 days. Some symptoms at diagnosis were predictive of other persistent symptom types at follow-up. For example, having initial rheumatologic symptoms was associated with increased odds of neurological symptoms (OR 1.93, 95% CI 1.01 to 3.68) and psychiatric symptoms (OR 1.8, 95% CI 0.98 to 3.3) after 90 days of diagnosis. Similarly, early upper respiratory symptoms (OR 1.99, 95% CI 1.03 to 3.87) were associated with neurological symptoms after 90 days.

Regarding the test location, being tested in hospital also showed greater odds of experiencing cardiorespiratory (OR 2.37, 95% CI 1.21 to 4.67), neurological (OR 1.93, 95% CI 1.01 to 3.71), and psychiatric (OR 1.89, 95% CI 1.02 to 3.51) symptoms after 90 days.

Presence of a cardiorespiratory comorbidity was associated with higher odds of having any cardiopulmonary symptoms after 90 days of diagnosis (OR 2.03, 95% CI 1.06 to 3.89).

DISCUSSION

In this retrospective cohort study across the full spectrum of consecutive patients with COVID-19, a substantial proportion of patients (28.5%) reported at least one persistent symptom during their 90-day follow-up assessment. Fatigue was the most common persistent individual symptom, and constitutional symptoms were the most common persistent symptom group, but symptomatology in this group was diverse, with 10%–15% still experiencing some cardiorespiratory, neurologic, rheumatologic, and psychiatric symptoms. However, these rates of persistent symptoms, and those from other studies, likely over-estimate the burden of persistent illness, given that patients who did not respond to follow-up invitations tended to be younger, have less comorbidities, and be more likely to have been originally diagnosed in the outpatient setting. Further, even in the context of persistent symptoms, more than 90% of patients reported returning 'back to baseline,' suggesting that only the minority were experiencing symptoms severe enough to prevent resumption of daily activities, or that some of the persistent symptoms could have been related to other chronic disease conditions and pre-dated COVID-19 diagnosis.

Several studies have followed survivors of COVID-19 and found that many patients experience a protracted course. While some studies found a prevalence of symptoms of 50% or more, (11,13–16) our study aligns with findings of other groups detecting persistent symptoms in approximately 1/3 of patients (17,18). Our study also contradicts previous findings from a prevalence study in France were 30% of patients did not return to work after 6 months due to disabling consequences (6). Our study focused on the full spectrum of patients with COVID-19 illness, whereas most prior research has been limited to those with initial infection that was severe enough to require hospitalization. Similar to previous studies, fatigue, dyspnea, and anosmia (11,13–17,19) were among the most prevalent persistent symptoms.

Persistent symptoms at 90 days were associated with older patient age, comorbidity, in-hospital diagnosis, and extent of initial symptoms. Our findings support data from the United Kingdom, United States, Sweden, and France, in which patients with older age and more extensive initial symptoms were more likely to experience prolonged symptoms (11,20). Since older and sicker patients, and those with more significant initial infection are more likely to participate in follow-up visits, most long-term outcome studies will naturally over-estimate the prevalence of persistent symptoms. Unlike some other studies, we did not detect a higher rate of most post-infectious symptoms in women (only higher neurologic symptoms). However, our comparison of patients presenting versus not presenting to follow-up, did indicate that women were more likely than men to present for full assessment.

Some of the post-COVID-19 persistent symptoms likely represent direct sequelae of SARS-CoV-2 infection. For example, anosmia is a highly specific symptom of this virus (20) and has been attributed to invasion of the olfactory nerve and supportive tissues. Other SARS-CoV-2 specific effects may range from tachycardia due to autonomic dysfunction to fibrosis from lung injury and thrombosis (22). However, it is probable that most persistent symptoms following COVID-19 are not specific to the SARS-CoV-2 virus. One clear example is telogen effluvium, hair loss characterized by diffuse hair shedding, resulting from early entry of hair into the telogen phase. It is not specific to COVID-19 and can be triggered by any acute infection, systemic disease, stressful life event or other insults (23). Among patients with severe disease requiring intensive care unit and ventilator support, many of the persistent symptoms involve common sequelae of critical illness and acute respiratory distress syndrome, including deconditioning, muscle weakness, polyneuropathy, respiratory dysfunction, and post-traumatic stress (24). Even among patients with milder disease, many of the common post-COVID-19 symptoms are similar to post-infectious functional symptomatology seen after other routine viral infections (25).

As with most studies of long-term COVID-19 complications, our cohort is limited by potential selection bias given that not all patients returned for follow-up. However, unlike

Table 4: Multivariate analysis of predictors of persistent symptoms at 90 days, by symptom group

	Odds ratio (95% CI)							
	Any symptoms at 90 days	Constitutional symptoms at 90 days	Cardiorespiratory symptoms at 90 days	Upper respiratory symptoms at 90 days*	Neurological symptoms at 90 days	Gastrointestinal symptoms at 90 days*	Rheumatologic symptoms at 90 days	Psychiatric symptoms at 90 days
Age	1.11 (1.04 to 1.18)	1.13 (1.04 to 1.22)	0.99 (0.91 to 1.09)	-	1.08 (0.99 to 1.18)	-	1.13 (1.04 to 1.23)	1.05 (0.97 to 1.13)
Sex								
Female	1.46 (0.94 to 2.28)	1.46 (0.85 to 2.51)	1.35 (0.73 to 2.50)	-	2.39 (1.28 to 4.48)	-	1.43 (0.79 to 2.59)	1.42 (0.81 to 2.48)
Comorbidities								
Cardiorespiratory	1.50 (0.88 to 2.55)	1.15(0.61 to 2.19)	2.03 (1.06 to 3.89)	-	1.32 (0.67 to 2.61)	-	1.31 (0.66 to 2.60)	1.10 (0.57 to 2.14)
Test location								
In-hospital	2.03 (1.24 to 3.33)	1.48 (0.81 to 2.70)	2.37 (1.21 to 4.67)	-	1.93 (1.01 to 3.7)	-	1.74 (0.89 to 3.37)	1.89 (1.02 to 3.51)
Hospital admission	0.89 (0.49 to 1.61)	1.21 (0.61 to 2.43)	1.13 (0.53 to 2.42)	-	1.58 (0.74 to 3.35)	-	2.38 (1.18 to 4.77)	1.25 (0.61 to 2.54)
Constitutional	2.24 (1.23 to 4.08)	2.12 (1.01 to 4.44)	1.84 (0.75 to 4.5)	-	1.00 (0.45 to 2.25)	-	1.38 (0.62 to 3.08)	1.68 (0.77 to 3.66)
Cardiorespiratory	0.82 (0.50 to 1.36)	0.82 (0.44 to 1.50)	1.38 (0.65 to 2.91)	-	1.05 (0.52 to 2.12)	-	0.84 (0.43 to 1.65)	0.78 (0.41 to 1.47)
Upper respiratory	1.33 (0.82 to 2.16)	1.38 (0.77 to 2.50)	1.06 (0.54 to 2.07)	-	1.99 (1.03 to 3.87)	-	1.16 (0.6 to 2.22)	1.29 (0.7 to 2.37)
Neurological	1.12 (0.68 to 1.85)	1.04 (0.57 to 1.90)	1.00 (0.5 to 2.01)	-	1.61 (0.8 to 3.24)	-	1.09 (0.57 to 2.10)	1.01 (0.54 to 1.89)
Gastrointestinal	0.90 (0.55 to 1.49)	0.65 (0.35 to 1.21)	0.75 (0.38 to 1.46)	-	0.83 (0.43 to 1.61)	-	1.30 (0.68 to 2.51)	0.96 (0.52 to 1.77)
Rheumatologic	1.64 (1.01 to 2.64)	1.40 (0.78 to 2.52)	1.59 (0.82 to 3.07)	-	1.93 (1.01 to 3.68)	-	1.49 (0.78 to 2.83)	1.80 (0.98 to 3.30)
Psychiatric	1.03 (0.63 to 1.68)	1.21 (0.67 to 2.18)	1.99 (1.03 to 3.84)	-	1.19 (0.63 to 2.26)	-	0.83 (0.43 to 1.60)	1.19 (0.65 to 2.19)

* Insufficient events for multivariable modelling for those two outcomes

other studies, we are able to compare baseline characteristics among those with and without long-term follow-up, and in doing so we can infer that the rates of long-term complications are likely over-estimates rather than under-estimates—given that younger, healthier patients were less likely to return to clinic. Another reason that our study is likely to over-estimate long-term COVID-19 complication rates, as will other studies, is that it is difficult to determine whether some of the reported symptoms may be chronic, with onset pre-dating the COVID-19 infection. We established our symptom checklist at the onset of pandemic and maintained the same list throughout, and therefore we did not systematically capture some symptoms related to new and unexpected syndromes which became notable as the pandemic progressed, such as palpitations. Our follow-up was limited to 3 months, and so cannot extrapolate to later time points following infection. Lastly, our study was intentionally pragmatic and derived from routinely offered clinical care, and so does not provide comprehensive data on physiologic, laboratory and radiology outcomes. In contrast with most literature, our cohort was strengthened by inclusion of all consecutive patients, across the full spectrum of disease severity, with standardized assessments on initial assessment and again at 90 days.

In a pandemic unrivalled in the past century, hundreds of millions of patients have developed the same new virus infection over a short period of time. Our data suggest that among survivors we should expect that close to one-third may experience persistent symptoms at 3 months, but far fewer will have symptoms severe enough to limit their return to routine activities. Therefore, most studies likely over-estimate the burden of post-COVID-19 symptoms. Persistent symptoms will likely be more common among older patients, those with baseline comorbidity, and those hospitalized for their acute illness. Younger, healthier patients are more likely to be non-responders to follow-up offers, and so most studies likely over-estimate the prevalence of post-COVID-19 symptoms. Given the scope of the pandemic, we will require novel approaches to address COVID-19-specific pathology and to manage post-infectious functional impairment. A greater understanding of the mechanisms underpinning post-COVID-19 symptoms will also be needed to guide development of effective preventative and therapeutic strategies.

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