Post-COVID-19 Condition Characterizing the Burden of Symptoms Using Standardized Assessment: A Prospective Observational Cohort British Columbia, Canada

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Abstract

Background: Systematic evaluation of patients with the post-COVID-19 infections using standardized symptom assessment tools and laboratory testing in the context of clinical care has not been reported previously.

Methods: This is a cohort of individuals referred to post-COVID-19 recovery clinics in British Columbia from July 9, 2020 to March 10, 2022. The purpose of the clinics was to systematically assess patients for 3-month post-COVID-19 infections, using validated symptom assessment tools for shortness of breath, fatigue, neuropsychiatric symptoms, and organ dysfunction as measured by laboratory tests. Patients were referred according to specified criteria, including hospitalization or persistence of symptoms. For our analysis, we included the patients who were referred and evaluated at 3-month post-COVID-19 infection with persistent symptoms. The period chosen corresponds to waves 1–4 in British Columbia.

Results: In total, 892 patients were included (median [IQR] age, 53 [42,63] years, with 54.0% females, 39.7% white ethnicity, and 62.0% hospitalized). Shortness of breath (85.9%), fatigue (75.7%), weakness (56.1%), memory problem (47.3%), and myalgia (45.6%) were the most common symptoms reported. Phenotypes of different patients and wave of infection were found associated with different long COVID-19 clinical manifestations after controlling for vaccination status and the underlying comorbidities.
Conclusions: Using validated symptom assessment tools, we describe the variability, severity, and frequency of symptoms in this cohort with long COVID-19. Further studies are required to assess the heterogeneity of the long COVID-19 manifestations using standardized assessments to better target therapeutic treatments.

Résumé
Contexte: L’évaluation systématique des patients après une infection par le SRAS-CoV-2 à l’aide d’outils normalisés d'évaluation des symptômes et d’examens de laboratoire dans le contexte des soins cliniques n’a jamais été mise en évidence auparavant.
Résultats: Au total, 892 patients ont fait partie de l’analyse (âge médian de 53 ans, écart interquartile [EIQ] de 42 à 63; 54,0% sont des femmes; 39,7% sont de race blanche; 62,0% ont été hospitalisés). L’essoufflement (85,9%), la fatigue (75,7%), la faiblesse (56,1%), les troubles de la mémoire (47,3%) et la myalgie (45,6%) sont les symptômes mentionnés le plus souvent. On constate que les différents phénotypes des patients et la vague au cours de laquelle est survenue l’infection sont associés à des symptômes différents de la COVID-19 longue après la prise en compte du statut vaccinal et des affections comorbides sous-jacentes.

Keywords: Long COVID, post-COVID-19 condition, long haul COVID-19, post acute COVID-19 syndrome, risk factors

Introduction
The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus has affected almost 650 million people worldwide. The long COVID-19 or post-COVID-19 condition (PCC) is a complex condition defined by the World Health Organization (WHO) as patients with probable or confirmed SARS-CoV-2 infection, 3 months from onset, with symptoms lasting for at least 2 months, that cannot be explained by alternative diagnosis. Weakness, fatigue, impaired concentration, and shortness of breath are commonly reported symptoms. The pathophysiology of the post-COVID-19 condition is unclear, but the proposed mechanism includes direct viral infection, hyperinflammation, immunological response, microthrombosis, and component of post-critical care illness.

A growing recognition of the diversity of clinical manifestations of post-COVID-19 infection is observed, but minuscule to describe manifestations during different waves of the COVID-19 infection in British Columbia (BC), Canada. We established the Post-COVID-19 Interdisciplinary Clinic Care Network (PC-ICCN) to systematically provide care and ensure standardization of follow-up and assessments using validated tools to assess the long-term effects of acute COVID-19 infection. We sought to objectively quantify burden of illness as measured by standardized questionnaires and validated patient-reported outcome measures (PROMs) at 3 months, referred to Post-COVID-19 Recovery Clinics (PCRC) in BC, Canada.
Post-COVID-19 condition characterizing burden of symptoms

Definitions of the COVID-19 waves
Definitions of the COVID-19 waves 1–4 were derived from Canadian national reports by visual examination of waves for BC.9,10 Wave 1 was defined as March 1, 2020–September 30, 2020, wave 2 as October 1, 2020–February 14, 2021, wave 3 as February 15, 2021 to July 31, 2021, and wave 4 as August 1, 2021–January 2, 2022. It was assumed as wild type phenotype (wave 1), Alpha (B.1.1.7 and Q lineages; wave 2); Beta (B.1.351 and descendent lineages) and Gamma (P.1 and descendent lineages) (wave 3), and Delta (B.1.617.2 and AY lineages; wave 4).11 The patients were assigned to waves based on date of their SARS-CoV-2 PCR test.

Outcomes
All patients were examined for during initial visits at approximately 3 month from the initial COVID-19 positive PCR test, and subsequently planned for standardized clinic visits at 6-, 12-, and 18-month intervals. All were interviewed either in-person or through telehealth by a team, including general internal medicine specialists, nurses, and research assistants. All patients were administered standardized questionnaires and PROMs and surveillance laboratory testing at 3-month to 6-month intervals according to clinical protocols.8 Shortness of breath was self-reported by the patient, and was measured using the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ); score of >10 was considered abnormal.12 Fatigue was self-reported by the patient as well as assessed using the Fatigue Severity Scale (FSS); mean score of ≥4 was considered abnormal.13 The patients were also asked to report of other manifestations persistent for 3 months. General anxiety disorder (GAD), depression, and post-traumatic stress disorder (PTSD) were screened using the Generalized Anxiety Disorder-2 (GAD-2; score ≥3 was conceived positive for anxiety),14 the Patient Health Questionnaire-2 (PHQ-2; score ≥3 was considered positive for depression),15 and the Primary Care (PC) PTSD Screen for the Diagnostic and Statistical Manual (DSM)-5 (PC-PTSD-5; score ≥3 was considered positive for PTSD),16 respectively.

Statistical analyses
Descriptive statistics were used to summarize the cohort characteristics at the time of COVID-19 infection. Continuous variables were presented as median (interquartile range [IQR]), and categorical variables were presented as frequency (proportions).

For the purpose of analysis, presence or absence for shortness of breath and fatigue was defined by

Methods
Settings and population
The PC-ICCN has PCRC located at four institutions, in two out of five health authorities in BC, representing almost 75% of the provincial population. The PCRC referral criteria were (1) standardized discharge protocol from hospital for acute COVID-19 admission in the Vancouver Coastal Health/ Providence Health Care and Fraser Health Authorities, and (2) nonhospitalized patients with persistent manifestations at 3 months (beginning Spring 2021). Central triage was established in September 2021 and referral criterion was revised based on clinical considerations and data as per learning health systems methodology.

Inclusion criteria
The analytic cohort inclusion criteria were PC-ICCN patients (as defined above) composed of: (1) formerly hospitalized patients with acute COVID-19 infection, and (2) nonhospitalized patients with persistent symptoms at 3 months. All patients were aged 19 years or older with laboratory-confirmed polymerase chain reaction (PCR) test for SARS-CoV-2 infection, referred to the PCRC from June 12, 2020 to January 2, 2022, who had completed standardized initial questionnaires at 3 months (±45 days) from their initial COVID-19 infection.

Exclusion criteria for analysis
Since referral criteria were different for hospitalized versus nonhospitalized patients (former did not require having persistent manifestations whereas the latter did), we sought to describe those with persistent symptoms. Thus, by excluding those without symptoms, we had a cohort of patients who by WHO definition had persistent symptoms at 3 months and represented the “long COVID-19” cohort, assessed using the same tools, and exposed to the same clinical care.

Definitions of patients’ characteristics
Demographic data were collected at the time of referral to PC-ICCN clinic and program registration. Race/ethnicity was self-identified by patients and grouped into four categories. Comorbidities prior to the COVID-19 infection were derived based on the International Classification of Diseases (ICD)-9 and ICD-10 diagnostic codes (see Supplementary Table S1). Cancer status was self-reported. The COVID-19 vaccination status was obtained from the provincial public health information system.
abnormal scores on the UCSD SOBQ and FSS tool, respectively. Abnormal laboratory test results were determined from laboratory-generated abnormality based on laboratory reference range or provincial median of the upper limit or the lower limit of the reference range, as appropriate.

We employed rank-biserial or point-biserial correlation coefficient (bounded between −1 and 1) to explore the relationship between a selected set of laboratory measures and the long COVID-19 symptoms. Specifically, we were interested in the association between (1) fatigue with hemoglobin and ferritin, (2) shortness of breath with hemoglobin, B-type natriuretic peptide (BNP)/N-terminal (NT)-proBNP, D-dimer, and C-reactive protein (CRP), (3) weakness with hemoglobin and CRP, and (4) myalgia with CRP. The interpretation of the correlation coefficient in absolute terms was similar to Pearson’s correlation coefficient.

Multiple logistic regression was used to examine association between a priori list of patient characteristics and symptoms, namely shortness of breath, fatigue, weakness, myalgia, cough, headaches, and memory problems. A priori patient characteristics of interest were age, gender, race/ethnicity, the COVID-19 infection wave, and patient’s clinic referral criteria (hospitalization or nonhospitalization for the initial COVID-19 infection). The measure of association was reported as odds ratio (OR) with corresponding 95% confidence interval (CI) after controlling for vaccination status (vaccinated with at least 1 dose versus not vaccinated) and the underlying comorbidities, such as asthma, chronic obstructive pulmonary disease, diabetes, cardiovascular disease, and hypertension. For sensitivity analyses, we also examined the association between patient characteristics and self-reported shortness of breath and fatigue.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R Studio version 2021.9.2.382 (R Studio PBC, Boston, MA).

Ethics
Ethical approval was obtained from the University of British Columbia Research Ethics Board (#H21-0266). As this study was a part of clinical care, written consent was not required from patients, because this was considered for secondary use of clinically acquired data.

Results
Figure 1 describes the patient flow of our analytic cohort from the population referred to PC-ICCN. In total, 5138 patients were referred, of which 1551 hospitalized and 1691 nonhospitalized patient referrals were accepted to PCRC during the enrolment period. In total, 1293 hospitalized patient referrals were not examined in clinic because of the following reasons: not meeting clinical criteria (n = 495), inability to contact patient for appointment (n = 382), patient declined clinic visit (n = 395), moved out of province (n = 2), or transferred to long-term care/other facility (n = 15). In all, 602 nonhospitalized patient referrals were not examined in clinic because of the following reasons: not meeting clinical criteria (n = 284), inability to contact patient for appointment (n = 136), patient declined clinic visit (n = 170), moved out of province (n = 13), or transferred to long-term care/other facility (n = 0). In total, 874 of the accepted hospitalized patient referrals were excluded from analysis because the first clinic visit occurred more than 3 months after infection (n = 868), absence of the confirmed COVID-19 test (n = 0), aged less than 19 years (n = 6), and no persistent symptoms at 3 months (n = 124). In total, 1325 of the accepted nonhospitalized patient referrals were excluded from analysis because the first clinic visit occurred more than 3 months after the infection (n = 978), absence of the confirmed COVID-19 test (n = 311), aged less than 19 years (n = 36), and no persistent symptoms at 3 months (n = 27). The final analyzed population comprised 892 patients (553 hospitalized patient and 339 nonhospitalized patient referral pathways).

Table 1 describes the characteristics of our cohort as stratified by wave of the initial COVID-19 infection, median age of 53 (IQR: 42, 63) years, 54.0% females, 39.7% white ethnicity, hospitalized 62.0%, and intensive care admission 24.0%. The majority of patients did not have baseline comorbidities.

Classical Long COVID-19 Symptoms
Figure 2 shows the distribution of the long COVID-19 symptoms in our cohort. The most common symptoms were shortness of breath (85.9%), fatigue (75.7%), and weakness (56.1%). Other symptoms reported in our cohort were with variable distribution (Supplement Figure S1).

Figure 3 shows burden of the long COVID-19 symptoms in our cohort, with 85.2% of patients experiencing two or more long COVID-19 symptoms concurrently. Most commonly, 20.9% of patients reported having four symptoms, and 8.5% had all six symptoms. The most common cluster of symptoms included shortness of breath, fatigue, weakness, and myalgia.
Post-COVID-19 condition characterizing burden of symptoms

Figure 1. Flow chart of participants in PCRC leading to analyzed population.

Organ Dysfunction and Laboratory Abnormalities
Using standardized laboratory testing of participants at 3 months, variability in abnormal laboratory test results are shown in Figure 4. The most common laboratory abnormalities were D-Dimer (34.4%), CRP (28.7%), and urine albumin creatinine ratio (ACR) (23.9%).

Correlation between Selected Sets of Laboratory Markers and Classical Long COVID-19 Symptoms
No association was observed between fatigue and hemoglobin (r = 0.013) and ferritin (r = 0.034). Similarly, shortness of breath was not associated with hemoglobin (r = –0.063), BNP/NT Pro-BNP (r = 0.041, –0.041), D-dimer (r = 0.015), or CRP (r = 0.040). No relationship was observed between weakness and hemoglobin (r = 0.010) or CRP (r = 0.046), and between myalgia and CRP (r = 0.092).

Association between Patient Characteristics and Long COVID-19 Symptoms
Figure 5 summarizes ORs for age, gender, race/ethnicity, the COVID-19 infection wave, and clinic referral criteria for the long COVID-19 symptoms. Compared to younger age group, older age groups were more likely to experience memory problems (OR 1.23 [95% CI 0.84, 1.79], P = 0.002). Older age groups (age ≥ 60 years) were less likely to experience headaches than younger age (<45 years) (OR 0.52 [95% CI 0.33, 0.81], P = 0.015). Females were more likely to experience memory problems (OR 0.59 [95% CI 0.44, 0.80], P < 0.001). Asian and other race were less likely to experience memory issues compared to white race (OR 0.52 [95% CI 0.33, 0.81], P = 0.015). Females were more likely to experience memory problems compared to white race (OR 0.59 [95% CI 0.44, 0.80], P < 0.001). Asian and other race were less likely to experience memory issues compared to white race (OR 0.52 [95% CI 0.33, 0.81], P = 0.015). Females were more likely to experience memory problems compared to white race (OR 0.59 [95% CI 0.44, 0.80], P < 0.001). Asian and other race were less likely to experience memory issues compared to white race (OR 0.52 [95% CI 0.33, 0.81], P = 0.015). Females were more likely to experience memory problems compared to white race (OR 0.59 [95% CI 0.44, 0.80], P < 0.001). Asian and other race were less likely to experience memory issues compared to white race (OR 0.52 [95% CI 0.33, 0.81], P = 0.015). Females were more likely to experience memory problems compared to white race (OR 0.59 [95% CI 0.44, 0.80], P < 0.001). Asian and other race were less likely to experience memory issues compared to white race (OR 0.52 [95% CI 0.33, 0.81], P = 0.015). Females were more likely to experience memory problems compared to white race (OR 0.59 [95% CI 0.44, 0.80], P < 0.001). Asian and other race were less likely to experience memory issues compared to white race (OR 0.52 [95% CI 0.33, 0.81], P = 0.015). Females were more likely to experience memory problems compared to white race (OR 0.59 [95% CI 0.44, 0.80], P < 0.001). Asian and other race were less likely to experience memory issues compared to white race (OR 0.52 [95% CI 0.33, 0.81], P = 0.015). Females were more likely to experience memory problems compared to white race (OR 0.59 [95% CI 0.44, 0.80], P < 0.001). Asian and other race were less likely to experience memory issues compared to white race (OR 0.52 [95% CI 0.33, 0.81], P = 0.015). Females were more likely to experience memory problems compared to white race (OR 0.59 [95% CI 0.44, 0.80], P < 0.001). Asian and other race were less likely to experience memory issues compared to white race (OR 0.52 [95% CI 0.33, 0.81], P = 0.015). Females were more likely to experience memory problems compared to white race (OR 0.59 [95% CI 0.44, 0.80], P < 0.001). Asian and other race were less likely to experience memory issues compared to white race (OR 0.52 [95% CI 0.33, 0.81], P = 0.015). Females were more likely to experience memory problems compared to white race (OR 0.59 [95% CI 0.44, 0.80], P < 0.001).
Table 1. Demographics of Participants Enrolled in PCRC at their First Clinical Visit with At Least One Persistent Symptom Stratified by Wave

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Wave 1</th>
<th>Wave 2</th>
<th>Wave 3</th>
<th>Wave 4</th>
</tr>
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<tbody>
<tr>
<td># Patients</td>
<td>892</td>
<td>25</td>
<td>294</td>
<td>456</td>
<td>117</td>
</tr>
<tr>
<td>Age at COVID-19 infection (median, IQR)</td>
<td>53 (42,63)</td>
<td>42 (36,61)</td>
<td>52 (41,62)</td>
<td>53 (42,64)</td>
<td>52 (44,64)</td>
</tr>
<tr>
<td>&lt;45</td>
<td>287 (32.2%)</td>
<td>15 (60.0%)</td>
<td>100 (34.0%)</td>
<td>138 (30.3%)</td>
<td>34 (29.0%)</td>
</tr>
<tr>
<td>45–59</td>
<td>303 (34.0%)</td>
<td>3 (12.0%)</td>
<td>102 (34.7%)</td>
<td>153 (33.5%)</td>
<td>45 (38.5%)</td>
</tr>
<tr>
<td>≥60</td>
<td>302 (33.8%)</td>
<td>7 (28.0%)</td>
<td>92 (31.3%)</td>
<td>165 (36.2%)</td>
<td>38 (32.5%)</td>
</tr>
<tr>
<td>Female Sex (n, %)</td>
<td>482 (54.0%)</td>
<td>8 (32.0%)</td>
<td>179 (60.9%)</td>
<td>236 (51.8%)</td>
<td>59 (50.4%)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>354 (39.7%)</td>
<td>0 (0%)</td>
<td>104 (35.4%)</td>
<td>170 (37.3%)</td>
<td>80 (68.4%)</td>
</tr>
<tr>
<td>Asian</td>
<td>341 (38.2%)</td>
<td>0 (0%)</td>
<td>111 (37.7%)</td>
<td>218 (47.8%)</td>
<td>12 (10.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>131 (14.7%)</td>
<td>1 (4.0%)</td>
<td>44 (15.0%)</td>
<td>64 (14.0%)</td>
<td>22 (18.8%)</td>
</tr>
<tr>
<td>Unanswered</td>
<td>66 (7.4%)</td>
<td>24 (96.0%)</td>
<td>35 (11.9%)</td>
<td>4 (0.9%)</td>
<td>3 (2.6%)</td>
</tr>
<tr>
<td>Comorbidities prior to Infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>239 (26.8%)</td>
<td>8 (32.0%)</td>
<td>83 (28.2%)</td>
<td>115 (25.2%)</td>
<td>33 (28.2%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>31 (3.5%)</td>
<td>1 (4.0%)</td>
<td>12 (4.1%)</td>
<td>15 (3.3%)</td>
<td>3 (2.6%)</td>
</tr>
<tr>
<td>COPD</td>
<td>219 (24.6%)</td>
<td>3 (12.0%)</td>
<td>83 (28.2%)</td>
<td>99 (21.7%)</td>
<td>34 (29.1%)</td>
</tr>
<tr>
<td>Dementia</td>
<td>29 (3.3%)</td>
<td>1 (4.0%)</td>
<td>13 (4.4%)</td>
<td>11 (2.4%)</td>
<td>4 (3.4%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>315 (35.3%)</td>
<td>8 (32.0%)</td>
<td>106 (36.1%)</td>
<td>166 (36.4%)</td>
<td>35 (29.9%)</td>
</tr>
<tr>
<td>CVD</td>
<td>313 (35.1%)</td>
<td>8 (32.0%)</td>
<td>105 (35.7%)</td>
<td>154 (33.8%)</td>
<td>46 (39.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>395 (44.3%)</td>
<td>6 (24.0%)</td>
<td>128 (43.5%)</td>
<td>218 (47.8%)</td>
<td>43 (36.8%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>36 (4.0%)</td>
<td>0 (0%)</td>
<td>15 (5.1%)</td>
<td>15 (3.3%)</td>
<td>6 (5.1%)</td>
</tr>
<tr>
<td>Clinic referral criteria: Hospitalized for initial COVID-19 infection</td>
<td>553 (62.0%)</td>
<td>10 (40.0%)</td>
<td>141 (48.0%)</td>
<td>324 (71.1%)</td>
<td>78 (66.7%)</td>
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<tr>
<td>ICU</td>
<td>214 (24.0%)</td>
<td>5 (20.0%)</td>
<td>50 (17.0%)</td>
<td>115 (25.2%)</td>
<td>44 (37.6%)</td>
</tr>
<tr>
<td>COVID-19 Vaccine status prior to COVID-19 Infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>767 (86.0%)</td>
<td>25 (100%)</td>
<td>289 (98.3%)</td>
<td>371 (81.3%)</td>
<td>82 (70.1%)</td>
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<tr>
<td>1 dose</td>
<td>95 (10.7%)</td>
<td>0 (0%)</td>
<td>5 (1.7%)</td>
<td>81 (17.8%)</td>
<td>9 (7.7%)</td>
</tr>
<tr>
<td>2 doses</td>
<td>28 (3.1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4 (0.9%)</td>
<td>24 (20.5%)</td>
</tr>
<tr>
<td>3 doses</td>
<td>2 (0.2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (1.7%)</td>
</tr>
</tbody>
</table>

headaches (OR 1.50 [95% CI 1.06, 2.13], P = 0.044) than wave 3. Hospitalized clinic referral patients were associated with less fatigue (OR 0.33 [95% CI 0.22, 0.50], P < 0.001), weakness (OR 0.4 [95% CI 0.28, 0.56], P < 0.001), headaches (OR 0.41 [95% CI 0.29, 0.57], P < 0.001), and memory problems (OR 0.53 [95% CI 0.38, 0.75], P < 0.001), compared to nonhospitalized referral patients.

Sensitivity analyses showed that self-reported shortness of breath was associated with race (P = 0.047) and wave of infection (P = 0.048), but these associations were not present with UCSD SOBQ tool. Similarly, self-reported fatigue was associated with gender (P = 0.061), and race (P = 0.013), but these associations were not present with FSS tool (Supplementary Table S2).

**Discussion**

We described a cohort of persistently symptomatic patients referred to PCRC. These patients were evaluated using standardized validated symptom assessment tools and laboratory testing at 3 months post-COVID-19 infection. We observed variability and burden of symptoms, with the most common being shortness of breath, fatigue, and weakness. Wave of
Post-COVID-19 condition characterizing burden of symptoms

**Figure 2.** Distribution of the classical long COVID-19 symptoms at 3-month period in our cohort referred to PCRC.

**Figure 3.** Burden of the classic long COVID-19 symptoms at 3-month period in our cohort referred to PCRC.
initial COVID-19 infection was associated with weakness and headaches. Overall, laboratory abnormalities were variable and prevalent in the cohort, and did not correlate to symptoms.

The strengths of our study included standardized testing within the context of clinical evaluation in a large and multi-ethnic cohort of the COVID-19 survivors referred to PCRC. Recognizing the difference in referral criteria, we focused only on the patients who met criteria for “long COVID-19” with persistent symptoms at 3 months. Unlike previous studies, our use of standardized tools within clinical context, facilitated objective assessment of multiple dimensions of individual function post-COVID-19 infection. Discrepancies were observed between association of shortness of breath and fatigue using self-reported and validated tools with gender and ethnicity. This highlighted the importance of validated standardized tools as robust assessments, because it avoided intrinsic bias with self-reporting.

Our cohort had a high burden and variability of symptoms than previously reported ones. This could be due to the use of standardized reporting tools and referral criteria of PC-ICCN population, which is not commonly reported in the literature. Variability in symptoms could be explained by different phenotypes of PCC. From the literature, cognitive disturbances were more common with those treated as an outpatient. Similarly, among ICU survivors, symptoms could be due to post-critical illness rather than the post-COVID-19 condition. Identifying different phenotypes of PCC using standardized assessments was critical, as it could help tailor clinical pathways, therapeutic treatments, and pathophysiology research.

We add to the literature by showing that wave of the initial COVID-19 infection was only associated with weakness and headaches, despite being well-reported differences in the acute course of COVID-19 according to wave. Wave of infection was a proxy for different variants of COVID-19, which could lead to differences in infectivity and virulence. Given that burden of symptoms did not seem to vary much with wave, we hypothesized that symptoms were more likely related to host factors, or host–virus interaction factors rather than the severity of infection per se.

Unlike previous studies observing that females, older age, and severity at acute phase of the disease were associated with PCC, we did not observe this in our cohort. This could be due to the use of validated reporting tools, rather than self-reporting. Another observation was that clinic referral criteria (nonhospitalized for initial COVID-19) infection was associated with fatigue, weakness, headaches, and memory problems but not shortness of breath. This was not understood in clear terms and therefore supported further investigations.
Figure 5. Association between patient characteristics and the classic long COVID-19 manifestations.
Distribution and variability in laboratory abnormalities were not described previously in a cohort, such as the present study, and deserved further follow-up. We noted that symptoms were independent of hematological, cardiac, and inflammatory laboratory tests. The clinical significance of these laboratory abnormalities in better understanding symptoms and pathophysiology of PCC was not clear. More research is required to understand pathophysiology of PCC and development of better biomarkers.

Limitations to this analysis were discerned of a contemporaneous cohort of patients referred according to standardized but different criteria for assessment and care. First, those with persistent symptoms were de facto those with the “long COVID-19” condition whereas those automatically referred from hospitalization status did not have symptoms. It was observed that 28% of the hospitalized patients had no symptoms, and this information is important to acknowledge. We included only those patients having persistent symptoms in analytic cohort in order to describe and evaluate those symptoms by severity and type. We excluded patients that we were unable to contact or never attended PCRC. Therefore, we did not know whether this patient population was different from the study cohort. Second, some data were missing because this was a clinical database; thus, evaluating only those with complete data could skew some of the findings. Third, sample size, especially for wave 1, was another limitation, given that the first PCRC, with limited capacity, was opened on June 12, 2020 (4 months after the beginning of the pandemic), thus limiting the number of patients examined during the first 6 months of the pandemic. Finally, we did not have a control group of patients hospitalized during the same period without COVID-19 and those in the community with these symptoms without history of the COVID-19 infection. However, as the goal was to describe the symptom burden of those referred to PCRC, these are relative limitations.

Conclusions

Standardized evaluation of symptoms at 3 months post-COVID-19 infection in the context of clinical care identified wide variation of persistent symptoms in a multiethnic population of BC, Canada. The future research must better understand the determinants and variability of symptoms to design and test therapeutic interventions. We believe that standardized assessment using validated tools of people who have had the COVID-19 infection is critical for the future research.

Author Contributions

Adeera Levin and Karen C. Tran were responsible for the conception and designing of the paper. Lee Er and Selena Shao were responsible for analysis of the data. All the authors were accountable for interpretation of the data and drafting of the manuscript for important intellectual content.

Declaration of interest

Dr. James A. Russell reported patents owned by the University of British Columbia (UBC) that were related to the use of PCSK9 inhibitor(s) in sepsis, and related to the use of vasopressin in septic shock and a patent owned by Ferring for use of selepressin in septic shock. Dr. Russell is an inventor on these patents. He was a founder director and shareholder in Cyon Therapeutics Inc. and a shareholder in Molecular You Corp. Dr. Russell is a member of the Data and Safety Monitoring Board (DSMB) of an NIH-sponsored trial of plasma in COVID-19 (PASS-IT-ON).

Dr. Russell is no longer actively consulting for any industry. He received consulting fees during the last 3 years from the following:

1. Asahi Kesai Pharmaceuticals of America (AKPA) (was developing recombinant thrombomodulin in sepsis)
2. SIB Therapeutics LLC (for developing a sepsis drug)
3. Ferring Pharmaceuticals (for manufacturing vasopressin and developing selepressin) Dr. Russell is no longer actively consulting for the following:
   a. La Jolla Pharmaceuticals (developing angiotensin II; Dr. Russell chaired the DSMB of a trial of angiotensin II from 2015 to 2017)
   b. PAR Pharma (sells prepared bags of vasopressin)

Dr. Russell reports having received an investigator-initiated grant from Grifols (entitled “Is HBP a mechanism of albumin’s efficacy in human septic shock?”) that was provided to and administered by UBC.

All other authors declared no conflict of interest.

Acknowledgements

We thank the patients for providing data to understand long COVID-19. We also thank physicians, allied health care team, and research assistant who provided care to patients at PCRC.
References


Supplementary

Prevalence proportion of general symptoms

- Shortness of breath (self-reported): 66.5%
- Fatigue (self-reported): 66.3%
- Weakness: 56.1%
- Muscle of joint aches: 45.6%
- Cough: 34.6%
- Headache: 33.5%
- Palpitations: 25.4%
- Chest pain: 25.4%
- Other: 21.4%
- Loss of taste and smell: 20.4%
- Chest congestion (phlegm production): 19.7%
- Hoarse voice/change in voice: 15.7%
- Sore throat: 12.2%
- Nausea or vomiting: 11.8%
- Rash: 9.5%
- Diarrhea: 9.1%
- Fever: 5.2%
- Discolouration of fingers or toes: 4.5%

Prevalence proportion of neurologic symptoms

- Trouble with sleep: 51.0%
- Memory problems searching for word: 47.3%
- Muscle stiffness or slowness of movement: 41.6%
- Weakness in face arms or legs: 38.1%
- Headache necks tightness or eye pain: 36.1%
- Shooting stabbing or burning pains: 34.4%
- Dizziness spinning unsteadiness: 31.1%
- Difficulty with walking or balance: 27.7%
- Numbness loss of feeling in face him: 22.3%
- Vision loss in one or both eyes: 21.5%
- Bowel or bladder problems: 18.7%
- Loss of sense of smell or taste: 17.9%
- Tinnitus ringing in your ears: 17.0%
- Tremor shaking: 13.9%
- Muscle twitches or involuntary movement: 13.6%
- Loss of the ability to speak or understand others: 8.9%
- Hearing loss: 7.8%
- Loss of consciousness reduced awareness: 3.9%
- Seizures: 1.0%

Figure S1. Distribution of general symptoms and neurological symptoms at 3 months.
### Table S1. Definition for Race/Ethnicity and Comorbidities Based on ICD-9 and ICD-10 Codes

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>—</td>
</tr>
<tr>
<td>Asian</td>
<td>Including East Asian, South Asian and Southeast Asian</td>
</tr>
<tr>
<td>Other</td>
<td>including Indigenous, Black, Middle East, Latin American, multiracial and other</td>
</tr>
<tr>
<td>Unanswered categories</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbidity condition</th>
<th>ICD-9 &amp; ICD-10 code</th>
</tr>
</thead>
</table>
| Stroke                | ICD-9: 430, 431, 432, 434, 436  
                      | ICD-10: I60, I61, I63, I64, H34.1 |
| COPD                  | ICD-9: 490, 491, 492, 496  
                      | ICD-10: J40, J41, J42, J43, J44 |
| Asthma                | ICD-9: 493  
                      | ICD-10: J45 |
| Dementia              | ICD-9: 290, 294, 331, 797, 291.1, 291.2  
| Hypertension          | ICD-9: 401, 402, 403, 404, 405  
                      | ICD-10: I10, I11, I12, I13, I15 |
| Cardiovascular Disease| ICD-9: 410, 411, 412, 413, 414, 441, 428, 430, 431, 432, 433, 434, 436, 437, 438, 427.3  
| Diabetes              | ICD-9: 250  
                      | ICD-10: E10, E11 |

### Table S2. Sensitivity Analyses on the association between patient characteristics and self-reported prevalence of shortness of breath and fatigue

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Shortness of Breath (Self-reported)</th>
<th>Fatigue (Self-reported)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 45-59 (vs. Age &lt;45)</td>
<td>1.40 [95% CI: 0.96, 2.04]</td>
<td>0.1082</td>
</tr>
<tr>
<td>Age &gt;=60 (vs. Age &lt;45)</td>
<td>1.01 [95% CI: 0.66, 1.53]</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (vs. Female)</td>
<td>1.09 [95% CI: 0.81, 1.46]</td>
<td>0.5762</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian race (vs. White)</td>
<td>0.74 [95% CI: 0.52, 1.05]</td>
<td>0.0047</td>
</tr>
<tr>
<td>Other race (vs. White)</td>
<td>0.92 [95% CI: 0.59, 1.45]</td>
<td></td>
</tr>
<tr>
<td>Unspecified race (vs. White)</td>
<td>0.36 [95% CI: 0.20, 0.64]</td>
<td></td>
</tr>
<tr>
<td>COVID-19 Infection Wave</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wave 1 &amp; 2 (vs. Wave 3)</td>
<td>1.25 [95% CI: 0.89, 1.77]</td>
<td>0.3283</td>
</tr>
<tr>
<td>Wave 4 (vs. Wave 3)</td>
<td>1.29 [95% CI: 0.80, 2.07]</td>
<td></td>
</tr>
<tr>
<td>Clinic referral criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized for COVID (vs. Non-hospitalized)</td>
<td>0.70 [95% CI: 0.50, 0.99]</td>
<td>0.0448</td>
</tr>
</tbody>
</table>