Post-COVID-19 Condition Symptoms Among Emergency Department Patients Tested for SARS-CoV-2 Infection

Patrick Archambault (patrick.m.archambault@gmail.com)
Université Laval

Rhonda Rosychuk
University of Alberta

Martyne Audet
Centre de recherche du CISSS de Chaudi&#x00E8 https://orcid.org/0000-0002-9557-022X

Jeffrey Hau
The University of British Columbia

Lorraine Graves
Long COVID Web of Canada

Simon Décary
Université de Sherbrooke

Jeffrey Perry
University of Ottawa

Steven Brooks
Queen's University

Laurie Morrison
University of Toronto

Raoul Daoust
Université de Montréal

David Yeom
The University of British Columbia

Hana Wiemer
Dalhousie University

Patrick Fok
Dalhousie University

Andrew McRae
University of Calgary

Kavish Chandra
Horizon Health Network

Michelle Kho

McMaster Univeersity
Dawn Stacey
University of Ottawa
Bilkis Vissandjée
Université de Montréal
Matthew Menear
Université Laval
Eric Mercier
Centre de recherche du CHU de Québec – Université Laval
Samuel Vaillancourt
University of Toronto
Samina Aziz
Public Health Agency of Canada
Dianne Zakaria
Public Health Agency of Canada
Phil Davis
University of Saskatchewan
Katie Dainty
University of Toronto
Jean-Sébastien Paquette
Université Laval
Murdoch Leeies
University of Manitoba
Susie Goulding
COVID Long-Haulers Support Group - Canada
Elyse Berger-Pelletier
Université Laval
Corinne Hohl
The University of British-Columbia

Article

Keywords:

Posted Date: December 22nd, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3783929/v1

Additional Declarations: There is **NO** Competing Interest.

Abstract

Importance: Symptoms of Post-COVID-19 Condition (PCC) are non-specific and can occur due to other medical conditions, making it a challenge to distinguish PCC from other health conditions.

Objective: To compare the proportion of emergency department (ED) patients who developed symptoms consistent with PCC between those who tested positive for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection and time-matched patients who tested negative.

Design: Observational cohort study that enrolled consecutive eligible patients between October 18, 2020, and February 28, 2022.

Setting: Thirty-three Canadian COVID-19 ED Rapid Response Network sites.

Participants: Eligible patients were aged ≥18 years and tested for SARS-CoV-2. We excluded patients not contacted after 5 attempts, unable to communicate due to language or cognitive barriers, deceased, or those who reported a subsequent positive test or symptomatic infection.

Exposure: SARS-CoV-2 infection.

Main outcome and Measure: Based on the World Health Organization (WHO) clinical case definition, our primary outcome was the proportion of ED patients reporting at least one new PCC-consistent symptom arising in the three months after the ED visit that was still present at the three-month mark and lasted >2 months.

Results: Of 29,838 individuals assessed for eligibility, 6,723 were included (58% SARS-CoV-2 positive; 51% female; mean age, 54.4 years [SD: 17.9]). Among 3,933 test-positive patients, 38.9% (1532/3933, 95% CI: 37.4-40.4%) reported PCC symptoms at 3 months compared to 20.7% (578/2790, 95% CI: 19.2-22.2%) of test-negative patients. Test-positive patients reported experiencing each individual PCC-consistent symptom at least twice as often as test-negative patients. The top three most frequently reported symptoms reported by test-positive patients were post-exertional malaise, dyspnea and memory problems. The most important predictor of subsequent PCC was a positive SARS-CoV-2 test during the index ED visit (adjusted OR=4.42).

Conclusions and Relevance: Over one-third of ED patients with a proven acute SARS-CoV-2 infection met PCC criteria at 3 months post-index ED visit, however one in five test-negative patients also reported PCC-consistent symptoms highlighting the lack of specificity of the WHO clinical case definition. Testing for SARS-CoV-2 during the acute phase of a suspected infection should continue until specific biomarkers of PCC become available for diagnosis and treatment referral.

Trial registration: Clinicaltrials.gov, no. NCT04702945

INTRODUCTION

The COVID-19 pandemic has had a staggering toll on global health with over 772 million documented infections.[1] Millions of survivors have reported persistent or recurring symptoms that are debilitating.[2,3] The World Health Organization (WHO) defined this condition as the Post-COVID-19 Condition (PCC), also known as Long COVID.[4,5] The WHO defines PCC as a condition that "*occurs in individuals with a history of probable or confirmed Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months, that cannot be explained by an alternative diagnosis*".[6] Based on conservative prevalence estimates, more than 77 million individuals could be living with PCC worldwide.[7] Preliminary data show that people with PCC may have increased use of primary care, hospital admissions and mortality in the months post infection.[8,9] Unfortunately, the true assessment of the burden of PCC is still inaccurate because its definition and diagnostic criteria are difficult to operationalize.[8] Currently, PCC is challenging to distinguish from other physical and mental health conditions. The WHO listed 50 symptoms associated with PCC including dyspnea, post-exertional malaise (PEM), anosmia, and cough among others.[10] Yet, many of these symptoms could occur due to comorbidity or other viral infections. Furthermore, in 2023, fewer people are seeking or being offered diagnostic testing for SARS-CoV-2 now that the virus is less virulent and endemic.[11–13] As a result, people who were never tested for SARS-CoV-2 infection may develop WHO PCC criteria without ever being diagnosed with SARS-CoV-2.

Our objective was to compare the proportion of all emergency department (ED) patients tested for SARS-CoV-2 who met PCC criteria at 3 months who tested positive compared to those who tested negative and did not report subsequent symptomatic infection. Our secondary objective was to assess risk factors for reporting PCC symptoms at 3 months.

METHODS

Study design and setting

The Canadian COVID-19 Emergency Department Rapid Response Network (CCEDRRN) is a pan-Canadian collaboration that harmonized data collection among all patients tested for SARS-CoV-2 in 50 EDs in 8 provinces to enable observational studies.[14–19] This specific PCC sub-study was conducted in 33 out of the 50 CCEDRRN sites in five provinces (NS, QC, ON, SK, BC). All sites were eligible to participate, but site participation was determined by local human resource capacity at each site. The research ethics boards of participating institutions approved the study with a waiver of informed consent for patient enrollment and provided permission to contact patients to seek verbal consent to follow-up using phone interviews. We followed the STROBE guidelines[20] (Supplemental material - Table 1) and report our patient engagement strategy[21] using the GRIPP2-SF guideline (Supplemental material - Table 2).[22]

Participants

We enrolled consecutive consenting eligible patients aged ≥ 18 years who presented to one of 33 participating ED between October 18, 2020, and February 28, 2022, and were tested for SARS-CoV-2

(Supplemental material - Table 3). We excluded patients who had died, were hospitalized or out of the country at the time of follow-up, could not be contacted after 5 attempts, were unable to communicate due to language or cognitive barriers, or found the follow-up interview too long. We excluded all patients reporting a positive SARS-CoV-2 test or a symptomatic SARS-CoV-2 infection after the index ED encounter to prevent any confounding effect on the assessment of ongoing symptoms during phone follow-up.

Six out of 33 sites collected data on randomly selected time-matched test-negative controls aiming for a 1:4 case to control ratio (Supplemental material - Table 3).[19] The final ratio of SARS-CoV-2 positive to negative controls varied during the pandemic due to periods with high SARS-CoV-2 test positivity (> 25%) limiting recruitment of time-matched controls. The remaining 27 sites only collected data on test-positive patients due to human resources constraints (Supplemental material - Table 3).

Definitions

We defined SARS-CoV-2 positive patients as those who had a laboratory-confirmed infection, detected by ≥ 1 nucleic acid amplification or rapid antigen test from a specimen collected in the community ≤ 14 days before the ED visit and ongoing symptoms until the ED visit, or those with a specimen collected during the ED visit or ≤ 14 days after ED arrival, reflecting the maximum possible incubation period.[18]

We defined SARS-CoV-2 negative controls as those in whom all recorded SARS-CoV-2 tests were negative, who never reported a subsequent positive test, or symptoms of acute infection at phone follow-up.

Based on the WHO clinical case definition, we defined meeting clinical PCC criteria as reporting (1) at least one new PCC-consistent symptom arising in the 3 months after the ED visit that continued to be present at the three-month mark, and (2) lasted ≥ 2 months.[23] The PCC symptoms we considered were dyspnea, pain, cough, loss of sense of smell and taste, sleep disturbance, dizziness, trouble concentrating, memory problems, and PEM. Participants could also report any other new symptom they were experiencing since their ED index visit.

Data collection

Trained research assistants: (1) abstracted data on SARS-CoV-2 tested patients including their baseline comorbidities by chart review,[14] (2) attempted to contact patients up to five times to obtain consent for phone follow-up six months after the ED visit, (3) collected sociocultural and demographic variables including age, sex, race, baseline level of fitness, and self-reported SARS-CoV-2 vaccination status,[24] (4) documented any self-reported new or repeat SARS-CoV-2 infections, and (5) documented ongoing or resolved symptoms consistent with PCC using the PCC Assessment Questionnaire (PCCAQ; Supplemental material - Methods). All symptoms documented had to be new since the ED index visit. We developed the PCCAQ based on the WHO PCC case definition and case report form[10] in collaboration with patient partners, PCC experts, emergency physicians, rehabilitation specialists, and public health policy makers. We piloted the PCCAQ in English and French with patient partners and the first 100 participants. Phone follow-ups occurred between November 16, 2021, and July 31, 2022.

Measures, outcomes and candidate risk factor variables

Our primary outcome was the proportion of ED patients reporting at least one PCC-consistent symptom at 3 months. Our secondary outcomes were the proportions of individual PCC-consistent symptoms reported at 3 months. The candidate risk factors hypothesized to be covariates associated with PCC were selected based on a review of existing studies[25–27] and the clinical knowledge of the investigator team and patient partners (Supplementary Table 4). We selected baseline sociodemographic characteristics and clinical variables that can easily be assessed in the ED including SARS-CoV-2 testing. We excluded other laboratory testing and imaging because they are not available in all patients.

Statistical analyses

We used Stata (Version 16.1, StataCorp, College Station, Texas) to calculate summary statistics (eg, count, percentage, mean, standard deviation [SD]) and stratified data by SARS-CoV-2 status (ie, test-positive or test-negative) and PCC status (ie, with or without PCC symptoms). T-tests and chi-squared tests assessed differences between PCC groups within cohorts. We calculated the proportion of patients with PCC symptoms with 95% confidence intervals (95% CI). Mixed effects logistic regression models modelled the association between the risk factors selected as covariates and the primary outcome. Univariable models for each covariate provided unadjusted odds ratios (ORs). The multivariable model included key covariates including SARS-CoV-2 status and a random effect for site to account for the correlation of patients presenting to the same ED. A p-value $< .05$ was considered statistically significant.

RESULTS

Of 29,838 individuals assessed for eligibility, 6,723 met inclusion criteria (58.5% (3,933/6723) SARS-CoV-2 positive (Fig. 1); 50.6% (3405/6723) female; mean age, 54.4 years [SD: 17.9]). Among test-positive patients, the proportion reporting at least one PCC symptom at three months was 38.9% (1532/3933, 95% CI: 37.4–40.4%) compared to 20.7% (578/2790, 95% CI: 19.2–22.2%) among test-negative patients.

Test-positive patients with PCC differed from those without PCC with regards to mean age, sex, pandemic period, race, education level, ambulance arrival, comorbidities, acute symptoms, ICU admissions, and perceived fitness (Table 1). Test-negative patients with PCC-consistent symptoms differed from those without PCC-consistent symptoms in terms of pandemic period, race, educational level, ambulance arrival, comorbidities, ICU admissions, number SARS-CoV-2 vaccine doses, and perceived fitness. PCC symptoms differed by SARS-CoV-2 status with positive patients reporting each individual PCC-consistent symptom at least twice more often than negative patients (Fig. 2). Few test-negative patients reported anosmia (0.4%, 95% CI: 0.2–0.8%), dysgeusia (0.9%, 95% CI: 0.6–1.4%) or a new persistent cough (1.2%, 95% CI: 0.8–1.7%). There were 21.4% (95% CI: 20.2–22.7%) of test-positive patients who reported three or more symptoms, compared to 6.1% (95% CI: 2.2-7.0%) of test-negative patients.

Table 1
Baseline characteristics of emergency department patients by SARS-CoV-2 and PCC status (n = 6,723).

Variables [a]	SARS-CoV-2 Positive (n = 3,933)			SARS-CoV-2 Negative (n = 2,790)		
	Without PCC symptoms (n = 2,401)	With PCC symptoms (n = 1,532)	P-value [b]	Without PCC symptoms (n = 2,212)	With PCC symptoms (n = 578)	P-value [b]
Age (in years) mean (SD)	49.7 (17.0)	52.3 (16.2)	< 0.001	59.3 (18.5)	60.9 (17.3)	0.06
Sex, No./total (%)						
Female	1045/2401 (43.5)	871/1532 (56.8)	< 0.001	1187/2212 (53.7)	302/578 (52.3)	0.54
Pandemic period, No./total (%)						
Prior to Omicron (October 16, 2020, to November 27, 2021)	2078/2401 (86.5)	1297/1532 (84.7)	0.10	2108/2212 (95.3)	526/578 (91.0)	< 0.001
During Omicron (November 28, 2021, to February 28, 2022)	323/2401 (13.5)	235/1532 (15.3)		104/2212 (4.7)	52/578 (9.0)	
Self-reported race, No./total (%)						
Arab/Middle Eastern	208/2401 (8.7)	140/1532 (9.1)	< 0.001	69/2122 (3.1)	38/578 (6.6)	0.002
Black	156/2401 (6.5)	84/1532 (5.5)		80/2122 (3.6)	19/578 (3.3)	
East/Southeast Asian	205/2401 (8.5)	114/1532 (7.4)		167/2122 (7.5)	51/578 (8.8)	
Indigenous	58/2401 (2.4)	38/1532 (2.5)		34/2122 (1.5)	13/578 (2.2)	
Latin American	63/2401 (2.6)	58/1532 (3.8)		30/2122 (1.4)	10/578 (1.7)	
South Asian	502/2401 (20.9)	136/1532 (8.9)		79/2122 (3.6)	28/578 (4.8)	
White	1012/2401 (42.1)	851/1532 (55.5)		1587/2122 (71.7)	374/578 (64.7)	
Other	44/2401 (1.8)	16/1532 (1)		15/2122 (0.7)	6/578 (1.0)	
Unknown	153/2401 (6.4)	95/1532 (6.2)		151/2122 (6.8)	39/578 (6.7)	

Variables [a]	SARS-CoV-2 Positive (n = 3,933)			SARS-CoV-2 Negative (n = 2,790)		
	Without PCC symptoms (n = 2,401)	With PCC symptoms (n = 1,532)	P-value [b]	Without PCC symptoms (n = 2,212)	With PCC symptoms (n = 578)	P-value [b]
ED arrival by ambulance, No./total (%)						
Self	1567/2401 (65.3)	925/1532 (60.4)	0.002	1492/2212 (67.5)	362/578 (62.6)	0.03
Ambulance	834/2401 (34.7)	607/1532 (39.6)		720/2212 (32.6)	216/578 (37.4)	
Comorbidities documented during ED index visit, No./total (%)						
Hypertension	580/2401 (24.2)	432/1532 (28.2)	0.006	830/2212 (37.5)	247/578 (42.7)	0.02
Diabetes	371/2401 (15.5)	255/1532 (16.6)	0.32	374/2212 (16.9)	113/578 (19.6)	0.14
Asthma	210/2401 (8.7)	179/1532 (11.7)	0.003	178/2212 (8)	58/578 (10)	0.13
Mental health diagnosis	189/2401 (7.9)	176/1532 (11.5)	< 0.001	382/2212 (17.3)	97/578 (16.8)	0.78
Coronary artery disease	94/2401 (3.9)	105/1532 (6.9)	< 0.001	240/2212 (10.8)	76/578 (13.1)	0.12
Rheumatologic disorder	94/2401 (3.9)	101/1532 (6.6)	< 0.001	287/2212 (13)	76/578 (13.1)	0.91
Chronic lung disease	59/2401 (2.5)	68/1532 (4.4)	0.001	199/2212 (9)	54/578 (9.3)	0.8
Obesity	62/2401 (2.6)	67/1532 (4.4)	0.002	65/2212 (2.9)	12/578 (2.1)	0.26
Chronic kidney disease	62/2401 (2.6)	51/1532 (3.3)	0.17	123/2212 (5.6)	31/578 (5.4)	0.85
Active cancer	87/2401 (3.6)	40/1532 (2.6)	0.08	185/2212 (8.4)	57/578 (9.9)	0.26
Heart failure	38/2401 (1.6)	33/1532 (2.2)	0.19	75/2212 (3.4)	28/578 (4.8)	0.09
Organ transplant	25/2401 (1.0)	8/1532 (0.5)	0.08	25/2212 (1.1)	12/578 (2.1)	0.08
Acute COVID-19 symptoms reported during ED index visit,[c] No./total (%)						

Variables [a]	SARS-CoV-2 Positive (n = 3,933)			SARS-CoV-2 Negative (n = 2,790)		
	Without PCC symptoms (n = 2,401)	With PCC symptoms (n = 1,532)	P-value [b]	Without PCC symptoms (n = 2,212)	With PCC symptoms (n = 578)	P-value [b]
Cough	1512/2401 (63.0)	1006/1532 (65.7)	0.09	268/2212 (12.1)	84/578 (14.5)	0.12
Dyspnea	1291/2401 (53.8)	936/1532 (61.1)	< 0.001	529/2212 (23.9)	154/578 (26.6)	0.14
Fever	1175/2401 (48.9)	729/1532 (47.6)	0.41	311/2212 (14.1)	68/578 (11.8)	0.05
Chills	802/2401 (33.4)	661/1532 (43.1)	< 0.001	174/2212 (7.9)	46/578 (8.0)	0.94
General weakness	802/2401 (33.4)	569/1532 (37.1)	0.02	433/2212 (19.6)	128/578 (22.1)	0.17
Chest pain	543/2401 (22.6)	385/1532 (25.1)	0.07	584/2212 (26.4)	167/578 (28.9)	0.23
Abdominal pain	537/2401 (22.4)	374/1532 (24.4)	0.14	484/2212 (21.9)	111/578 (19.2)	0.16
Diarrhea	412/2401 (17.2)	332/1532 (21.7)	< 0.001	221/2212 (10.0)	39/578 (6.7)	0.02
Nausea/vomiting	499/2401 (20.8)	319/1532 (20.8)	0.97	504/2212 (22.8)	135/578 (23.4)	0.77
Headache	619/2401 (25.8)	278/1532 (18.1)	< 0.001	249/2212 (11.3)	69/578 (11.9)	0.65
Rhinorrhea	305/2401 (12.7)	222/1532 (14.5)	0.11	46/2212 (2.1)	11/578 (1.9)	0.79
Myalgia/Arthralgia	248/2401 (10.3)	148/1532 (9.7)	0.49	76/2212 (3.4)	22/578 (3.8)	0.67
Sore throat	143/2401 (6.0)	137/1532 (8.9)	< 0.001	100/2212 (4.5)	26/578 (4.5)	0.98
Altered mental status	120/2401 (5.0)	84/1532 (5.5)	0.50	196/2212 (8.9)	66/578 (11.4)	0.60
Dysgeusia/anosmia	117/2401 (4.9)	81/1532 (5.3)	0.56	7/2212 (0.3)	< 5	0.91
Admission status during ED index visit, No./total (%)						
Not admitted	1690/2401 (70.4)	1016/1532 (66.3)	< 0.001	1221/2212 (55.2)	244/578 (42.2)	< 0.001

Variables [a]	SARS-CoV-2 Positive (n = 3,933)			SARS-CoV-2 Negative (n = 2,790)		
	Without PCC symptoms (n = 2,401)	With PCC symptoms (n = 1,532)	P-value [b]	Without PCC symptoms (n = 2,212)	With PCC symptoms (n = 578)	P-value [b]
Admitted to ward	583/2401 (24.3)	734/1532 (24.4)		940/2212 (42.5)	305/578 (52.8)	
Admitted to ICU	128/2401 (5.3)	142/1532 (9.3)		51/2212 (2.3)	29/578 (5.0)	
Hospital medications, No./total (%)						
Dexamethasone	378/2401 (15.7)	297/1532 (19.4)	0.003	66/2212 (3.0)	33/578 (5.7)	0.002
Self-reported doses of SARS-CoV-2 vaccine received before ED index visit [c], No./total (%)						
None	1917/2401 (79.8)	1190/1532 (77.7)	0.14	1430/2122 (64.7)	342/578 (59.3)	0.03
1	232/2401 (9.7)	162/1532 (10.6)		521/2122 (23.6)	143/578 (24.7)	
2 or more	227/2401 (9.5)	170/1532 (11.1)		260/2122 (11.7)	92/578 (15.9)	
Unknown	25/2401 (1.0)	10/1532 (0.7)		< 5	< 5	
Self-reported education level, No./total (%)						
None	197/2401 (8.2)	98/1532 (6.4)	0.003	173/2122 (7.8)	33/578 (5.7)	0.02
High school diploma	555/2401 (23.1)	362/1532 (23.6)		485/2122 (21.9)	112/578 (19.4)	
Trade certification or diploma	136/2401 (5.7)	115/1532 (7.5)		156/2122 (7.1)	34/578 (5.9)	
University certificate or diploma	254/2401 (10.6)	127/1532 (8.3)		188/2122 (8.5)	62/578 (10.7)	
University bachelor level or above	1137/2401 (47.4)	772/1532 (50.4)		1078/2122 (48.7)	214/578 (54.3)	
Unknown	122/2401 (5.1)	58/1532 (3.8)		132/2122 (6.0)	23/578 (4.0)	
Self-reported perceived level of fitness at baseline [d], No./total (%)						
Fit and well	1545/2401 (64.4)	828/1532 (54.1)	< 0.001	847/2122 (38.3)	176/578 (30.5)	< 0.001

Variables [a]	SARS-CoV-2 Positive (n = 3,933)			SARS-CoV-2 Negative (n = 2,790)		
	Without PCC symptoms (n = 2,401)	With PCC symptoms (n = 1,532)	P-value [b]	Without PCC symptoms (n = 2,212)	With PCC symptoms (n = 578)	P-value [b]
Managing well	680/2401 (28.3)	586/1532 (38.3)		1061/2122 (48.0)	308/578 (53.3)	
Frail	100/2401 (4.2)	87/1532 (5.7)		243/2122 (11.0)	68/578 (11.8)	
Unknown	76/2401 (3.2)	31/1532 (2.0)		61/2122 (2.8)	26/578 (4.5)	

[a] Variables extracted through chart review were: age, sex, pandemic period, ED arrival by ambulance, comorbidities, acute COVID-19 symptoms, admission status, hospital medications. All other variables were self-reported by patients during phone follow-up: race, number of vaccine doses before ED visit, education level, perceived level of fitness at baseline.

[b] P-value comparing patients with PCC symptoms and patients without PCC symptoms stratified by SARS-CoV-2 status.

[c] Data confidentiality policies prevented reporting counts < 5.

[d] The perceived level of fitness variable and questionnaire item was developed in collaboration with patient partners and rehabilitation experts based on a published patient-reported outcome questionnaire.[27] “Fit and well” was defined as exercising occasionally or regularly and had no medical problems. “Managing well” was defined as having some medical problems that limited regular activities but didn’t require help. “Frail” was defined as having medical problems that limited regular activities and needed help with daily activities and personal care.

The most important predictor of reporting PCC symptoms was having tested SARS-CoV-2 positive during index ED visit (adjusted OR (aOR) = 4.42, 95% CI: 3.60–5.43; Fig. 3, Supplemental material - Table 5). Other predictors included ICU admission (aOR = 1.84, 95% CI: 1.34–2.51), female sex (aOR = 1.51, 95% CI: 1.33–1.73), dysgeusia/anosmia at the time of index ED visit (aOR = 1.38, 95% CI: 1.03–1.85), treatment with dexamethasone (aOR = 1.27, 95% CI: 1.00-1.61), fatigue at the time of index ED visit (aOR = 1.17, 95% CI: 1.02–1.35), and arrival by ambulance (aOR = 1.16, 95% CI: 1.01–1.33). Frailty at baseline did not increase risk of PCC. However, patients reporting “managing well” compared to those “fit and well” at baseline increased risk of PCC (aOR = 1.31, 95% CI: 1.14–1.52). Lower education level was the only factor that decreased the risk of PCC (aOR = 0.75, 95% CI: 0.58–0.97). Vaccination did not have an effect (aOR = 1.00, 95%F CI: 0.79–1.26).

DISCUSSION

Interpretation

A high proportion of ED patients reported PCC symptoms at three-month follow-up, regardless of whether they were infected with SARS-CoV-2. Test-positive patients reported each individual PCC-consistent symptom at least twice as often as negative patients. While a positive SARS-CoV-2 test during the index ED visit was the main risk factor for developing PCC, other risk factors included female sex, arriving by ambulance, ICU admission, exposure to dexamethasone, and reporting fatigue and olfactory symptoms at baseline. We did not identify any comorbidities that increased the risk of PCC. Interestingly, vaccination was not associated with less PCC in patients with or without SARS CoV-2.

Our study is consistent with existing observational studies on PCC symptoms.[28,29] Four in 10 ED patients diagnosed with acute SARS-CoV-2 infection without evidence of subsequent infection reported PCC symptoms at 3 months, consistent with studies reporting that a third of hospitalized patients in Canada reported PCC after hospitalization.[30] Systematic reviews from around the world also produced similar results.[31–38] Our results differed from a Canadian survey study in the general population,[39,40] that reported that only 15% of patients developed PCC after an acute infection,[41] suggesting that ED patients are at higher risk of developing PCC than in the general population.[42]

We found a high rate of PCC-consistent symptoms in test-negative patients. This is consistent with other investigators[28,43] who found that approximately one-quarter of SARS-CoV-2 negative participants had at least one persistent symptom at 3 months. While others have found a high proportion of PCC in test-negative patients,[28,43–46] our study is unique because it is the largest and longest running ED prospective cohort that spans pre-omicron and post-omicron waves with consecutive patients including time-concurrent negative controls that limits selection bias found in other large cohorts that included self-referred patients.[28,43,45]

Our high rate of PCC-consistent symptoms in test-negative patients is unlikely to be explained by asymptomatic SARS-CoV-2 infections or missed infections from the early pandemic when SARS-CoV-2 testing was limited.[47,48] Data from Canadian seroprevalence studies confirmed that fewer than 9% of Canadians had serological evidence of SARS-CoV-2 infection prior to the Omicron wave that started on November 28, 2021,[49–51] when 94% of our cohort was recruited. Very few patients in our cohort were tested for other viruses, making it possible that we identified other post-viral syndromes. However, strict COVID-19 public health restrictions in Canada during the study period reduced the circulation of other viruses,[52,53] making this less likely. Thus, our data indicate that the development of PCC after suspected but not confirmed SARS-CoV-2 infection is non-specific and can occur in SARS-CoV-2 naïve patients. This limits our ability to accurately identify patients for treatment, and develop, prioritize and evaluate interventions to prevent and treat PCC.

A more specific WHO definition, potentially used in combination with serology testing[54] or biomarker for an underlying process that underpins the development of PCC is needed,[45,55,56] given the high prevalence

of PCC-consistent symptoms in test-negative patients. When comparing symptoms in test-positive and test-negative patients, our results indicate that three or more symptoms or the presence of certain symptoms such as anosmia, dysgeusia, newly persistent cough, and dyspnea were noticeably more common in test-positive patients compared to test-negative patients. This may indicate an opportunity to refine the WHO definition for greater specificity. Anosmia and dysgeusia have been reported as common early symptoms in patients with COVID-19.[57] While most patients with olfactory symptoms in the acute phase recovered within one month,[58,59] anosmia and dysgeusia persisted in some patients for several months. Our study suggests that olfactory symptoms during the acute infection may predict PCC.

Our study differs from a recent meta-analysis[25] showing that age increases the risk of PCC. Compared to this meta-analysis of 860 783 patients with COVID-19, we included patients tested for SARS-CoV-2 and their time-matched negative controls. This means that patients with COVID-19 compared to patients the same age without COVID-19 have the same risk of experiencing PCC. However, consistent with this meta-analysis,[25] we found that female sex was associated with an increased risk of experiencing PCC.[26,31,60,61] Potential explanations include the role of sex hormones,[62] higher innate immune responses in females,[63] and social factors and gender biases making it more acceptable for women to disclose pain and distress compared to men.[36,64,65]

Many studies point to certain comorbidities as risk factors for PCC.[25] When controlling for all potential risk factors and including time-concurrent test-negative controls who presented to EDs, none of the comorbidities remained significant in our multivariable model. Being tested positive for SARS-CoV-2 represented the single most important risk factor for PCC. This supports an essential role for acute SARS-CoV-2 infection in PCC development.

Similar to prior studies, our finding that ICU admission was associated with PCC[66–68] indicates a potential overlap with post-intensive care syndrome[66] which presents with similar persistent physical and psychological symptoms. The use of dexamethasone was also associated with PCC. Dexamethasone has shown to decrease mortality in severe cases of COVID-19 but can also lead to worse outcomes such as myopathy when used inappropriately in patients without proven infections or in patients not requiring oxygen.[69,70] Therefore, dexamethasone may have been an indicator of disease severity, or alternately may have itself contributed the development of PCC symptoms.

Previous data on the association of education level with PCC is inconsistent. Contrary to other studies that show that higher education protects against severe COVID-19 and PCC,[71,72] we found that patients with lower education reported fewer PCC symptoms, consistent with other studies.[30,73] Researchers have raised the possibility that initial lack of awareness of the range of symptoms associated with acute COVID-19 could lead patients with lower education to seek out SARS-CoV-2 testing less frequently.[74] Patients with lower education and socio-economic status also face stigma related to PCC that might lead to underreporting of their symptoms.[75]

Although several studies reported that vaccination decreased the rates of PCC symptoms,[76–78] our study did not confirm this protective effect. With less than a third of our cohort vaccinated at the time of infection, it is possible that too few patients in our cohort were vaccinated before they were infected to detect a protective effect.

Strengths and Limitations

Our study has several strengths. First, this is one of the few cohorts of consecutive SARS-CoV-2 positive patients with time-matched test-negative controls that spans multiple pandemic waves.[33,55,56] Second, only a few studies systematically followed SARS-CoV-2 tested patients and integrated clinical data from the acute infection with patient-reported information.[45,79,80] Third, we rigorously applied the WHO definition using specific time cut-off points and asked patients to discern new versus chronic symptoms, improving the specificity of the patients identified as having PCC. Fourth, this study was developed with the participation of patient partners who provided guidance in its development, its conduct and interpretation.

Our study has several limitations. First, the WHO PCC definition is very broad and remains hard to operationalize.[23] It is not easy to apply in the case of relapsing symptoms, and currently includes non-specific symptoms.[44] Although our questionnaire was built to detect any new symptoms since the ED index visit, PCC remains a clinical diagnosis that relies on the exclusion of all other causes. As our study demonstrates, ruling-in PCC remains a challenge because the diagnostic criteria are not specific, and it remains difficult to differentiate new symptoms related to PCC from those of other new conditions that can be diagnosed concomitantly. Second, our PCC questionnaire was implemented without formal psychometric evaluation early during the pandemic when there was an urgency to capture PCC outcomes without any existing validated questionnaire. It was, however, co-developed with patient partners, experts in PCC and rehabilitation, then pilot-tested with a subset of patients, and implemented with training material to standardize its use.

Clinical and Research Implications

PCC as defined by the WHO is a non-specific syndrome that occurs in many patients who present to the ED for an acute illness requiring SARS-CoV-2 testing. While acute SARS-CoV-2 infection was its single most important risk factor, every fifth patient with no evidence of acute or subsequent SARS-CoV-2 infection met PCC criteria. The current WHO definition for suspected SARS-CoV-2 infections will lead to overdiagnosis of PCC among patients with suspected infections who are currently not being tested. Further studies are needed to improve our understanding of the pathophysiology of PCC to develop more specific diagnostic criteria.

CONCLUSIONS

Among patients presenting to Canadian EDs, more than a third of patients who tested positive for SARS-CoV-2 and one in five patients without SARS-CoV-2 infection met PCC criteria at 3 months after the ED

visit. A positive SARS-CoV-2 test was the single most important factor associated with PCC symptoms. Testing for SARS-CoV-2 during the acute phase of a suspected infection should continue until specific PCC biomarkers become available for diagnosis and treatment referral.

Abbreviations

CCEDRRN: Canadian COVID-19 Emergency Department Rapid Response Network

PCC: Post-COVID-19 Condition

CI: Confidence interval

COVID-19: Coronavirus Disease 2019

ED: Emergency department

SD: Standard deviation

PCCAQ: Post-COVID-19 Condition Assessment Questionnaire

Declarations

Data availability statement

Data is available on reasonable request. For investigators who wish to access CCEDRRN data, proposals may be submitted to the network for review and approval by the network's peer-review publication committee, the data access and management committee and the executive committee, as per the network's governance. Information regarding submitting proposals and accessing data may be found on the CCEDRRN website.[81]

Ethics statements

Data collection within the CCEDRRN registry was approved by the research ethics boards of record for all participating sites.

Acknowledgments

In memory of Roger Stoddard (1958-2022),[82] we recognize his outstanding contributions to our research team and project. He was an active patient partner within CCEDRRN, and he advocated strongly for more research on long term sequelae of COVID-19 and post-intensive care syndrome. This paper is a testament to his work within CCEDRRN's patient partner committee.

We also gratefully acknowledge the assistance of Ms. Amber Cragg and would like to thank The University of British Columbia clinical coordinating center staff, legal, ethics, privacy and contract staff, and the research staff at each of the participating institutions in the network outlined in the attached supplement (Supplementary Table 3). We would also like to thank CCEDRRN national coordinator Vi Ho, and provincial coordinators Josie Kanu (BC), Aimee Goss (SK), Connie Taylor and Vlad Latiu (ON), Corine DeMone (NS), and Chantal Lanthier, Alexandra Nadeau, Xiaoqing Xue, and David Ianuzzi (QC) for their support in collecting data for this study. The network would not exist today without the dedication of these professionals. We would also like to thank Catherine Truchon and Marie-Claude Breton at the Institut national d'excellence en santé et services sociaux for their collaboration with this project. Thank you to all the patient partners who shared their lived experiences and perspectives to ensure that the knowledge we cocreate addresses the concerns of patients and the public. Creating the largest network of collaboration across Canadian emergency departments would not have been possible without the tireless efforts of emergency department chiefs, and research assistants at participating sites. Finally, our most humble and sincere gratitude to all our colleagues in medicine, nursing and the allied health professions who have been on the frontlines of this pandemic from day 1 staffing our ambulances, emergency departments, intensive care units and hospitals bravely facing the risks of COVID-19 to look after our fellow citizens and after each other. We dedicate this network to you.

Funding

The network received peer-reviewed funding from the Canadian Institutes of Health Research (447679, 464947, and 466880), Ontario Ministry of Colleges and Universities (C-655-2129), Saskatchewan Health Research Foundation (5357), Genome BC (COV024 and VAC007), Fondation du CHU de Québec (Octroi No. 4007), and Sero-Surveillance and Research (COVID-19 Immunity Task Force Initiative). The BC Academic Health Science Network and BioTalent Canada provided non-peer reviewed funding. These organizations are not-for-profit, and had no role in study conduct, analysis, or manuscript preparation. Patrick Archambault has received a Fonds de recherche du Québec - Santé (FRQS) Senior Clinical Scholar Award.

Conflicts of interests

All authors have no competing interests.

Collaborators

Canadian COVID-19 Emergency Department Rapid Response Network (CCEDRRN) investigators for the Network of Canadian Emergency Researchers and the Canadian Critical Care Trials Group: Patrick Fok, Hana Wiemer, Samuel Campbell, Kory Arsenault, Tara Dahn, Kavish Chandra, Patrick Archambault, Joel Turner, Lars Grant, Éric Mercier, Gregory Clark, Sébastien Robert, Raoul Daoust, Laurie Morrison, Steven Brooks, Ivy Cheng, Krishan Yadav, Michelle Welsford, Rob Ohle, Justin Yan, Rohit Mohindra, Megan

Landes, Tomislav Jelic, Ankit Kapur, Phil Davis, Andrew McRae, Brian Rowe, Katie Lin, Stephanie VandenBerg, Jake Hayward, Jaspreet Khangura, Corinne Hohl, Daniel Ting, Maja Stachura, Frank Scheuermeyer, Balijeet Braar, Craig Murray, John Taylor, Ian Martin, Sean Wormsbecker, Matt Bouchard, Lee Graham, Colleen McGavin.

Contributors

PMA, MA, CMH, RJR, JH conceived the study, with input on the design and selection of variables from the other contributors. PMA, LDG, CMH, SD, and RJR obtained funding on behalf of the Canadian COVID-19 Emergency Department Rapid Response Network (CCEDRRN) investigators. PMA and MA facilitated training of research assistants and data collection along with other members of the CCEDRRN and can verify the underlying data. RJR, JH, and DSY developed the analytic plan. JH and DSY performed the analysis, with assistance from RJR, PMA, CMH and MA including accessing and verification of underlying data. All contributors provided input on interpretation of findings. PA, MA, RJR, LDG, CMH and JH drafted the manuscript with additional input from all contributors. PMA is the guarantor of this work. All authors have approved the final manuscript.

References

1. WHO Coronavirus (COVID-19) Dashboard. Updated November 30, 2023. https://covid19.who.int/. Accessed December 2, 2023.
2. Nordvig AS, Rajan M, Lau JD, et al. Brain fog in long COVID limits function and health status, independently of hospital severity and preexisting conditions. *Front Neurol*. 2023;May 11; (14):1150096 doi:10.3389/fneur.2023.1150096
3. Gallegos M, Morgan ML, Burgos-Videla C, Caycho-Rodríguez T, Martino P, Cervigni M. The impact of long Covid on people's capacity to work. *Ann Work Expo Health*. 2023;67(7):801-804. doi: 10.1093/annweh/wxad029.
4. Powell M. Living with Covid19. NIHR Themed Review: Living with Covid19; October 2020; doi:10.3310/themedreview_41169
5. BMJ. Paul Garner: For 7 weeks I have been through a roller coaster of ill health, extreme emotions, and utter exhaustion. The BMJ. Published May 5, 2020. https://blogs.bmj.com/bmj/2020/05/05/paul-garner-people-who-have-a-more-protracted-illness-need-help-to-understand-and-cope-with-the-constantly-shifting-bizarre-symptoms/. Accessed October 11, 2022.
6. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. Published October 6, 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1. Accessed May 26, 2023.
7. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21(3):133-146.

8. Katz GM, Bach K, Bobos P, et al. Understanding How Post–COVID-19 Condition Affects Adults and Health Care Systems. *JAMA Health Forum*. 2023;4(7):e231933-e231933.
9. McNaughton CD, Austin PC, Sivaswamy A, et al. Post-acute health care burden after SARS-CoV-2 infection: a retrospective cohort study. *CMAJ*. 2022;194(40):E1368-E1376.
10. WHO. Global COVID-19 Clinical Platform Case Report Form (CRF) for Post COVID condition (Post COVID-19 CRF). Published February 9, 2021. https://www.who.int/publications/i/item/global-covid-19-clinical-platform-case-report-form-(crf)-for-post-covid-conditions-(post-covid-19-crf-). Accessed May 25, 2023.
11. Chu RYK, Szeto KC, Wong IOL, Chung PH. A global scale COVID-19 variants time-series analysis across 48 countries. *Front Public Health*. 2023; Apr 27;(11):1085020 doi:10.3389/fpubh.2023.1085020
12. Abdul Rashid MR, Syed Mohamad SN, Tajjudin AIA, et al. COVID-19 Pandemic Fatigue and Its Sociodemographic, Mental Health Status, and Perceived Causes: A Cross-Sectional Study Nearing the Transition to an Endemic Phase in Malaysia. *Int J Environ Res Public Health*. 2023;20(5):4476.
13. Are EB, Song Y, Stockdale JE, Tupper P, Colijn C. COVID-19 endgame: From pandemic to endemic? Vaccination, reopening and evolution in low- and high-vaccinated populations. J Theor Biol. 2023; (559):111368.
14. Hohl CM, Rosychuk RJ, McRae AD, et al. Development of the Canadian COVID-19 Emergency Department Rapid Response Network population-based registry: a methodology study. *Canadian Medical Association Open Access Journal*. 2021;9(1):E261-E270.
15. Hohl CM, Rosychuk RJ, Archambault PM, et al. The CCEDRRN COVID-19 Mortality Score to predict death among nonpalliative patients with COVID-19 presenting to emergency departments: a derivation and validation study. *Canadian Medical Association Open Access Journal*. 2022;10(1):E90-E99.
16. McRae AD, Hohl CM, Rosychuk R, et al. CCEDRRN COVID-19 Infection Score (CCIS): development and validation in a Canadian cohort of a clinical risk score to predict SARS-CoV-2 infection in patients presenting to the emergency department with suspected COVID-19. *BMJ Open*. 2021;11(12):e055832.
17. Hohl CM, Hau JP, Vaillancourt S, et al. Sensitivity and Diagnostic Yield of the First SARS-CoV-2 Nucleic Acid Amplification Test Performed for Patients Presenting to the Hospital. *JAMA Netw Open*. 2022;5(10):e2236288-e2236288.
18. Hohl CM, Rosychuk RJ, Hau JP, et al. Treatments, resource utilization, and outcomes of COVID-19 patients presenting to emergency departments across pandemic waves: an observational study by the Canadian COVID-19 Emergency Department Rapid Response Network (CCEDRRN). *CJEM*. 2022;24(4):397-407.
19. Bola R, Sutherland J, Murphy RA, et al. Patient-reported health outcomes of SARS-CoV-2-tested patients presenting to emergency departments: a propensity score-matched prospective cohort study. Public Health. 2023;(215):1-11.

20. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596). doi:10.1016/S0140-6736(07)61602-X.
21. Archambault PM, McGavin C, Dainty KN, et al. Recommendations for patient engagement in patient-oriented emergency medicine research. *CJEM*. 2018;20(3):435-442.
22. Staniszewska S, Brett J, Simera I, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. Res Involv Engagem. 2017;(3):13.
23. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*. 2022;22(4). doi:10.1016/S1473-3099(21)00703-9
24. Archambault PM, Rosychuk RJ, Audet M, et al. Accuracy of Self-Reported COVID-19 Vaccination Status Compared With a Public Health Vaccination Registry in Québec: Observational Diagnostic Study. *JMIR Public Health and Surveillance*. 2023;9(1):e44465.
25. Tsampasian V, Elghazaly H, Chattopadhyay R, et al. Risk Factors Associated With Post–COVID-19 Condition: A Systematic Review and Meta-analysis. *JAMA Intern Med*. 2023;183(6):566-580.
26. Notarte KI, de Oliveira MHS, Peligro PJ, et al. Age, Sex and Previous Comorbidities as Risk Factors Not Associated with SARS-CoV-2 Infection for Long COVID-19: A Systematic Review and Meta-Analysis. *J Clin Med Res*. 2022;11(24):7314.
27. Jones R, Davis A, Stanley B, et al. Risk Predictors and Symptom Features of Long COVID Within a Broad Primary Care Patient Population Including Both Tested and Untested Patients. *Pathol Oncol Res*. 2021;(12):93-104.
28. van der Maaden T, Mutubuki EN, de Bruijn S, et al. Prevalence and Severity of Symptoms 3 Months After Infection With SARS-CoV-2 Compared to Test-Negative and Population Controls in the Netherlands. *J Infect Dis*. 2022;227(9):1059-1067.
29. Hastie CE, Lowe DJ, McAuley A, et al. Outcomes among confirmed cases and a matched comparison group in the Long-COVID in Scotland study. *Nat Commun*. 2022;13(1):1-9.
30. Feldman DE, Boudrias MH, Mazer B. Long COVID symptoms in a population-based sample of persons discharged home from hospital. *Can J Public Health*. 2022;113(6):930-939.
31. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global Prevalence of Post-Coronavirus Disease 2019 (COVID-19) Condition or Long COVID: A Meta-Analysis and Systematic Review. *J Infect Dis*. 2022;226(9):1593-1607.
32. Jennings G, Monaghan A, Xue F, Mockler D, Romero-Ortuño R. A Systematic Review of Persistent Symptoms and Residual Abnormal Functioning following Acute COVID-19: Ongoing Symptomatic Phase vs. Post-COVID-19 Syndrome. *J Clin Med Res*. 2021;10(24). doi:10.3390/jcm10245913
33. Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2022;28(5):657-666.
34. Jiang DH, Roy DJ, Gu BJ, Hassett LC, McCoy RG. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A State-of-the-Art Review. *JACC Basic Transl Sci*. 2021;6(9):796-

811.

35. Groff D, Sun A, Ssentongo AE, et al. Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection: A Systematic Review. *JAMA Netw Open*. 2021;4(10):e2128568.
36. Epidemiological and clinical perspectives of long COVID syndrome. *American Journal of Medicine Open*. 2023;(9):100033.
37. O'Mahoney LL, Routen A, Gillies C, et al. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. *EClinicalMedicine*. 2023;(55):101762.
38. Natarajan A, Shetty A, Delanerolle G, et al. A systematic review and meta-analysis of long COVID symptoms. *Syst Rev*. 2023;12(1):88.
39. Government of Canada: Statistics Canada. Long-term symptoms in Canadian adults who tested positive for COVID-19 or suspected an infection, January 2020 to August 2022. Published October 17, 2022. https://www150.statcan.gc.ca/n1/daily-quotidien/221017/dq221017b-eng.htm. Accessed March 16, 2023.
40. Government of Canada: Office of the Chief Science Advisor. Post-COVID-19 Condition in Canada: What we know, what we don't know, and a framework for action (Pre-Report). Published December 14, 2022. https://science.gc.ca/site/science/en/office-chief-science-advisor/initiatives-covid-19/post-covid-19-condition-canada-what-we-know-what-we-dont-know-and-framework-action-pre-report. Accessed March 16, 2023.
41. Government of Canada: Office of the Chief Science Advisor. Post-COVID-19 Condition in Canada: What we know, what we don't know, and a framework for action. Published May 17, 2023. https://science.gc.ca/site/science/en/office-chief-science-advisor/initiatives-covid-19/post-covid-19-condition-canada-what-we-know-what-we-dont-know-and-framework-action. Accessed June 6, 2023.
42. Venturelli S, Benatti SV, Casati M, et al. Surviving COVID-19 in Bergamo province: a post-acute outpatient re-evaluation. *Epidemiology & Infection*. 2021;(149):e32.
43. Spatz ES, Gottlieb M, Wisk LE, et al. Three-Month Symptom Profiles Among Symptomatic Adults With Positive and Negative Severe Acute Respiratory Syndrome Coronavirus 2 Tests: A Prospective Cohort Study From the INSPIRE Group. *Clin Infect Dis*. 2022;76(9):1559-1566.
44. Selvakumar J, Havdal LB, Drevvatne M, et al. Prevalence and Characteristics Associated With Post–COVID-19 Condition Among Nonhospitalized Adolescents and Young Adults. *JAMA Netw Open*. 2023;6(3):e235763-e235763.
45. Thaweethai T, Jolley SE, Karlson EW, et al. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. *JAMA*. 2023;329(22):1934-1946. doi:10.1001/jama.2023.8823.
46. Magnusson K, Turkiewicz A, Flottorp SA, Englund M. Prevalence of long COVID complaints in persons with and without COVID-19. *Sci Rep*. 2023;13(1):1-9.
47. Marossy A, Rakowicz S, Bhan A, et al. A Study of Universal Severe Acute Respiratory Syndrome Coronavirus 2 RNA Testing Among Residents and Staff in a Large Group of Care Homes in South London. *J Infect Dis*. 2020;223(3):381-388.

48. Gandhi M, Yokoe DS, Havlir DV. Asymptomatic Transmission, the Achilles' Heel of Current Strategies to Control Covid-19. *N Engl J Med*. 2020;382(22):2158-2160.
49. Akinbami LJ, Kruszon-Moran D, Wang CY, et al. SARS-CoV-2 Serology and Self-Reported Infection Among Adults - National Health and Nutrition Examination Survey, United States, August 2021-May 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(48). doi:10.15585/mmwr.mm7148a4.
50. Canadian Blood Services. COVID-19 seroprevalence increasing. https://www.blood.ca/en/stories/latest-study-results-show-upward-shift-covid-19-prevalence. Accessed November 29, 2023.
51. Caminsky N. Seroprevalence in Canada. COVID-19 Immunity Task Force. Published October 8, 2021. https://www.covid19immunitytaskforce.ca/seroprevalence-in-canada/. Accessed May 26, 2023.
52. Doroshenko A, Lee N, MacDonald C, Zelyas N, Asadi L, Kanji JN. Decline of Influenza and Respiratory Viruses With COVID-19 Public Health Measures: Alberta, Canada. *Mayo Clin Proc*. 2021;96(12):3042-3052.
53. The impact of the COVID-19 pandemic on influenza, respiratory syncytial virus, and other seasonal respiratory virus circulation in Canada: A population-based study. *The Lancet Regional Health - Americas*. 2021;(1):100015.
54. Chaichana U, Man KKC, Chen A, et al. Definition of Post–COVID-19 Condition Among Published Research Studies. *JAMA Netw Open*. 2023;6(4):e235856-e235856.
55. Subramanian A, Nirantharakumar K, Hughes S, et al. Symptoms and risk factors for long COVID in non-hospitalized adults. *Nat Med*. 2022;28(8):1706-1714.
56. Horberg MA, Watson E, Bhatia M, et al. Post-acute sequelae of SARS-CoV-2 with clinical condition definitions and comparison in a matched cohort. *Nat Commun*. 2022;13(1):1-13.
57. Saniasiaya J, Islam MA, Abdullah B. Prevalence of Olfactory Dysfunction in Coronavirus Disease 2019 (COVID-19): A Meta-analysis of 27,492 Patients. *Laryngoscope*. 2021;131(4):865-878.
58. Renaud M, Thibault C, Le Normand F, et al. Clinical Outcomes for Patients With Anosmia 1 Year After COVID-19 Diagnosis. *JAMA Netw Open*. 2021;4(6):e2115352-e2115352.
59. Paderno A, Mattavelli D, Rampinelli V, et al. Olfactory and Gustatory Outcomes in COVID-19: A Prospective Evaluation in Nonhospitalized Subjects. *Otolaryngology–Head and Neck Surgery*. 2020;163(6):1144-1149.
60. Sylvester SV, Rusu R, Chan B, Bellows M, O'Keefe C, Nicholson S. Sex differences in sequelae from COVID-19 infection and in long COVID syndrome: a review. *Curr Med Res Opin*. 2022; 38(8):1391-1399. doi:10.1080/03007995.2022.2081454
61. Bai F, Tomasoni D, Falcinella C, et al. Female gender is associated with long COVID syndrome: a prospective cohort study. *Clin Microbiol Infect*. 2022;28(4):611.e9-e611.e16.
62. Newson L, Lewis R, O'Hara M. Long Covid and menopause - the important role of hormones in Long Covid must be considered. *Maturitas*. 2021;(152):74.

63. Ortona E, Malorni W. Long COVID: to investigate immunological mechanisms and sex/gender related aspects as fundamental steps for tailored therapy. *Eur Respir J*. 2022;59(2). doi:10.1183/13993003.02245-2021
64. Samulowitz A, Gremyr I, Eriksson E, Hensing G. “Brave Men” and “Emotional Women”: A Theory-Guided Literature Review on Gender Bias in Health Care and Gendered Norms towards Patients with Chronic Pain. *Pain Res Manag*. 2018;2018. doi:10.1155/2018/6358624
65. D’Souza A, Fabricius A, Amodio V, et al. Men’s gendered experiences of rehabilitation and recovery following traumatic brain injury: A reflexive thematic analysis. *Neuropsychol Rehabil*. 2022;32(3):337-358. doi:10.1080/09602011.2020.1822882
66. Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol*. 2021;93(2):1013-1022.
67. The Writing Committee for the COMEBAC Study Group, Morin L, Savale L, et al. Four-Month Clinical Status of a Cohort of Patients After Hospitalization for COVID-19. *JAMA*. 2021;325(15):1525-1534.
68. Heesakkers H, van der Hoeven JG, Corsten S, et al. Clinical Outcomes Among Patients With 1-Year Survival Following Intensive Care Unit Treatment for COVID-19. *JAMA*. 2022;327(6):559-565.
69. Bradley MC, Perez-Vilar S, Chillarige Y, et al. Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings From April 2020 to August 2021. *JAMA*. 2022;327(20):2015.
70. Covello RD, Pasin L, Fresilli S, et al. Meta-Analysis of Glucocorticoids for Covid-19 Patients Not Receiving Oxygen. *NEJM Evidence*. 2023;2(5). doi:10.1056/EVIDoa2200283
71. Yoshikawa M, Asaba K. Educational Attainment Decreases the Risk of COVID-19 Severity in the European Population: A Two-Sample Mendelian Randomization Study. *Front Public Health*. 2021;(9):673451.
72. Perlis RH, Santillana M, Ognyanova K, et al. Prevalence and Correlates of Long COVID Symptoms Among US Adults. *JAMA Netw Open*. 2022;5(10):e2238804-e2238804.
73. Thompson EJ, Williams DM, Walker AJ, et al. Long COVID burden and risk factors in 10 UK longitudinal studies and electronic health records. *Nat Commun*. 2022;13(1):1-11.
74. Pan D, Pareek M. Toward a Universal Definition of Post–COVID-19 Condition—How Do We Proceed? *JAMA Netw Open*. 2023;6(4):e235779-e235779.
75. Damant RW, Rourke L, Cui Y, et al. Reliability and validity of the post COVID-19 condition stigma questionnaire: a prospective cohort study. *eClinicalMedicine*. 2023;(55). doi:10.1016/j.eclinm.2022.101755
76. Antonelli M, Penfold RS, Merino J, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *Lancet Infect Dis*. 2022;22(1):43-55.
77. Azzolini E, Levi R, Sarti R, et al. Association Between BNT162b2 Vaccination and Long COVID After Infections Not Requiring Hospitalization in Health Care Workers. *JAMA*. 2022;328(7):676-678.

78. Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. *Nat Med*. 2022;28(7):1461-1467.
79. Jimeno-Almazán A, Martínez-Cava A, Buendía-Romero Á, et al. Relationship between the severity of persistent symptoms, physical fitness, and cardiopulmonary function in post-COVID-19 condition. A population-based analysis. *Intern Emerg Med*. 2022;17(8):2199-2208.
80. Bahmer T, Borzikowsky C, Lieb W, et al. Severity, predictors and clinical correlates of Post-COVID syndrome (PCS) in Germany: A prospective, multi-centre, population-based cohort study. *eClinicalMedicine*. 2022;(51). doi:10.1016/j.eclinm.2022.101549
81. Canadian COVID-19 Emergency Department Rapid Response Network. https://www.ccedrrn.com. Accessed December 3, 2023
82. Roger Stoddard (he/him)1958-2022. Canadian Medical Association. https://www.cma.ca/get-involved/patient-voice/roger-stoddard-hehim1958-2022. Accessed November 29, 2023.

Figures

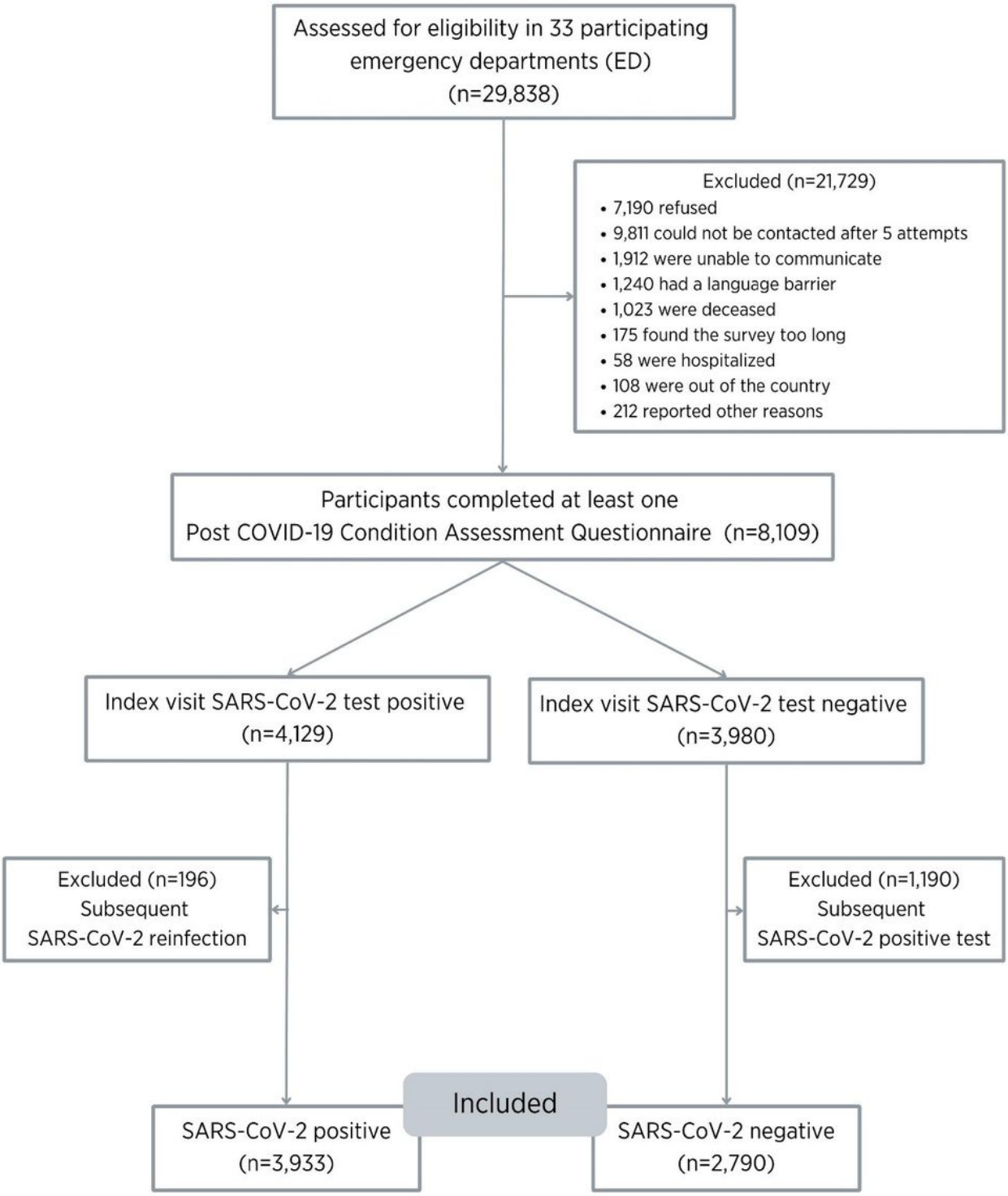
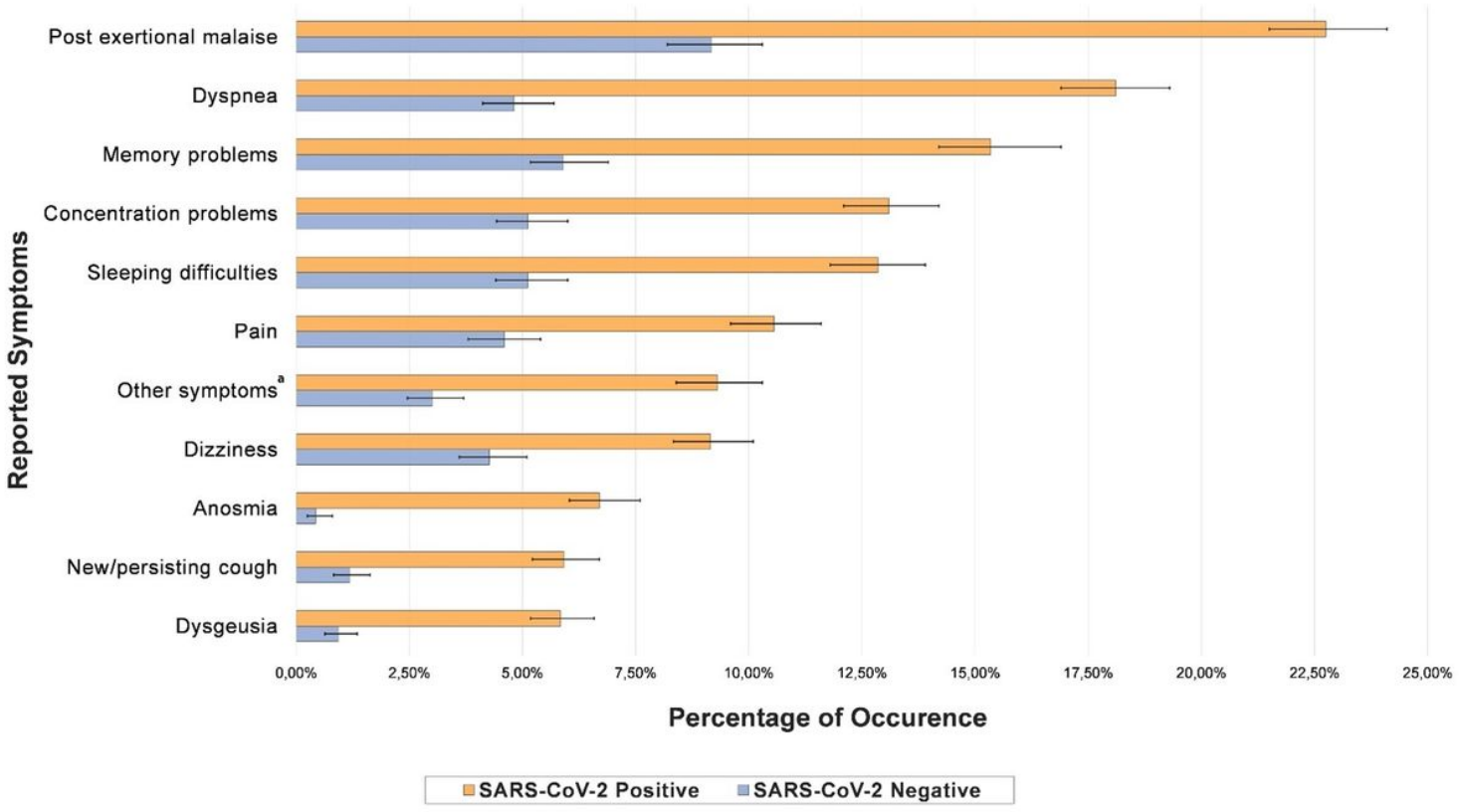


Figure 1

Flow diagram showing included and excluded emergency department patients.

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; Index visit refers to the initial visit to the emergency department associated with the SARS-CoV-2 test, either a nucleic acid amplification test or a rapid antigen test.



	Dysgeusia	New or persisting cough	Anosmia	Dizziness	Other symptoms[a]	Pain	Sleeping difficulties	Concentration problems	Memory problems	Dyspnea	Post exertional malaise
SARS-CoV-2 positive, % (95% CI)	5.84 (5.18-6.58)	5.92 (5.22-6.70)	6.7 (6.04-7.60)	9.15 (8.34-10.10)	9.31 (8.40-10.30)	10.56 (9.60-11.60)	12.85 (11.80-13.90)	13.10 (12.10-14.20)	15.35 (14.20-16.90)	18.11 (16.90-19.30)	22.75 (21.50-24.10)
SARS-CoV-2 negative, % (95% CI)	0.93 (0.64-1.35)	1.18 (0.83-1.64)	0.43 (0.24-0.80)	4.26 (3.60-5.10)	3.00 (2.46-3.70)	4.60 (3.80-5.40)	5.12 (4.41-6.00)	5.12 (4.43-6.00)	5.90 (5.18-6.90)	4.80 (4.12-5.70)	9.17 (8.20-10.30)

Figure 2

Symptoms consistent with Post-COVID-19 condition among patients stratified by SARS-CoV-2 status at baseline.

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; Error bars indicate 95% confidence intervals (95% CI).

[a] The five most reported “other symptoms” by SARS-CoV-2 positive patients were persistent fatigue, hair loss, anxiety, weakness in limbs, and palpitations. The five most reported “other symptoms” by SARS-CoV-2 negative patients were anxiety, persistent fatigue, weakness in limbs, loss of appetite, and problems passing urine.

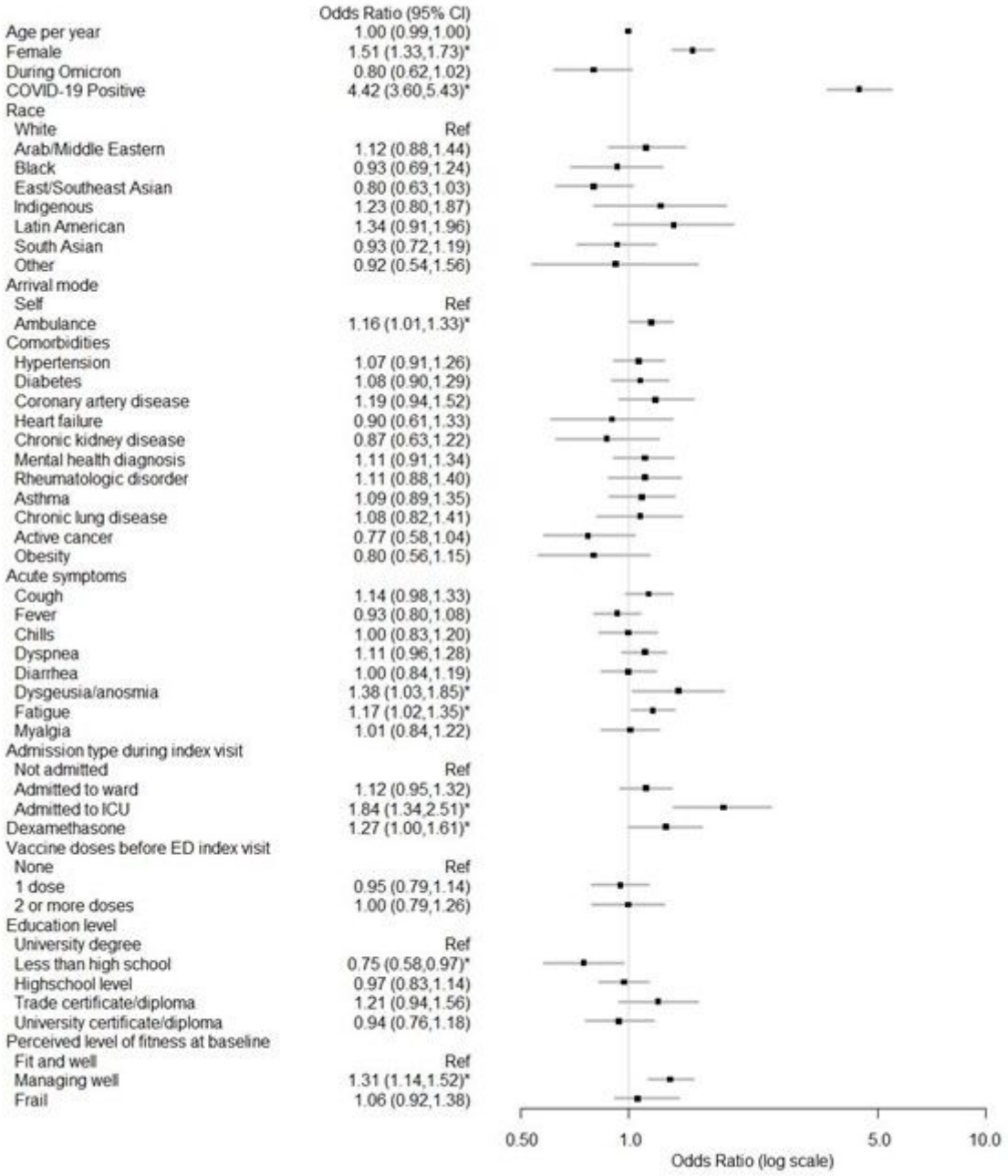


Figure 3

Adjusted odds ratio of factors associated with patients having Post-COVID-19 Condition symptoms following SARS-CoV-2 testing at baseline in emergency departments (N=5,751). [a]

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; Testing refers to nucleic acid amplification test or rapid antigen test.

[a] These results exclude the participants with unknown or missing information on race, education, perceived level of fitness, and vaccination

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalMaterial.docx