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SYNTHESIS

(ARCHIVED) Persistent Symptoms and Post-Acute COVID-19 in Adults – What We Know So Far

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Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents are intended to provide a rapid review of the evidence on a specific aspect or emerging issue related to COVID-19.

Updates to Latest Version

This document replaces the previous version *COVID-19 – What We Know So Far About… Long-Term Sequelae* (July 10, 2020).[1] Since the previous version, meta-analyses, case series and cohort studies with larger sample sizes have been published on the topic. The previous version concentrated on long-term sequelae such as smell and taste dysfunction and multisystem inflammatory syndrome in children (MIS-C), while postulating that other neurological, respiratory and cardiovascular sequelae could emerge based on the pathology of other respiratory viral pathogens.

This rapid review updates the evidence on the persistent symptoms of post-acute COVID-19 by organ system, explores the risk factors associated with persistent symptoms, and outlines the implications of post-acute COVID-19.

Key Findings

- The most prevalent persistent (>21 days since symptom-onset) symptoms in patients with post-acute COVID-19 (range of mean or median in the included studies, noting high heterogeneity among studies) were:

    - Fatigue: 30–78%
    - Cough: 20–27%
    - Joint and/or muscle pain: 19–44%
    - Headache: 18–50%
    - Shortness of breath: 16–55%
- The primary risk factors for having persistent post-acute COVID-19 symptoms were the presence of comorbidities (6 out of 11 studies), increased disease severity during acute infection (6 out of 11 studies), and female sex (3 out of 11 studies). The presence of these comorbidities increased the risk of persistent symptoms by at least 70%.
- Central to planning for the healthcare and social support of recovering patients, there needs to be a standardized definition of post-acute COVID-19. Further research is required to better characterize post-acute COVID-19, including longitudinal research into the risk factors contributing to an increased risk of persistent symptoms, taking into consideration racial and ethnic disparities.

Background

For the purposes of this "What We Know So Far", we consider persistent symptoms (sequelae) as those that develop or last beyond 3 weeks or 21 days since symptom-onset. The three-week period is consistent with evidence that live or viable virus is rarely detected past 10 days in mild to moderate cases and rarely detected past 20 days in severe cases.[2] Some patients with persistent symptoms have been termed "long-haulers" and the condition called "long COVID".[3,4] Others have described a "post-acute" phase of the disease with symptoms persisting 3–4 weeks after symptom-onset (or after discharge from inpatient care), or a "chronic" phase with symptoms persisting past 12 weeks.[5-7] There are no agreed-upon definitions for these time points after initial infection.[7-9]

Amenta et al. (2021) described three categories of post-acute COVID-19: 1) residual symptoms that persist after recovery from acute infection; 2) organ dysfunction that persists after initial recovery; and 3) new symptoms or syndromes that develop after initial asymptomatic or mild infection.[6] For the purposes of this rapid review, post-acute COVID-19 will include all these subcategories. Shah et al. (2021) noted that post-acute symptoms can be "singular, multiple, constant, transient, or fluctuating, and can change in nature over time."[9]

In order to plan for a potential increased use of healthcare resources post-COVID-19, the healthcare system needs to understand the post-acute symptoms of recovering patients. Risk factors that can contribute to post-acute COVID-19 can be used to monitor patients at risk of further morbidity and direct resources appropriately. The purpose of this document is to examine what is known about the persistent symptoms of post-acute COVID-19, along with the associated risk factors for post-acute disease.

Methods and Scope

In considering feasibility, scope, and a need for responsiveness, we chose a rapid review as an appropriate approach to understanding the persistent symptoms of post-acute COVID-19. A rapid review is a knowledge synthesis where certain steps of the systematic review process are omitted (e.g., quality assessment) in order to be timely.[10]

Literature searches were conducted in MEDLINE (March 1, 2021), National Institutes of Health COVID-19 Portfolio (Preprints) (March 5, 2021), Embase (March 2, 2021) and Global Health/Scopus (March 4, 2021) (search strategies available upon request). We searched PubMed and Google Scholar on April 7, 2021 for additional articles of interest.

English-language peer-reviewed and non-peer-reviewed records that described persistent symptoms post-acute COVID-19 were included. We restricted the search to articles published after January 1, 2020. This rapid review concentrated on evidence from systematic reviews and meta-analyses, supplemented by primary literature where appropriate and necessary. We reviewed citations from included articles to identify additional research.

Where prevalence data were reported for multiple end-points for follow-up, we report the latest follow-up period. To limit the amount of reviewed studies, we excluded primary research studies with less than 200 patients. Unless otherwise stated and to limit the number of relatively rare symptoms, we only included symptoms reported in at least 10% of patients in a study. Studies were restricted to those with adult patients greater than 17 years of age. Several symptoms were potentially associated with multiple organ systems; however, we reported these symptoms with the organ system where they were most often reported in the literature (e.g., fatigue in neuropsychiatric section, chest pain in cardiovascular section).

Prior to posting, PHO subject-matter experts review all "What We Know So Far" documents. As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in this document is only current as of the date of the respective literature searches.

This document does not report on the indirect impacts of pandemic public health measures on long-term sequelae; e.g., impact of social distancing on mental health or the consequences of deferred health care on chronic disease management. In addition, this "What We Know So Far" does not address the management of patients with long-term sequelae, the underlying mechanisms for the emergence of sequelae, or sequelae related to treatment (e.g., post-intensive care unit [ICU] admission, invasive mechanical ventilation, therapeutics). For information on post-acute COVID-19 in children, please see PHO's upcoming review *Post-Acute COVID-19 and Multisystem Inflammatory Syndrome in Children (MIS-C) – What We Know So Far*.

Results

We screened 2,705 articles identified from database searches: MEDLINE (n=1,523 articles), Global Health and Scopus (n=663), Embase (n=398), and National Institutes of Health COVID-19 Portfolio (Preprints) (n=121). After screening and full-text review, we included four systematic reviews and meta-analyses, and 22 primary research articles. Seven of the 26 (26.9%) articles were non-peer-reviewed preprints.

One-third of the studies included patients from multiple countries (30.8%, 8/26), followed by Italy (15.4%, 4/26), China (11.5%, 3/26), France/England/United States (US) (7.7% each, 2/26), and Germany/Spain/Sweden/Switzerland/Russia (3.8% each, 1/26) (Appendix A). Half of studies included inpatients and outpatients ("mixed") (50.0%, 13/26), followed by inpatients only (46.2%, 12/26) and outpatients only (3.8%; 1/26). Thirteen (50.0%) studies used objective measures of symptoms, seven (26.9%) used a mix of subjective and objective measures, and six (23.1%) used objective measures only. Please refer to Appendix A for additional details on each study (e.g., inpatient vs. outpatient).

Prevalence of Post-acute COVID-19

The prevalence of persistent symptoms ranges widely by study and depends largely on the population studied. Overall, the prevalence of patients with at least one persistent symptom ranged from 31–51%: 31.1% (n=234 patients),[11] 38.5% (n=431),[12] 45.9 (n=246),[13] 49.6% (n=538),[14] 50.9% (n=422),[15] 51.0% (n=478)[16] and 51.4% (n=767).[17]

The prevalence of persistent symptoms decreased with increasing time since symptom-onset. Sudre et al. (2021) noted that the prevalence of persistent symptoms decreased over time (n=558 patients) from 13.3% experiencing persistent symptoms 28 days after symptom-onset, to 4.5% at 56 days, and 2.3% at 84 days.[18] In a study of 20,000 patients in the United Kingdom (UK), 21.0% experienced at least one persistent symptom 45 days after symptom-onset, 13.7% at 84 days.[19] In a cohort study of 323 seropositive cases (mild disease) and 1,072 seronegative cases in Sweden, Havervall et al. (2021) reported on persistent symptoms in healthcare workers, where at least one moderate to severe persistent symptom was reported at 56 days since initial serological test in 26.0% of seropositive cases (seronegative cases: 8.9%), 21.4% (7.2%) at 112 days, and 14.9% (3.4%) at 224 days.[20]

Persistent Symptoms in Post-Acute COVID-19 by System

Neuropsychiatric

The most commonly reported persistent neuropsychiatric symptoms were fatigue (range: 30–78%) and headache (18–50%), followed by cognitive symptoms (e.g., attention disorder, memory loss, anxiety [11–55%]), sleep disorder (11–65%), and smell/taste dysfunction (10–43%).

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)-associated long-term neuropsychiatric symptoms may occur through direct viral neuroinvasion or inflammatory mediators.[21,22] In a systematic review of 35 articles and 123 patients, Parsons et al. (2020) (preprint) modelled and quantified the locations of neurological events using magnetic resonance imaging.[23] 77.2% (95/123) of patients had white matter changes (i.e., corticospinal tract), 74.0% (91/123) had grey matter changes (i.e., bilateral superior temporal cortices, precentral cortices, pallidum), and 58.5% (72/123) had cerebral microbleeds. In a systematic review of seven articles and 1,643 patients, Neishaboori et al. (2020) investigated central nervous system (CNS) neurological complications.[24] The incidence of any CNS complication was 6.3% (95% confidence interval [CI]: 3.32–9.98), with encephalopathy in 2.6% (95% CI: 1.31–4.25) of patients. Other CNS findings (i.e., brain leptomeningeal enhancement, dysexecutive syndrome, brain perfusion abnormalities and ataxia) were found in 13.4% (95% CI: 0.90–35.5) of patients.

SYSTEMATIC REVIEWS AND META-ANALYSES (N=2)

- In a systematic review and meta-analysis of 28 studies and 9,442 patients, Michelen et al. (2020) (preprint) reported the most common and persistent neuropsychiatric symptom was smell/taste dysfunction (43%), followed by fatigue (39%) and anxiety (25%).[25] Follow-up of patients occurred a median of 14–111 days from illness-onset, diagnosis or hospital discharge.
- In a systematic review of 15 articles, Lopez-Leon et al. (2021) (preprint) reported on the long-term effects of COVID-19, including neurological sequelae.[26] Fatigue was reported in 58% (95% CI: 42–73), followed by headache (44%; 95% CI: 13–78), attention disorder (27%; 95% CI: 19–36), taste dysfunction (23%; 95% CI: 14–33), smell dysfunction (21%; 95% CI: 12–32), memory loss (16%; 95% CI: 0–0.55), hearing loss/tinnitus (15% (95% CI: 10–20), anxiety (13%; 95% CI: 3–26),

depression (12%; 95% CI: 3–23) and sleep disorder (11%; 95% CI: 3–24). Follow-up of patients ranged from a mean of 14–110 days post-viral infection.

PRIMARY RESEARCH ARTICLES (N=14)

- Retrospective cohort study and time-to-event analysis of 236,379 patients, Taquet et al. (2021) reported on neuropsychiatric symptoms in patients assessed 168 days after initial diagnosis.[27] Approximately a third of patients at follow-up had a neuropsychiatric diagnosis (33.6%; 95% CI: 33.2–34.1), and 12.8% (95% CI: 12.4–13.3) of patients received a neuropsychiatric diagnosis for the first time. Mood, anxiety or psychotic disorder was reported for the first time in 8.6% (95% CI: 8.3–9.0) of patients.
- Davis et al. (2020) (preprint) reported on an international web-based survey of 3,767 suspected and confirmed COVID-19 cases.[28] 168 days after illness-onset, the most common neuropsychiatric symptoms were fatigue (77.7%, 95% CI: 74.9–80.3), cognitive dysfunction (55.4%; 95% CI: 52.4–58.8), memory problems (50.5%; 95% CI: 47.3–53.6), headache (50%), speech and language issues (38.0%; 95% CI: 34.5–41.0), smell and taste dysfunction (25.2%; 95% CI: 22.5–28.0), and tinnitus (26.2%; 95% CI: 23.5–29.1).
- In an ambidirectional cohort study of 1,733 patients in China, Huang et al. (2021) reported on sequelae at 168 days post-hospitalization.[29] The most commonly reported neuropsychiatric sequelae were fatigue and muscle weakness (63%), sleep difficulties (26%), and smell dysfunction (11%).
- In a study of 1,363 patients assessed 60 days after symptom-onset, Lechien et al. (2021) reported that 24.1% of patients did not subjectively recover from smell dysfunction. In a subset of 233 patients, 15.3% did not recover objectively from smell dysfunction (4.7% not recovered at 168 days).[30]
- In a prospective survey of 751 patients re-examined at a mean 47±7 days (range: 30–71) since first consultation, Chiesa-Estomba et al. (2020) reported that 37% of patients had persistent subjective loss of smell.[31]
- Anastasio et al. (2021) reported on 595 patients assessed at a median of 135 days (interquartile range [IQR]: 102–175) after the onset of symptoms, where 10.3% of patients reported smell/taste dysfunction (10.3%).[32]
- Xiong et al. (2021), in a single-centre longitudinal study of 538 survivors, reported on sequelae experienced 97.0 days (IQR: 95.0–102.0) after hospital discharge.[14] The most common neuropsychiatric sequelae were fatigue (28.3%) and sleep disorder (17.7%).
- Venturelli et al. (2021) reported on persistent symptoms in 510 patients evaluated at a median of 105 days (IQR: 84–127) since symptom-onset, where 36.5% had fatigue.[17]
- In a prospective observational cohort study in the UK, Sudre et al. (2021) reported on symptoms that persisted 28 days or more since illness-onset in 558 patients.[18] Fatigue was reported in 68% of patients, followed by headache (40%), loss of smell (39%) and delirium (11%).
- In a prospective uncontrolled cohort study of 478 patients assessed 112 days after hospital discharge, 31.1% of patients reported fatigue and 12.1% reported tingling in their extremities.[16]
- In a population-based prospective cohort study of 431 patients assessed at 7 months (IQR: 6–8) since diagnosis, Menges et al. (2021) (preprint) reported the most common neuropsychiatric persistent symptom was fatigue (54.7%), followed by mild to moderate anxiety (24.2%), mild to moderate depression (19.9%), and mild to moderate stress (12.0%).[12]
- In a cohort study of 323 seropositive cases and 1,072 seronegative cases in Sweden, Havervall et al. (2021) reported on persistent symptoms in healthcare workers.[20] At 56 days since initial

serological test, 14.6% of seropositive cases (seronegative: 0.6%) had smell dysfunction, followed by fatigue (8.4% vs. 5.3%) and taste dysfunction (7.7% vs. 0.6%).
- In a cross-sectional study of 276 patients with a follow-up at a median of 54 days (IQR: 47–59) since hospital discharge, Mandal et al. (2021) reported 67.3% experienced fatigue and 61.1% had sleeping problems (for those that required at least oxygen supplementation during hospitalization).[33]
- In a prospective cohort study of 277 patients assessed 56–84 days after symptom-onset, Moreno-Perez et al. (2021) reported 34.8% of patients reported fatigue, followed by smell/taste dysfunction (21.4%) and headache (17.8%).[15]

Respiratory

The most commonly reported persistent respiratory symptoms were cough (range: 20–27%) and shortness of breath (16–55%).

Post-mortem studies and reviews have noted diffuse alveolar damage, indicating that longer-term pulmonary sequelae are also possible from COVID-19; for example, interstitial pulmonary fibrosis and pulmonary hypertension.[34-37]

SYSTEMATIC REVIEWS AND META-ANALYSES (N=3)

- In a systematic review and meta-analysis of 28 studies and 9,442 patients, Michelen et al. (2020) (preprint) described 46% of patients reported shortness of breath.[25] Follow-up of patients occurred a mean/median of 14–111 days from illness-onset, diagnosis or hospital discharge.
- In a systematic review and meta-analysis of 15 articles, Lopez-Leon et al. (2021) (preprint) reported on the long-term effects of COVID-19, including respiratory sequelae.[26] Shortness of breath was reported in about a quarter of patients (24%; 95% CI: 14–36), followed by cough (19%; 95% CI: 7–34). Follow-up of patients ranged from a mean of 14–110 days post-viral infection.
- In a systematic review and meta-analysis of seven articles and 380 patients, Torres-Castro et al. (2020) reported that the most common persistent respiratory findings (14–84 days after discharge, measured by spirometry) were altered diffusion capacity of the lungs for carbon monoxide (39%; 95% CI: 24–56) and restrictive pattern (15%; 95% CI: 9–22).[38]

PRIMARY RESEARCH ARTICLES (N=10)

- Davis et al. (2020) (preprint) reported on an international web-based survey of 3,767 suspected and confirmed COVID-19 cases.[28] 168 days after illness-onset, the most common respiratory sequelae were sore throat (59.5%, 95% CI: 57.9–61.1), shortness of breath (37.9%, 95% CI: 34.8–41.0), and cough (20.1%; 95% CI: 17.8–22.8).
- Anastasio et al. (2021) reported on 595 patients assessed at a median of 135 days (IQR: 102–175) after the onset of symptoms, where 42.7% of patients reported shortness of breath.[32]
- In a prospective observational cohort study in the UK, Sudre et al. (2021) reported on symptoms that persisted 28 days or more since illness-onset in 558 patients.[18] The most common respiratory sequelae reported were shortness of breath (37%), followed by persistent cough (27%), sore throat (27%) and hoarse voice (17%).
- Xiong et al. (2021), in a single-centre longitudinal study of 538 survivors, reported on sequelae experienced at 97.0 days (IQR: 95.0–102.0) since hospital discharge.[14] The most common respiratory sequela was post-activity shortness of breath (21.4%).

- Venturelli et al. (2021) reported on persistent symptoms in 510 patients evaluated at a median of 105 days (IQR: 84–127) since symptom-onset, where 29.8% had shortness of breath.[17]
- In a prospective uncontrolled cohort study of 478 patients assessed 112 days after hospital discharge, 16.3% had shortness of breath.[16]
- In a population-based prospective cohort study of 431 patients assessed at 7 months (IQR: 6–8) since diagnosis, Menges et al. (2021) (preprint) reported the most common respiratory sequela (objectively measured using the modified Medical Research Council [mMRC] dyspnea scale) was shortness of breath (24.3%).[12]
- In a cohort study of 323 seropositive cases and 1,072 seronegative cases in Sweden, Havervall et al. (2021) reported on persistent symptoms in healthcare workers.[20] At 56 days since initial serological test, the most common respiratory symptom was shortness of breath (seropositive: 4.3%; seronegative: 1.1%).
- In a prospective cohort study of 277 patients assessed 56–84 days after symptom-onset, Moreno-Perez et al. (2021) reported the most common respiratory sequelae were shortness of breath (34.4%) and cough (21.3%).[15]
- In a cross-sectional study of 276 patients with a follow-up at a median of 54 days (IQR: 47–59) since hospital discharge, Mandal et al. (2021) reported 54.8% experienced shortness of breath (for those requiring oxygen supplementation or respiratory support).[33]
- In a follow-up study of 246 patients assessed at 68 ± 16 days since infection, Trinkmann et al. (2021) reported there was decreased lung function in approximately 50% of patients, as measured by spirometry.[13]

Cardiovascular and Cerebrovascular

The most commonly reported persistent cardiovascular and cerebrovascular symptoms were chest pain (range: 12–24%), tachycardia (11–34%), and palpitations (10–40%).

The expression of the angiotensin-converting enzyme 2 (ACE2) receptor on myocytes, coronary endothelial cells and arterial smooth muscle increases the risk of organ damage in individuals with COVID-19, as the virus uses these receptors to gain entry into cells.[39-41] Thrombosis and acute ischemic stroke are recognized complications of COVID-19.[42,43] In a systematic review and meta-analysis of seven studies and 970 patients, Vakhshoori et al. (2020) reported that acute cardiac injury occurred in 15% (95% CI: 11–20) of patients.[44] In autopsies of 41 patients that died from COVID-19, evidence of cardiac infection was found in 30 patients, resulting in cardiac inflammation and electrocardiographic changes.[45]

SYSTEMATIC REVIEWS AND META-ANALYSES (N=2)

- In a systematic review and meta-analysis of 35 studies and 9,249 patients, Kunutsor and Laukkanen (2020) reported the prevalence of venous thromboembolism was 18.4% (95% CI: 12.0–25.7).[46] Patient follow-up occurred 2–30 days after hospital discharge.
- In a systematic review and meta-analysis of 15 articles, Lopez-Leon et al. (2021) (preprint) reported on the long-term effects of COVID-19.[26] The most common cardiovascular symptom was chest pain (16%; 95% CI: 10–22), followed by tachycardia (11%; 95% CI: 9–14) and palpitations (11%, 95% CI: 6–17). Follow-up of patients ranged from a mean of 14–110 days post-viral infection.

PRIMARY RESEARCH ARTICLES (N=4)

- Davis et al. (2020) (preprint) reported on an international web-based survey of 3,767 suspected and confirmed COVID-19 cases.[28] 168 days after illness-onset, the most common cardiovascular symptoms were palpitations (40.1%; 95% CI: 37.9–44.1), tachycardia (33.7%, 95% CI: 30.8–36.8) and chest pain (23.7%; 95% CI: 20.7–26.0).
- Qin et al. (2021), in a prospective cohort study of 647 patients assessed 84 days following hospital discharge, reported the most persistent symptom was palpitations (10%).[47]
- Anastasio et al. (2021) reported on 595 patients assessed at median of 135 days (IQR: 102–175) after the onset of symptoms, with 11.9% of patients reporting chest pain.[32]
- Xiong et al. (2021), in a single-centre longitudinal study of 538 survivors, reported on sequelae experienced at 97.0 days (IQR: 95.0–102.0) since hospital discharge.[14] The most common cardiovascular sequelae were chest pain (12.3%) and tachycardia (11.2%).

Other Organ Systems

The most commonly reported persistent symptoms (among other organ systems) were joint and/or muscle pain (range: 19–44%), fever/chills/sweats (12–24%), and gastrointestinal symptoms (diarrhea/vomiting/nausea/loss of appetite) (12–21%).

For this section, we included the following systems: immune, endocrine, musculoskeletal, reproductive, urinary, digestive, metabolic, and integumentary.

SYSTEMATIC REVIEWS AND META-ANALYSES (N=1)

- In a systematic review of 15 articles, Lopez-Leon et al. (2021) (preprint) reported on the long-term effects of COVID-19.[26] The most common persistent symptom for other organ systems in this review was hair loss (25%; 95% CI: 17–43), followed by arthralgia (19%; 95% CI: 7–34), sweats (17%; 95% CI: 6–30), nausea/vomiting (16%; 95% CI: 10–23) and weight loss (12%; 95% CI: 7–18). Follow-up of patients ranged from a mean of 14–110 days post-viral infection.

PRIMARY RESEARCH ARTICLES (N=6)

- Davis et al. (2020) (preprint) reported on an international web-based survey of 3,767 suspected and confirmed COVID-19 cases.[28] 168 days after illness onset, myalgia (43.7%; 95% CI: 40.6–46.9) was commonly reported among patients, followed by diarrhea (20.5%, 95% CI: 18.1–23.2), fever (15.0%) and loss of appetite (13.7%, 95% CI: 11.6–16.0).
- In an ambidirectional cohort study of 1,655 patients in China, Huang et al. (2021) reported on sequelae at 168 days post-hospitalization, in which 22% reported hair loss.[29]
- In a prospective observational cohort study in the UK, Sudre et al. (2021) reported on symptoms that persisted 28 days or more since illness-onset in 558 patients.[18] Reported sequelae included were muscle pain (20%), diarrhea (15%), abdominal pain (15%), loss of appetite (13%) and fever (12%).
- Xiong et al. (2021), in a single-centre longitudinal study of 538 survivors, reported on sequelae experienced at 97.0 days (IQR: 95.0–102.0) since hospital discharge, with 23.6% of patients reporting sweating.[14]
- In a population-based prospective cohort study of 431 patients assessed at 7 months (IQR: 6–8) since diagnosis, Menges et al. (2021) (preprint) reported 35.3% of patients experienced pain and discomfort.[12]

- In a prospective cohort study of 277 patients assessed 56–84 days after symptom-onset, Moreno-Perez et al. (2021) reported that 19.6% of patients experienced myalgia/arthralgia and 10.5% reported diarrhea.[15]

Risk Factors

The primary risk factors for having persistent symptoms during post-acute COVID-19 are the presence of comorbidities (e.g., obesity, asthma) (6/11 studies), increased disease severity (6/11 studies), and female sex (3/11).

We reviewed the literature investigating risk factors associated with long-term sequelae. Advanced age, comorbidities, hypertension, diabetes and obesity were risk factors for developing severe disease as well as for subsequent cognitive decline (Baker et al. 2020).[4]

PRIMARY RESEARCH ARTICLES (N=11)

- Retrospective cohort study and time-to-event analysis of 236,379 patients, Taquet et al. (2021) reported on neuropsychiatric symptoms in patients assessed 168 after initial diagnosis.[27] Patients that were admitted to an ICU or hospitalized had a higher risk of neuropsychiatric sequelae, compared to outpatients (see article for full account of neuropsychiatric diagnoses made). The risk of neuropsychiatric first diagnosis was higher in those admitted to an ICU compared to those who were not (hazard ratio [HR]: 2.9; 95% CI: 2.5–3.4).
- In an observational, retrospective, matched cohort study of 47,780 patients, Ayoubkhani et al. (2021) (preprint) reported 29.4% were readmitted after discharge.[48] The risk of respiratory disease after discharge was higher for non-white patients (relative risk [RR]: 11.4; 95% CI: 9.8–13.3) compared to white patients (RR: 5.2; 95% CI: 5.0–5.5). The mean follow-up period was 140±50 days since hospital discharge.
- In a longitudinal cohort study of 2,649 patients, Munblit et al. (2021) (preprint) reported on assessments performed at a median follow-up time since hospital discharge of 218 days (IQR: 200–236).[49] Having pre-existing asthma was associated with an increased risk of persistent neurological (odds ratio [OR]: 2.0; 95% CI: 1.3–3.0) and mood/behavioural (OR: 2.0; 95% CI: 1.2–3.2) symptoms (unclear in paper if OR was adjusted for disease severity). Chronic pulmonary disease was associated with chronic fatigue (OR: 1.7; 95% CI: 1.2–2.3). Female patients were at greater risk of long-term sequelae (all symptom groups).
- In an ambidirectional cohort study of 1,655 patients in China, Huang et al. (2021) reported on sequelae at 168 days post-hospitalization.[29] Comparing those with non-invasive or invasive ventilation to those who did not receive supplementary oxygen, there was a higher risk of persistent fatigue/muscle weakness (OR: 2.7; 95% CI: 1.5–5.0), difficulty walking (OR: 2.5; 95% CI: 1.1–5.5), pain (OR: 1.9; 95% CI: 1.2–3.2), anxiety/depression (OR: 1.8; 95% CI: 1.1–3.0), and decreased walking distance (OR: 2.2; 95% CI: 1.2–4.0).
- Qin et al. (2021), in a prospective cohort study of 647 patients assessed 84 days following hospital discharge, reported there was an increased risk of persistent symptoms as disease severity increased (OR: 1.7; 95% CI: 1.1–2.6) and as hospitalization duration increased (OR: 1.0; 95% CI: 1.0–1.1).[47]
- In a study of 558 patients with symptoms lasting 28 days or more since symptom-onset, Sudre et al. (2021) reported patients that experienced more than five symptoms during the first week of illness had a higher risk of persistent symptoms (OR: 3.5; 95% CI: 2.8–4.5).[18] The only comorbidity that was predictive of persistent symptoms was asthma (OR: 2.1; 95% CI: 1.6–3.0).

- In a population-based prospective cohort study of 431 patients assessed at 7 months (IQR: 6–8) since diagnosis, Menges et al. (2021) (preprint) reported in a multivariable analysis that women, those with more severe disease, and those with comorbidities were at higher risk of persistent symptoms.[12]
  - Increased risk of fatigue was associated with younger age (less than 40 years).
  - Increased risk of shortness of breath body mass index [as associated with being female, hospitalization during acute infection, higher body mass index and the presence of comorbidities.
- In a study of 364 patients assessed 28 days after hospital discharge, Chen et al. (2020) reported physical impairment was associated with being non-obese overweight (OR: 3.7; 95% CI: 1.4–9.7) or obese (OR: 3.9; 95% CI: 1.5–10.5).[50] Risk of neuropsychiatric impairment was higher in females (OR: 2.2; 95% CI: 1.3–3.8).
- In a study of 270 patients that responded to a follow-up questionnaire on their recovery 14–21 days after their initial test, Tenforde et al. (2020) reported an increased risk of sequelae in those >50 years old (adjusted odds ratio [aOR]: 2.3; 95% CI: 1.1–4.6), those with ≥3 underlying conditions (aOR: 2.3; 95% CI: 1.1–4.9), obesity (body mass index [BMI] >30 kg/m^2) (aOR: 2.3; 95% CI: 1.2–4.4) and having a pre-existing psychiatric condition (aOR: 2.3; 95% CI: 1.2–4.6).[51]
- In a study of 208 patients that have recovered from COVID-19, Pilotto et al. (2021) (preprint) followed up with patients 168 days after initial onset of symptoms.[52] Using logistic regression, those who were hospitalized longer and with comorbidities were the best predictors of neurological impairments.
- In a cross-sectional study of 204 patients assessed 84–168 days after hospital discharge, Baricich et al. (2021) reported physical impairment was associated with and increased risk of ICU admission and mechanical ventilation (OR: 3.1; 95% CI: 1.3–7.9).[53]

Implications

Care for post-acute COVID-19 patients will likely place added stresses on the healthcare and social support systems, including increased emergency department visits, outpatient care, inpatient care and rehabilitation involving multidisciplinary teams.[17,54-56] To date, there is evidence that COVID-19 can lead to decreased health-related quality of life (e.g., decreased ability to perform daily tasks, reduced capacity for physical activity, missing work).[15,20,29,57-59] Given the wide variety of persistent symptoms, guidance is currently being developed for the assessment and management of patients with post-acute COVID-19.[5] In addition to healthcare implications, there are economic implications for those unable to work or new requirements for social supports and disability insurance.

Particular attention is needed for those admitted to ICU because recovery usually involves post-intensive care syndrome.[60] Hosey et al. (2020) noted that ICU survivors will require help overcoming cognitive, psychiatric and physical sequelae.[60] In a population-based prospective cohort study in Switzerland, Menges et al. (2021) (preprint) noted that survivors were more likely to require post-acute care, including readmission to hospital, outpatient care and rehabilitation.[12] Even in non-hospitalized patients assessed about 80 days after symptom-onset, continued help with performing daily tasks was common (31%).[61]

Johnson et al. (2020) recognized that ethnic and racialized communities are more impacted by COVID-19, case prevalence and economic hardship.[62] In post-acute COVID-19, the authors suggest that more resources should be provided to racialized communities, given these communities experience higher risks from post-intensive care syndrome (persistent neuropsychiatric and cognitive symptoms).

Healthcare workers recovering from COVID-19 and experiencing persistent symptoms can place added stress on an already fragile healthcare system.[63] Praschan et al. (2021) has recognized that post-acute COVID-19 needs to be addressed in recovering healthcare workers who may need support to return and remain in the workplace.[64] In a cohort study of 323 seropositive cases (mild disease) and 1,072 seronegative cases in Sweden, Havervall et al. (2021) reported on persistent symptoms in healthcare workers. Seropositive cases had a higher risk of moderate to markedly disrupted work life (RR: 1.8; 95% CI: 1.2–2.9), social life (RR: 2.5; 95% CI: 1.8–3.6) and home life (RR: 2.3; 95% CI: 1.6–3.4).[20]

There have been 367,602 diagnosed cases and 7,458 deaths from COVID-19 in Ontario as of April 6 2021.[65] Based on numbers from Sudre et al. (2021), 2.3% have persistent symptoms at 84 days, which is over 8,000 Ontarians with persistent COVID-19-associated symptoms, and growing, which may require ongoing healthcare resources and multidisciplinary support.[18]

Limitations

We should acknowledge that a relatively large proportion (29%) of the research articles in this rapid review were non-peer-reviewed, preprint articles. Considering the rapid emergence of the COVID-19 pandemic, the volume of pre-print research is expected given the need for rapid dissemination of data.

We did not check systematic reviews for overlap among reviews in the studies that they included. Further, we did not check if our included primary studies were included in the systematic reviews. Thus, there is some duplication of findings.

A limitation is that symptoms at baseline or before COVID-19 are unknown, except where comorbidities were reported. Without pre-COVID-19 clinical assessments, it is difficult to attribute post-acute symptoms solely to COVID-19. As highlighted in the Background, there was no consistent definition of persistent symptoms. In most studies, it was not possible to determine the proportion of cases that had persistent symptoms but who had completely recovered, in contrast to those with ongoing symptoms from a lack of complete recovery from infection.

It remains unclear the extent to which some persistent neuropsychiatric symptoms are due to public health measures (lockdowns, physical distancing) rather than infection itself; further case-control studies would help disentangle the contribution of public health measures and infection to persistent symptoms. Most studies used subjective assessments of symptoms, which may be limited by recall bias. In addition, ICU admission, invasive mechanical ventilation, corticosteroids, and other medical treatments may contribute to persistent symptoms in recovering patients, and not necessarily due to infection itself. Self-selection bias was likely to occur in studies where people more concerned with their health may have participated, potentially inflating symptom prevalence. In addition, the majority of patients studied were hospitalized and likely had more severe disease, leading to higher prevalence of persistent symptoms. The numbers presented in this review may not be generalizable to all COVID-19 patients.

Conclusions

The literature identified that a significant proportion of people experience post-acute COVID-19. The most commonly reported persistent symptoms were neuropsychiatric or respiratory in nature; however, the results were highly heterogeneous. Neuropsychiatric sequelae following illness, including other viruses has been previously described. For example, following historical influenza pandemics, Severe

Acute Respiratory Syndrome (SARS, caused by SARS-CoV-1) and Middle East Respiratory Syndrome (MERS, MERS-CoV) pandemics, common long-term consequences included delirium, psychosis and anxiety.[3,66] Sullivan (2021) noted that SARS and MERS left patients with fatigue, shortness of breath, decreased quality of life and mental health problems, and suggested that planning is required for the current pandemic to address rehabilitation needs of survivors.[67]

Currently, there are a number of longitudinal studies underway to better characterise post-acute COVID-19, leading to better guidance on managing patients with persistent symptoms. For example, in a viewpoint article, del Rio et al. (2020) stated "Longer-ranging longitudinal observational studies and clinical trials will be critical to elucidate the durability and depth of health consequences attributable to COVID-19 and how these may compare with other serious illnesses."[8] In addition to longitudinal studies, research should focus on comparing symptoms present before and after infection, distinguishing persistent symptoms from chronic symptoms. To better plan and prepare health and social services for recovering patients, there is a need to study the factors contributing to increased risk of developing persistent symptoms, including how post-acute COVID-9 affects racialized communities. A central part of understanding the long-term sequelae is a unified definition of post-acute or long COVID-19.

On February 23, 2021, the National Institutes of Health (NIH) announced a study of the causes of long-COVID, in which they hope to improve prevention and treatment of persistent symptoms.[68] The NIH-led study looks to address the following questions:

- What does the spectrum of recovery from SARS-CoV-2 infection look like across the population?
- How many people continue to have symptoms of COVID-19, or even develop new symptoms, after acute SARS-CoV-2 infection?
- What is the underlying biological cause of these prolonged symptoms?
- What makes some people vulnerable to this but not others?
- Does SARS-CoV-2 infection trigger changes in the body that increase the risk of other conditions, such as chronic heart or brain disorders?

Guidance for managing the symptoms of post-acute COVID-19 is emerging. George et al. (2020) developed a guidance document outlining considerations in the respiratory follow-up of patients discharged after COVID-19 pneumonia.[37] Shah et al. (2021) have summarized guidance for managing those with post-acute COVID-19, as developed by The National Institute for Health and Care Excellence, the Scottish Intercollegiate Guidelines Network, and the Royal College of General Practitioners.[9]

We expect, based on the emerging available data, that post-acute COVID-19 will impact the physical and mental health of a substantial proportion of Ontario's population as well as impact healthcare system resources in the coming years.

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Appendix A. Study characteristics of included studies

Study first author	Study country	Study population during acute stage	Patient age*	% female patients	Was there an objective assessment of symptoms?
Anastasio	Italy	Mixed	55 (IQR: 49–63)	44.1	Yes
Ayoubkhani	England	Inpatient	64.5±19.2	45.1	Yes
Baricich	Italy	Inpatient	57.9±12.8	40.0	Yes
Chen KY	Multiple	Mixed	Not reported	Not reported	Mixed
Chiesa-Estomba	Multiple	Mixed	41±13	63.5	Mixed
COMEBAC	France	Inpatient	61±16	57.9	Mixed
Davis	Multiple	Mixed	>17	78.9	No
Havervall	Sweden	Outpatient	Varied by group	Varied by group	Mixed
Huang	China	Inpatient	57 (IQR: 47–65)	48.2	Yes
Kunutsor	Multiple	Inpatient	Range: 53–71	Not reported	Yes
Lechien	France	Inpatient	41±13	64.9	Yes
Lopez-Leon	Multiple	Mixed	Range: 17–87	Not reported	No
Mandal	England	Inpatient	59.9±16.1	38.0	No
Menges	Switzerland	Mixed	47 (IQR: 33–58)	50.0	Mixed
Michelen	Multiple	Mixed	Mean range: 37.7–73.9	Not reported	Mixed
Moreno-Perez	Spain	Mixed	62 (IQR: 53–72)	47.3	Yes

Study first author	Study country	Study population during acute stage	Patient age*	% female patients	Was there an objective assessment of symptoms?
Munblit	Russia	Inpatient	56 (IQR: 46–66)	51.1	Mixed
Pilotto	Italy	Inpatient	64.8±12.6	30.3	Yes
Qin	China	Inpatient	58±15	56.0	Yes
Sudre	Multiple	Mixed	42 (IQR: 32–53)	71.5	No
Taquet	USA	Mixed	46±19.7	55.6	No
Tenforde	USA	Mixed	43 (IQR: 31–54)	51.8	No
Torres-Castro	Multiple	Mixed	Average: 46.7–69.1	46.0	Yes
Trinkmann	Germany	Mixed	48±15	56.1	Yes
Venturelli	Italy	Inpatient	63±13.6	32.9	Yes
Xiong	China	Inpatient	52 (IQR: 41–62)	54.5	No

*Means reported with standard deviation; IQR, interquartile range

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