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Post-COVID-19 condition symptoms among emergency department patients tested for SARS-CoV-2 infection

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Symptoms of the Post-COVID-19 Condition are often non-specific making it a challenge to distinguish them from symptoms due to other medical conditions. In this study, we compare the proportion of emergency department patients who developed symptoms consistent with the World Health Organization's Post-COVID-19 Condition clinical case definition between those who tested positive for Severe Acute Respiratory Syndrome Coronavirus-2 infection and time-matched patients who tested negative. Our results show that over one-third of emergency department patients with a proven acute infection meet Post-COVID-19 Condition criteria 3 months post-index visit. However, one in five test-negative patients who claim never having been infected also report symptoms consistent with Post-COVID-19 Condition highlighting the lack of specificity of the clinical case definition. Testing for SARS-CoV-2 during the acute phase of a suspected infection should continue until specific biomarkers of Post-COVID-19 Condition become available for diagnosis and treatment.

The COVID-19 pandemic has had a staggering toll on global health with over 775 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

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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 2024, 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 objectives were to assess risk factors for reporting PCC symptoms at 3 months. We also compared the proportion of all ED patients tested for SARS-CoV-2 who met PCC criteria at 6 and 12 months who tested positive compared to those who tested negative and did not report subsequent symptomatic infection.

In this work, we show that 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 a proven acute SARS-CoV-2 infection was the single most important risk factor, one in five patients 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.

Results

Of 29,838 individuals assessed for eligibility, 6,723 met inclusion criteria (58.5% (3933/6723) SARS-CoV-2 positive (Fig. 1); 50.6% (3405/6723) female; mean age, 54.4 years [SD: 17.9] (Table 1; Supplementary Tables 1, 2)). Among all participants, there was very little difference between biological sex and self-reported gender with 3405 (50.6%) participants identified as being female and 3318 (49.4%) participants identified as being male based on chart review, and 3367 (50.1%) self-identifying as being a female and 3252 (48.4%) as being male on phone follow-up (Supplementary Tables 1, 2). 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. In test-positive patients, PCC symptoms were also more frequently reported in female participants (45.5% (871/1916)) compared to male participants (32.8% (662/2017)), (Supplementary Table 3). At 6 months, the proportion of test-positive patients reporting at least one PCC symptom was 38.2% (1317/3444, 95% CI: 36.6–39.9%) compared to 19.5% (526/2691, 95% CI: 18.1–21.1%) among test-negative patients. At 12 months, the proportion of test-positive patients reporting at least one PCC symptom was 33.1% (698/2109, 95% CI: 31.1–35.1%) compared to 17.3% (209/1207, 95% CI: 15.3–19.6%) among test-negative patients. Compared to the proportion of symptomatic patients at three months, 5.8% less SARS-CoV-2 positive patients and 3.4% less SARS-CoV-2 negative patients had at least one ongoing PCC-consistent symptom at twelve months.

At the three-month time point, 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, intensive care unit (ICU) admissions, and perceived fitness (Table 1). For test-positive patients with and without PCC, there were no differences for the number of vaccine doses (Table 1), types of vaccines administered before ED index visit (Supplementary Table 4), and days elapsed since last vaccine dose (141 days for test-positive patients with PCC vs. 142.5 days for test-positive patients without PCC; Supplementary Table 5). 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 of SARS-CoV-2 vaccine doses, and perceived fitness (Table 1). For test-negative patients with and without PCC-consistent symptoms, there were no differences for the types of vaccines administered before ED index visit (Supplementary Table 4), or days elapsed since last vaccine dose (61 days for test-negative patients with PCC-consistent symptoms vs. 67.5 days for test-positive patients without PCC; Supplementary Table 5). 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. When stratifying PCC symptoms reported by pandemic period (pre-Omicron vs. during Omicron) (Supplementary Fig. 1), patients infected during Omicron period report more memory problems, concentration problems, and dizziness than patients infected in pre-Omicron period. None of the SARS-CoV-2 negative patients reported olfactory symptoms during the Omicron period.

The most important predictor of reporting PCC symptoms at three months was having tested SARS-CoV-2 positive during index ED visit (adjusted OR (aOR) = 4.42, 95% CI: 3.60–5.43; Fig. 3, Supplementary Table 6). 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 the 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% CI: 0.79–1.26).

Discussion

A high proportion of ED patients reported ongoing PCC symptoms three months after their ED visit, regardless of whether they were infected with SARS-CoV-2 or not. The proportion of patients reporting ongoing symptoms at 6 and 12 months remained high with only a small decrease over time. At three months, 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[14,15,16]. 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[17]. Systematic reviews from around the world also produced similar results[18–25]. Our results differed from a Canadian survey study in the general population[26,27], that reported that only 15% of patients developed PCC after an acute infection[28], suggesting that ED patients are at higher risk of developing PCC than in the general population.

We found a high rate of PCC-consistent symptoms in test-negative patients. This is consistent with other investigators[14,29] who found that

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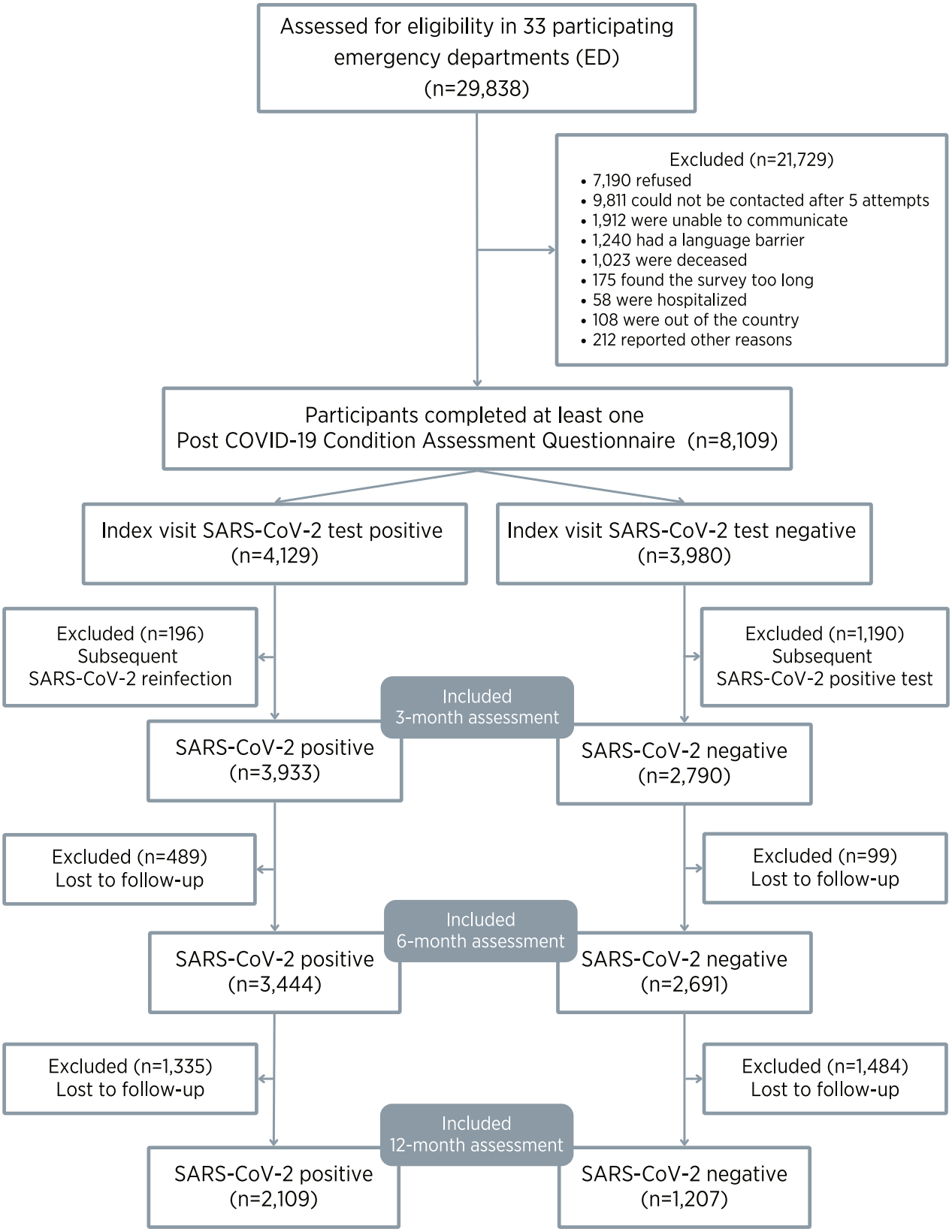

Fig. 1 | Flow diagram showing included and excluded emergency department patients at 3, 6, and 12 months. SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; Index visit refers to the initial visit to the emergency department associated with the SARS-CoV-2 test, either a nucleic acid amplification test or a rapid antigen test.

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Table 1 | Characteristics of emergency department patients at the time of index visit by SARS-CoV-2 and Post-COVID-19 Condition (PCC) status three months later (*N* = 6723)

Variables [a]	SARS-CoV-2 Positive (*n* = 3933)			SARS-CoV-2 Negative (*n* = 2790)		
	Without PCC symptoms (*n* = 2401)	With PCC symptoms (*n* = 1532)	*P*-value [b]	Without PCC symptoms (*n* = 2212)	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 variant (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)	
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 (%)						
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
Admitted to ward	583/2401 (24.3)	734/1532 (24.4)		940/2212 (42.5)	305/578 (52.8)	

Table 1 (continued) | Characteristics of emergency department patients at the time of index visit by SARS-CoV-2 and Post-COVID-19 Condition (PCC) status three months later (N = 6723)

Variables [a]	SARS-CoV-2 Positive (*n* = 3933)			SARS-CoV-2 Negative (*n* = 2790)		
	Without PCC symptoms (*n* = 2401)	With PCC symptoms (*n* = 1532)	*P*-value [b]	Without PCC symptoms (*n* = 2212)	With PCC symptoms (*n* = 578)	*P*-value [b]
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
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)	

SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus-2, *ED* emergency department, *SD* standard deviation, *ICU* intensive care unit.

[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. Data on self-reported gender is presented in Supplementary Tables 1, 2. Data on the type of vaccine administered for patients reporting two or more vaccine doses is presented in Supplementary Table 4. Data about the number of days between the last vaccine dose and the index ED visit for participants reporting two or more vaccine doses is reported in Supplementary Table 5.

[b]*P*-value comparing patients with PCC symptoms and patients without PCC symptoms stratified by SARS-CoV-2 status. *P*-values were calculated using two-sided T-tests for continuous variables and one-sided unadjusted Pearson's chi-squared tests for categorical variables.

[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[89]. "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.

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[14,29–32], 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[14,29,31].

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[33–35]. 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[36,37], 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[38,39], 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 or biomarker for an underlying process that underpins the development of PCC is needed[31,40–42], 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[43]. While most patients with olfactory symptoms in the acute phase recovered within one month[44,45], 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[46] 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[46], we found that female sex was associated with an increased risk of experiencing PCC[18,47–49]. Potential explanations include the role of sex hormones[50], higher innate immune responses in females[51], and social factors and gender biases that make it more acceptable for women to disclose pain and distress compared to men[22,52,53].

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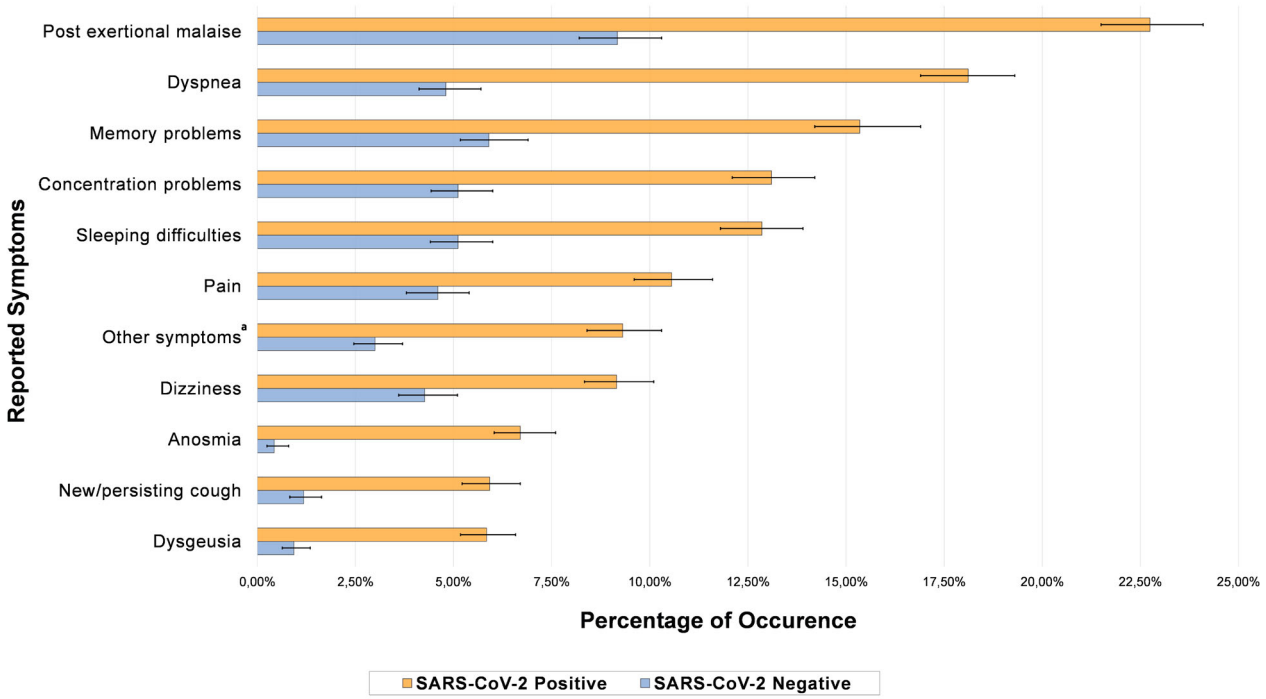

	Dysgeusia	New or persisting cough	Anosmia	Dizziness	Other symptoms[a]	Pain	Sleeping difficulties	Concentration problems	Memory problems	Dyspnea	Post exertional malaise
SARS-CoV-2 positive, % (95% CI)	5.84 (5.18-6.58)	5.92 (5.22-6.70)	6.7 (6.04-7.60)	9.15 (8.34-10.10)	9.31 (8.40-10.30)	10.56 (9.60-11.60)	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)

Fig. 2 | Symptoms consistent with Post-COVID-19 Condition among patients stratified by SARS-CoV-2 status at the time of the index visit to the emergency department. SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; Point estimates for each bar represent the proportion of patients reporting a given symptom in the SARS-CoV-2 positive ($n = 3933$) and SARS-CoV-2 negative ($n = 2790$) cohorts. All patients were included in the calculation of these point estimates. Proportions were calculated by dividing the number of patients reporting a symptom by the total number of patients in each cohort. 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.

Many studies point to certain comorbidities as risk factors for PCC[46]. 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[54–56] indicates a potential overlap with post-intensive care syndrome[54] 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[57,58]. Therefore, dexamethasone may have been an indicator of disease severity, or alternately may have itself contributed to 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[59,60], we found that patients with lower education reported fewer PCC symptoms, consistent with other studies[17,61]. 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[62]. Patients with lower education and socio-economic status also face stigma related to PCC that might lead to underreporting of their symptoms[63].

Although several studies reported that vaccination decreased the rates of PCC symptoms[64–67], 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. For patients who were vaccinated, we did not find any difference between patients with PCC vs. without PCC concerning the vaccine types used, full vaccination status, or time elapsed since last dose. Time elapsed between last dose and ED index visit largely surpassed the seven to fourteen-day period to develop an adequate immune response[68]. However, waning immunity[69] may explain why vaccinated patients were still infected, with more than half of adequately vaccinated SARS-CoV-2 positive patients having received their last dose more than 4 months before their ED visit for a SARS-CoV-2 infection compared to more than half of SARS-CoV-2 negative patients having received their last dose less than 3 months before their ED visit. Although our study

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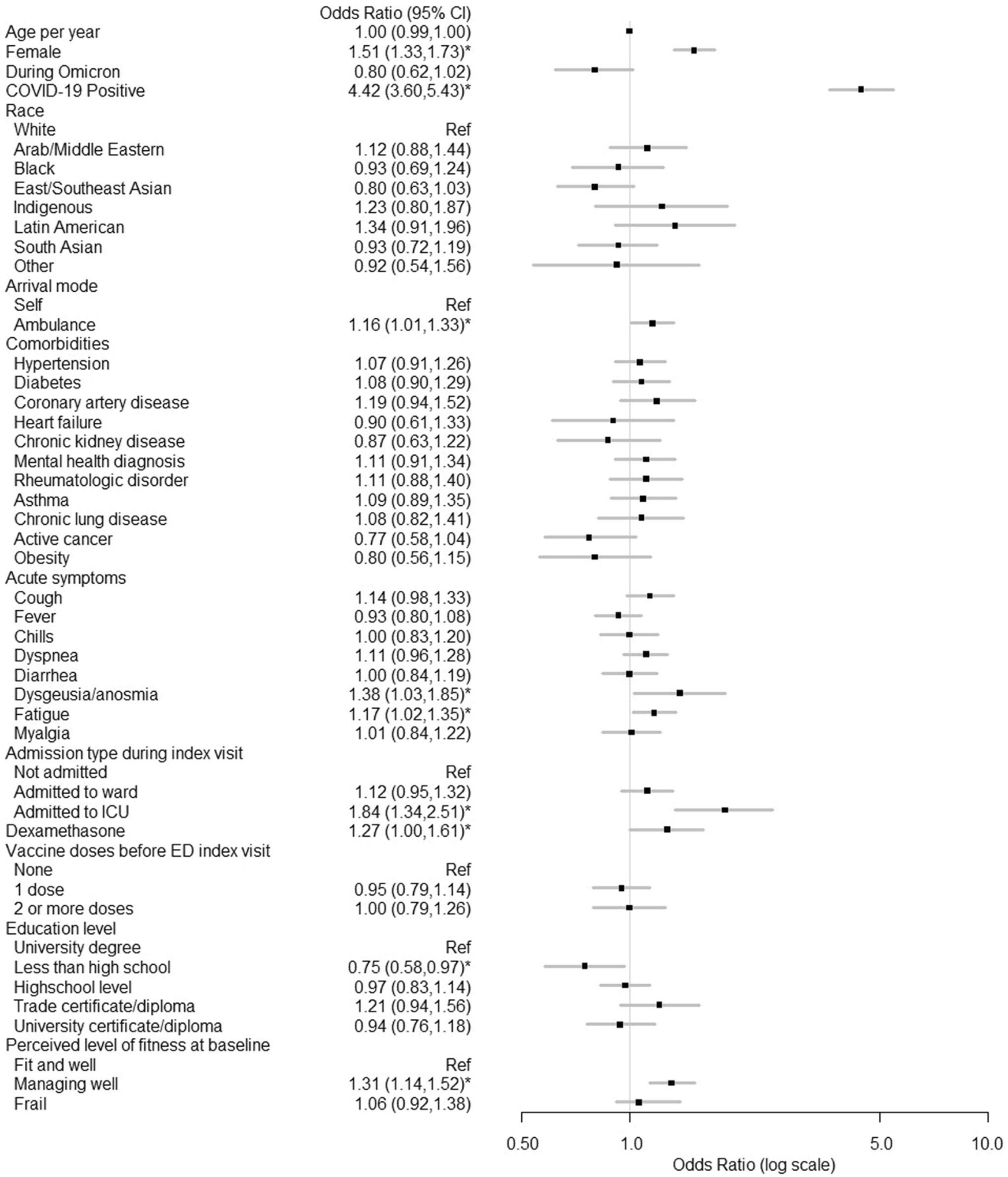

Fig. 3 | Adjusted odds ratio of factors associated with patients having Post-COVID-19 Condition symptoms three months after SARS-CoV-2 testing in emergency departments ($N = 5751$). [a]SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; Ref: Reference group; 95% CI: 95% confidence interval; COVID-19 Positive: refers to the positive COVID-19 status as determined by the result of the nucleic acid amplification test or rapid antigen test. Adjusted odds ratios were calculated using a mixed effects multivariable model. [a]These results exclude the participants with unknown or missing information on race, education, perceived level of fitness, and vaccination. Self-reported gender was not included in the model because biological sex and self-reported gender were highly correlated.

did not find a protective effect, a recent systematic review supports the protective effect of SARS-CoV-2 vaccination against PCC[70]. Moreover, the most effective way to prevent PCC is to prevent SARS-CoV-2 infection (e.g., vaccination, masking, social distancing, hand washing). It is likely that any measure that decreases the incidence of acute SARS-CoV-2 infection will in turn prevent PCC.

Our results concerning the duration of symptoms are also consistent with other studies. In a large Bayesian meta-regression study

that pooled the results of 54 studies and 2 medical record databases with data for 1.2 million individuals (from 22 countries) who had symptomatic SARS-CoV-2 infection, the proportion of patients with ongoing PCC at twelve months was 11.1% (95% CI: 4.7–19.7%) for patients requiring hospital care and 20.5% (9.8-32.9%) for patients requiring ICU admission[71].

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[20,41,42,72]. Second, only a few studies systematically followed SARS-CoV-2 tested patients and integrated clinical data from the acute infection with patient-reported information up to 12 months post infection[31,73,74]. 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[75]. It is not easy to apply in the case of relapsing symptoms and currently includes non-specific symptoms[30]. 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. Third, although we aimed to recruit 4 test-negative controls for each test-positive case, our final ratio was less than 1:1 (3933 cases for 2790 controls) because of periods where the rate of test positivity was very high making it hard to identify 4 time-concurrent negative controls for every positive case and high rates of patients initially testing negative at ED index visit subsequently reporting a positive SARS-CoV-2 test at the time of phone follow-up. This decreases the power of our study but does not impact the validity of its results. Fourth, the use of rapid antigen testing kits delivered to Canadians starting at the end of 2021 for home testing[76] may have helped to decrease less severely affected patients coming to the ED for testing. This may have inflated the estimate of PCC in the sicker ED population compared to lower estimates in the general population.

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 and better understand how to accelerate recovery.

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[77–82]. This specific PCC substudy 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 (Supplementary Table 7) 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. All participants consented to phone interviews. Participants did not receive any financial compensation. We followed the STROBE guidelines[83] (Supplementary Table 8) and reported our patient engagement strategy[84,85] using the GRIPP2-SF guideline (Supplementary Table 9)[85].

Participants

We enrolled consecutive consenting eligible patients aged ≥18 years who presented to one of 33 participating EDs between October 18, 2020, and February 28, 2022, and were tested for SARS-CoV-2 (Supplementary Table 7). 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 (Supplementary Table 7)[77,86]. 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 (Supplementary Table 7).

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[81].

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 3-month mark, and (2) lasted ≥2 months[75]. 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. To be considered having PCC at 6 or 12 months, patients had to have met PCC criteria at 3 months and have persistent symptoms at either 6- or 12-month follow-up times.

Data collection

Trained research assistants: (1) abstracted data on SARS-CoV-2 tested patients including their baseline comorbidities by chart review[77], (2) attempted to contact patients up to five times to obtain consent for phone follow-up six months and twelve months after the ED visit, (3) collected sociocultural and demographic variables including age, sex, self-reported gender, self-reported race, self-reported baseline level of fitness, and self-reported SARS-CoV-2 vaccination status (number of doses received ≥7 days before ED index visit, dates of vaccination, and

vaccine types)[87], (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; Supplementary Methods). Research assistants were instructed to present the questionnaire without mentioning that it was about Long COVID or Post COVID-19 Condition. Research assistants were trained to only document new symptoms that developed since the ED index visit. For each new symptom, we documented the start date reported by participants and determined if the symptom was still ongoing. If the symptom had resolved, research assistants asked patients to determine how long the symptom lasted (a couple of days, <1 week, <2 weeks, <1 month, between 1 and 2 months, between 2 and 6 months, or ≥6 months). 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. This is the first study to use the PCCAQ.

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. The proportion of participants experiencing ongoing symptoms at three months was determined retrospectively using data collected at the six and twelve-month follow-up periods. 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[46,48,88] and the clinical knowledge of the investigator team and patient partners (Supplementary Table 10). We selected baseline sociodemographic characteristics and clinical variables that can easily be assessed in the ED including SARS-CoV-2 testing and baseline acute COVID-19 symptoms reported during ED index visit. We excluded other laboratory testing and imaging because they are not available in all patients. Other secondary outcomes were the proportions of participants with at least one PCC-consistent symptom reported at 6 and 12 months.

Statistical analyses

We used Stata (Version 16.1, StataCorp, College Station, Texas) to calculate summary statistics (e.g., count, percentage, mean, standard deviation [SD]) and stratified data by SARS-CoV-2 status (i.e., test-positive or test-negative) and PCC status (i.e., with or without PCC symptoms). *P*-values were calculated using two-sided T-tests for continuous variables and one-sided unadjusted Pearson's chi-squared tests for categorical variables. We calculated the proportion of patients with PCC symptoms with 95% confidence intervals (95% CI). Mixed effects logistic regression models modeled 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 < 0.05 was considered statistically significant.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

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[89].

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P.M.A., M.A., C.M.H., R.J.R., and J.P.H. conceived the study, with input on the design and selection of variables from the other contributors. P.M.A., R.J.R., L.G., S.D., J.J.P., S.B., K.C., P.D., M.E.K., E.B.P., M.L., S.G., K.N.D., R.D., L.J.M., M.M., E.M., J.S.P., Se.V., D.S., A.D.M., B.V., H.W., P.T.F. and C.M.H. obtained funding on behalf of the Canadian COVID-19 Emergency Department Rapid Response Network (CCEDRRN) investigators, the Network of Canadian Emergency Researchers and the Canadian Critical Care Trials Group. P.M.A. and M.A. facilitated training of research assistants and data collection along with other members of the CCEDRRN and can verify the underlying data. R.J.R., J.P.H., and D.S.Y. developed the analytic plan. J.P.H. and D.S.Y. performed the analysis, with assistance from R.J.R., P.M.A., C.M.H., and M.A. including accessing and verification of underlying data. All contributors provided input on interpretation of findings namely P.M.A., R.J.R., M.A., J.P.H., L.G., S.D., J.J.P., S.B., L.J.M., R.D., D.S.Y., H.W., P.T.F., A.D.M., K.C., M.E.K., D.S., B.V., M.M., E.M., S.V., S.A., D.Z., P.D., K.N.D., J.S.P., M.L., S.G., E.B.P. and C.M.H. P.M.A., M.A., R.J.R., L.G., C.M.H., and J.P.H. drafted the manuscript with additional input from S.D., J.J.P., S.B., L.J.M., R.D., D.S.Y., H.W., P.T.F., A.D.M., K.C., M.E.K., D.S., B.V., M.M., E.M., S.V., S.A., D.Z., P.D., K.N.D., J.S.P., M.L., S.G., and E.B.P. P.M.A. is the guarantor of this work. All authors have approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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