

CADTH Health Technology Review

Subtypes of Post- COVID-19 Condition: A Review of the Emerging Evidence

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ISSN: 2563-6596

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

ME/CFS	myalgic encephalomyelitis/chronic fatigue syndrome
MIS	multisystem inflammatory syndrome
PICS	post-intensive care syndrome
POTS	postural orthostatic tachycardia syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Key Messages

- Post-COVID-19 condition is a growing health concern and has been associated with more than 200 possible symptoms. The diverse and varied ways the condition presents clinically creates challenges for developing standard diagnostic criteria, and for health systems aiming to provide effective treatment and management supports for people.
- To support health care, decision-makers and clinicians understand the different clinical presentations of the condition, we scanned the evidence base to examine early approaches being used to characterize and describe subtypes of post-COVID-19 condition. Subtypes can be developed with many different disease features and patient factors, but for this report we specifically reviewed potential subtypes based on symptoms and clinical presentation.
- We found that some of the early approaches used to develop subtypes are based on statistical methods that group together patterns of symptoms. These studies are beginning to reveal potential subtypes based on severity of symptoms, type and co-occurrence of symptoms, and symptoms affecting different organ systems.
- Many reported symptoms of post-COVID-19 condition are similar to previously characterized health conditions. In some cases, subtypes of post-COVID-19 may be manifestations of those other conditions. For example, certain subtypes may present with symptoms similar to myalgic encephalomyelitis/chronic fatigue syndrome or pulmonary fibrosis. It is uncertain whether those subtypes share the same or distinct pathophysiology and whether they may benefit from similar treatments.
- Early evidence comparing the variant of infection and its association with potential subtypes of post-COVID-19 condition is emerging, but the findings are currently mixed. Some studies suggest that variants such as Delta and Omicron may result in different clinical presentations, while other studies have not found significant differences. Further research assessing the association between variants and subtypes is likely needed.
- This review provides some implications and considerations for health systems should emerging research further characterize and validate proposed subtypes. These implications may be important for improving the diagnosis, treatment, and management of post-COVID-19 condition. With estimates in Canada suggesting that more than a million people could be affected by the condition, monitoring ongoing research on subtypes may help support the development of effective and tailored treatments, and guide health systems planning across the country.

Background

Post-COVID-19 condition is a growing health concern in Canada and across the world. The condition is defined as persisting or ongoing physical or psychological symptoms for more than 12 weeks or 3 months after acute COVID-19 illness.^{1,2} Symptoms of post-COVID-19 condition can vary and may occur in people after either mild or severe acute illness of COVID-19.^{3,4} Estimating the prevalence of post-COVID-19 condition is challenging due to an absence of a standard diagnostic criteria and varying definitions, leading to a wide range of reported prevalence (between 5% to 50%) of people with COVID-19.^{5,6} As of October 2022, estimates from Canada suggest that 14.8% (or 1.4 million) of people had or were suspected of having experienced symptoms indicative of post-COVID-19 condition.⁷

Post-COVID-19 condition is a diverse condition and has varying effects to people's health and well-being. While more than 200 symptoms have been associated with the condition across different studies, there are no standards for classifying or grouping the same symptoms, which can create challenges for characterizing the condition and for health systems planning.^{5,8} Post-COVID-19 condition may be multiple syndromes or have different subtypes, with possibly different pathophysiologies.^{2,9} Given the wide diversity of its clinical manifestation, people affected by the condition will have a range of treatment and management needs. Having a better understanding and characterization of possible post-COVID-19 condition subtypes may help identify its pathophysiology (or pathophysiologies) and could also help inform the development of multidisciplinary care tailored to people's diverse needs.¹⁰

What Are Subtypes?

Many health conditions can manifest in different ways in people. These differences can lead to varied presentations of the condition (e.g., symptoms), affect outcomes (e.g., severity or duration), and have implications for different treatments or care.¹¹ For example, certain cancers can manifest differently based on genetically distinct subtypes, which can be supported by tailored approaches for clinical management and care.¹² Being a relatively new health condition, research about different aspects of treating people with post-COVID-19 condition is in its infancy. As post-COVID-19 condition presents with a wide diversity and overlapping set of symptoms, it creates a challenge for describing the condition (what *is* it?) and differentiating it from other similar conditions (what is it *not*?).^{3,13,14} Understanding the early approaches being considered to group together the varied clinical presentations of the condition and to assess whether there may be distinct subtypes or patterns of symptoms, may provide useful information for patients, clinicians, and health care decision-makers.¹⁵ For example, different subtypes may require more support from certain health care professionals or have certain treatment needs, and early identification of those subtypes in people may help better direct resources or assist in coordination. Furthermore, understanding the early thinking about subtypes could potentially guide future research, help inform clinical management, and direct health systems planning for future care needs.

Objective

The objective of this review is to summarize and provide a narrative overview of the emerging evidence examining different subtypes of post-COVID-19 condition. We aimed to describe the emerging approaches used to propose or identify subtypes, including approaches based on statistical analyses or clinical groupings of disease features that could inform prognosis and treatments. We also aimed to describe the emerging evidence about whether different variants of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) are associated with different subtypes.

Owing to the complexity and rapidly evolving landscape of research on risk factors, we do not aim examine patient-level factors (e.g., demographics, sex, or age) that could affect people's varying experiences with the long-term effects of COVID-19 or how post-COVID-19 condition may manifest differently among subgroups of people.^{16,17} Rather, we aim to focus primarily on subtypes of clinical disease features.

Research Questions

The specific research questions we aimed to address were:

1. What are the proposed or identified subtypes of post-COVID-19 condition and how are they being developed?
2. What is the evidence about the association between different variants of SARS-CoV-2 and the development of different subtypes of post-COVID-19 condition?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE and Embase through Ovid, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were post-COVID-19 condition (long COVID) and terms for subtypes. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The initial search was completed on April 20, 2022, with an additional alert on September 16, 2022, and was limited to English-language documents published since January 1, 2019.

Screening and Study Selection

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in [Table 1](#). Given the emerging nature of the evidence for research question 2, preprints of studies were considered for inclusion if they met other eligibility criteria.

Synthesis Approach

The findings from the literature search were summarized narratively and grouped by research question. For research question 1, full-text review was conducted for studies fulfilling the selection criteria. Studies that explicitly described characterizing subtypes or groupings of post-COVID-19 condition clinical presentation were initially used to develop broad categories and themes based on their approach. These themes were iteratively refined, with the remaining studies used to identify the common approaches for proposing or developing subtypes.

For research question 2, studies that fulfilled the selection criteria and specifically examined variants of SARS-CoV-2 or implied there could be variants (e.g., different waves) were examined separately from question 1. The findings were summarized collectively.

Table 1: Components of Literature Screening and Information Gathering

Criteria	Description
Population	People of all ages with post-COVID-19 condition (i.e., defined as any symptoms experienced 12 weeks or more after initial infection, diagnosis, or symptom onset) or suspected to be experiencing long-term symptoms of COVID-19 (i.e., symptoms beyond at least 4 weeks)
Concept	Post-COVID-19 condition subtypes (i.e., some form of classification, stratification, or grouping of clinical manifestations of post-COVID-19 condition or symptoms)
Context	Any context or setting
Types of information	Q1: Evidence about proposed or characterized post-COVID-19 condition subtypes, groupings of clinical presentation or symptoms, phenotypes, and clustering Q2: Evidence of SARS-CoV-2 variants and their association with the development of post-COVID-19 condition and possible subtypes
Study designs	Systematic reviews; rapid reviews; narrative reviews Quantitative or qualitative primary studies of any design

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Findings

A total of 1,081 citations were identified in the literature search. Following screening of titles and abstracts, 769 citations were excluded and 312 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 43 studies were considered relevant, and their findings were synthesized to develop this report. Studies were excluded for a variety of reasons, such as studies that did not examine or stratify different clinical presentations of post-COVID-19 condition, were smaller case reports, were more related to other conditions occurring in people who had acute COVID-19, or were those that examined the prevalence of post-COVID-19 condition symptoms but did not describe subtypes or clustering of symptoms.

Varied Approaches for Developing Subtypes

Symptoms Clustering

We identified that 27 of the included studies used or proposed some form of symptoms clustering to identify possible subtypes of post-COVID-19 condition and to suggest that the condition may manifest in specific patterns. These patterns may not necessarily be distinct and could have some overlap. Studies developed or proposed clusters based on symptoms severity, type and co-occurrence of symptoms, and symptoms affecting a common organ system; their findings have been summarized in [Table 2](#), [Table 3](#), and [Table 4](#).

Symptoms Severity

We identified 4 studies that stratified clinical presentation based on the severity of people's symptoms. These included a cross-sectional study from the UK¹⁸ that assessed people attending a COVID-19 rehabilitation centre, a prospective cohort study from Spain¹⁹ that examined people who had been discharged from a hospital with acute COVID-19, a cross-sectional study²⁰ that assessed people from multiple countries recruited from online groups,

and a cross-sectional study from Germany²¹ that assessed people at least 4 months after a confirmed SARS-CoV-2 infection. All 4 studies used statistical-based clustering analyses to identify potential subtypes.

The UK study invited people from a rehabilitation centre to complete a standardized questionnaire (Covid-19 Yorkshire Rehabilitation Scale) and had responses from 370 patients.¹⁸ Clustering analysis of 12 key most-reported symptoms indicated 3 distinct phenotypes of severe, moderate, and mild, based on mean symptoms scores.¹⁸ Severity of symptoms were correlated with lower perceived health and higher functional difficulty. Clustering analysis, however, did not identify consistent grouping of specific symptoms.¹⁸

The Spanish study identified 3 clusters (termed Cluster 0, Cluster 1, and Cluster 2) based on analyses of symptoms (including both symptoms at initial hospital admission and post-COVID-19 condition symptoms), clinical features, and hospital-based data of 1,969 patients.¹⁹ People within Cluster 0 (21.9% of all study participants) reported more severe functional impacts (e.g., effects on daily living, occupation, and leisure activities) and the highest number of symptoms, most prominently fatigue, anxiety and depression, and changes to sleep quality.¹⁹ People grouped into Cluster 1 reported a similar number of symptoms as Cluster 0 and the presence of comorbidities but reported a lesser impact on functional activities.¹⁹ People in Cluster 2 reported the least number of post-COVID-19 condition symptoms and functional impairments.¹⁹ Among people in Cluster 0 (the most severely affected group), 73.4% reported experiencing dyspnea or shortness of breath, which was significantly higher than people in Cluster 1 (18.8%) or Cluster 2 (1.3%).¹⁹ The authors of the study suggested that the number of symptoms experienced by people (symptoms load) and the development of dyspnea could be used in early clinical assessment to guide care and inform prognosis for people affected by post-COVID-19 condition.¹⁹

One cross-sectional study recruited 2,550 people from long COVID online groups (international representation) to complete a questionnaire about their symptoms and experiences after their initial infection.²⁰ The study used hierarchical clustering analysis to characterize ongoing symptoms among people along with several analyses looking at the association with demographic factors, baseline health, and other socioeconomic factors.²⁰ The study indicated that there were likely 2 clusters of symptoms among participants. The majority of people (88.8%) reported experiencing cardiopulmonary (e.g., shortness of breath, chest pain) and neuro-cognitive (e.g., brain fog, poor concentration) symptoms.²⁰ The second cluster represented a smaller proportion (11.2%) of study participants and was termed the multisystem ongoing cluster as it was associated with symptoms affecting the gastrointestinal, cardiopulmonary, neurologic, systemic, skin, and other systems of the body. People within this cluster reported more severe impacts to their functional abilities, greater time away from work, higher fatigue, and greater disruption to daily activities.²⁰ The authors suggested that the minority group with more multisystem effects would be more likely have complex needs and require multidisciplinary care.²⁰

Another cross-sectional study invited people from a county health department in Germany who had acquired COVID-19 to complete a Quality of Life (QoL) questionnaire (the Short Form 36) and to provide other information about their health status and sociodemographics.²¹ Clustering analysis showed that, based on severity of QoL outcomes, a majority of people with post-COVID-19 condition symptoms (70.6%) had QoL scores similar to the general population in Germany, while about one-third (29.4%) reported significantly reduced QoL.²¹ Despite people within the majority cluster reporting symptoms such as fatigue, pain, and sleep disturbance, their QoL outcomes were not substantially different than what would be

expected for a healthy population.²¹ However, people with significantly reduced QoL were more likely to report a greater number of symptoms and other comorbidities.²¹

Type and Co-Occurrence of Symptoms

Another emerging approach to identify potential subtypes, used by at least 3 identified studies, is to employ analytical statistics to assess whether specific symptoms group together. These included a cohort study from Ireland that used multi-component analysis and identified 3 clusters among 232 study participants who had persisting symptoms beyond 4 weeks after their initial COVID-19 infection.²² Symptoms were recorded with clinical assessment, standardized questionnaires on health status and QoL, and biologic measurements (e.g., blood pressure, chest X-rays, electrocardiographs, and blood components). Analysis from these multiple components indicated that Cluster 1 (15.9%) had a higher proportion of people reporting musculoskeletal and pain symptoms, Cluster 2 (37.5%) had a higher proportion of cardiorespiratory symptoms, and Cluster 3 (46.6%) had the fewest reported symptoms.²² People within Cluster 1 and Cluster 2 reported more symptoms and functional impairments, including lower reported QoL and emotional health, and higher work absences following the initial acute phase.²² Authors of the study suggested that the distinction between musculoskeletal and cardiorespiratory symptoms highlights a need to understand possibly distinct disease mechanisms.²²

A retrospective cohort study from the US analyzed the electronic health records of more than 270,000 people who had been infected with SARS-CoV-2, and more than half (57.0%) of people reported clinical features that may be indicative of post-COVID-19 condition (i.e., long-term effects up to 180 days after COVID-19 infection).²³ The study used statistical approaches to assess the co-occurrence of symptoms and found that several symptoms were more likely to occur with each other among people with post-COVID-19 condition compared to a matched group of people with influenza. For example, abnormal breathing with chest pain, and abdominal symptoms with fatigue, were pairs of symptoms that had statistical associations of co-occurring.²³ Authors of the study also indicated that while the study was not powered or intended to identify subtypes, they did find associations between abnormal breathing, chest pain, fatigue, and anxiety and/or depression, suggesting these symptoms may be interconnected.²³

A Norwegian prospective cohort study examined people (n = 774) who had been infected with SARS-CoV-2 during the initial stages of the pandemic and who were assessed for 22 symptoms associated with long-term effects.²⁴ This study used correlative analysis to assess pairs of symptoms.²⁴ The study reported a positive association between fatigue and poor memory and a negative association between chest pain and anxiety or depression. The Norwegian study also reported changes in the pattern of symptoms co-occurring between 2 different periods of the pandemic (March 2020 to April 2020 and September 2020 to January 2021), but did not assess the effects of variants.²⁴

Organ Systems

Grouping symptoms by organs or body systems is another emerging approach to understand how post-COVID-19 condition may manifest differently.¹⁰ We identified at least 5 studies and clinical reviews that classified the heterogeneous symptoms of post-COVID-19 condition and mapped them to different organ systems ([Table 3](#)). These included a prospective study from Mexico that followed patients who were hospitalized with COVID-19 for up to 90 days after their discharge.²⁵ The study identified 45 symptoms in the cohort and categorized each into 1 of 8 body systems, which included neurologic; mood disorders; systemic; respiratory;

Table 2: Summary of Primary Studies Using Symptoms Clustering to Identify Possible Subtypes or Clusters of Post–COVID-19 Condition

Author (year), country	Study population	Major findings
Clustering based on symptom severity		
Fernández-de-las-Peñas et al. (2022), ¹⁹ Spain	n = 1,969 Patients who were previously hospitalized, randomly recruited from 5 hospitals, 6 to 10 months after discharge	Clustering analysis identified 3 subgroups based on symptoms severity: <ul style="list-style-type: none"> • Cluster 0 (21.9%) – highest number of symptoms and most severe functional impacts • Cluster 1 (35.4%) – similar number of symptoms as Cluster 0, but less severe impacts to daily living activities • Cluster 2 (42.7%) – least number of reported symptoms and almost no impacts to daily living activities
Giszas et al. (2022), ²¹ Germany	n = 909 Study participants were recruited from those who had had a positive RT-PCR test at local health departments at least 3 months after acute infection.	QoL assessment and clustering analysis identified that, of the 643 participants with persistent symptoms, there were 2 subgroups: <ul style="list-style-type: none"> • Cluster 1 (29.4%) had markedly reduced QoL and experienced more symptoms. • Cluster 2 (70.6%) had QoL comparable to the general population.
Sivan et al. (2022), ¹⁸ UK	n = 370 Study participants were recruited from the COVID Rehabilitation service, and had had symptoms persisting beyond 12 weeks.	Clustering analysis identified 3 phenotypes based on severity of symptoms: <ul style="list-style-type: none"> • Mild (24.3%) • Moderate (50.3%) • Severe (25.4%)
Ziauddeen et al. (2022), ²⁰ UK	n = 2,550 Study participants were recruited from online long COVID groups (they were primarily from the UK, but also North America and Europe) and had not been hospitalized for acute illness.	Clustering analysis of 35 ongoing symptoms identified 2 clusters: <ul style="list-style-type: none"> • Majority cluster (88.8%), reporting largely cardiopulmonary, cognitive, and exhaustion symptoms • Minority cluster (11.2%), with a greater number of symptoms affecting multiple systems and with more severe impacts to health, well-being, employment, and other aspects of life
Clustering based on the type and co-occurrence of symptoms		
Caspersen et al. (2022), ²⁴ Norway	n = 774 The study identified eligible participants from the Norwegian Mother, Father and Child Cohort Study; participants had a positive PCR test (total cohort of people was more than 70,000).	Correlative analysis used to assess occurrence of pairs of 22 symptoms and clustering of symptoms. Symptoms with significant ($P < 0.001$) positive correlations included: <ul style="list-style-type: none"> • joint pain and muscle pain • brain fog and poor memory • fatigue and poor memory. Symptoms with significant ($P < 0.001$) negative correlations included: <ul style="list-style-type: none"> • muscle pain and chest pain • cough and depression • reduced lung function and depression.

Author (year), country	Study population	Major findings
Kenny et al. (2022), ²² Ireland	n = 233 Study participants were recruited from the All-Ireland Infectious Diseases Cohort study; participants has had a positive PCR test and symptoms persisting beyond 4 weeks of acute infection.	Multiple correspondence analysis and clustering analysis identified 3 symptoms clusters: <ul style="list-style-type: none"> • Cluster 1 (16.0%) had a higher proportion of pain symptoms • Cluster 2 (37.5%) had a higher proportion of cardiovascular symptoms • Cluster 3 (46.5%) had fewer symptoms and reported less functional and QoL impact
Taquet et al. (2021), ²³ US	n = 273,618 The study identified eligible participants from electronic health records of people who had COVID-19.	Co-occurrence analysis of pairs of symptoms revealed some symptoms were more likely to be interconnected and may have distinct mechanisms or origins. Symptoms with hazard ratios above 2.0 (P < 0.01) included: <ul style="list-style-type: none"> • abnormal breathing with chest pain • abnormal breathing with anxiety or depression • abdominal symptoms with fatigue.

PCR = polymerase chain reaction; QoL = quality of life; RT- reverse transcription.

musculoskeletal; symptoms affecting the ear, nose, and throat; dermatological; and gastrointestinal.²⁵ The most prominent symptoms clusters (> 30% of people) at 90 days were related to the neurologic, dermatological, and mood disorders systems.²⁵ Authors of the study indicated that some of the specific symptom clusters were moderately associated with health status, corticosteroid use, and other factors.

Organ systems clustering was used by a cross-sectional study²⁶ with 3,762 online participants that characterized 203 symptoms into 10 organ systems and 1 systematic review²⁷ that categorized symptoms into 7 body systems. The cross-sectional study also reported that it is possible that symptoms affecting different organ systems could co-occur with one another as distinct clusters (e.g., the study found clustering of neurologic and systemic symptoms).²⁶

Different review articles have also proposed examining manifestations of post-COVID-19 condition by organ systems. One review aimed to standardize varying symptoms reported by different studies according to the [Human Phenotype Ontology](#)²⁸ classification system and mapped the symptoms onto a limited number of terms and possible organ systems that may be implicated.⁸ The authors of a narrative review examining symptoms associated with post-COVID-19 condition and its implications for rehabilitation care reported that based on their assessment of the evidence, the condition could affect at least 7 organ and body systems.¹⁰ The overlap among studies and reviews describing the specific organ systems that are associated with post-COVID-19 condition are shown in [Table 3](#). Note that some studies may have classified certain organ systems independently, such as cardiovascular and respiratory, while other studies may have described them as a single system (e.g., cardiorespiratory). In such cases, we denote the study as classifying both organ systems in the table.

Table 3: Studies Describe a Variety of Symptoms That Map on to Different Organ Systems and May be Associated With Post-COVID-19 Condition Subtypes

Author (year), country	Study population	Neurologic	Psycho-logical or mental health	Respiratory	Musculo-skeletal	Ear, nose, and throat	Dermato-logical	Gastro-intestinal or digestive	Cardio-vascular	Systemic	Non-specific	Other
Davis et al., (2021) ²⁶ Multi-country	n = 3,762 Online survey of people with confirmed or suspected COVID-19	Yes	–	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	Yes
Deer et al., (2021) ⁸ Multi-country ^a	Mapping review, 59 studies analyzed	Yes	Yes	Yes	–	–	Yes	Yes	Yes	Yes	–	Yes
Groff et al., (2021) ²⁷ Multi-country	Systematic review, 57 studies analyzed	Yes	Yes	Yes	–	Yes	Yes	Yes	Yes	–	Yes	Yes
Wong-Chew et al., (2022) ²⁵ Mexico	n = 4,670 Study recruited participants who had been discharged from the hospital with COVID-19	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	Yes	–	–

Author (year), country	Study population	Neurologic	Psychological or mental health	Respiratory	Musculoskeletal	Ear, nose, and throat	Dermatological	Gastrointestinal or digestive	Cardiovascular	Systemic	Non-specific	Other
Yan et al., (2021) ¹⁰ China	Narrative review	Yes	–	Yes	–	–	–	Yes	Yes	–	–	Yes

Note: Other categories included metabolic, hematological, mobility, urinary systems, and so forth. *Nonspecific* refers to general symptoms that may not be directly attributed to 1 organ system, such as fatigue, fever, and general pain.

^aThis review⁸ did not explicitly describe all organ systems that are implicated based on the Human Phenotype Ontology, but it listed the most commonly reported symptoms categories, and those symptoms have been aligned to the organ systems listed in the table.

We also identified at least 5 studies that have proposed that there may be a distinct post-COVID-19 neurologic syndrome or aim to characterize specific neurologic subtypes. For example, a cohort study from Switzerland suggested that in some people, neuroinflammation may reduce connectivity in the brain and could result in a specific neurologic post-COVID-19 syndrome associated with cognitive impairment.²⁹ An editorial review reported that because an estimated 20% of people with severe acute illness may develop neuropsychiatric symptoms and may have signs indicating neuroinflammation, there may be a unique post-COVID-19 neurologic syndrome or phenotype.³⁰

Other studies have reported that there may be different neurologic subtypes. A prospective cohort study from the US assessed neurologic symptoms among 100 participants with standardized questionnaires, cognitive tests, and brain scans.³¹ Early results from the study reported 2 clusters of neurocognitive impairment.³¹ One cluster had people with symptoms affecting all neurocognitive domains, whereas the other cluster had a milder impact limited to people's attention.³¹ Brain imaging results also revealed that people who reported experiencing anosmia – the loss of sense of smell – had structural neurologic differences compared to those who did not report anosmia.³¹ Similarly, a prospective study from Italy assessed 109 people from a post-COVID-19 neurologic clinic.³² Clustering analysis of symptoms proposed 2 neurologic subtypes that primarily affect either the central nervous system (symptoms of head ache, anosmia, memory) or the peripheral nervous system (neuropathy).³² One cross-sectional study from Colombia assessed 100 people attending a post-COVID-19 clinic and reported 2 clusters based on autonomic nervous system symptoms assessed by a standard neurologic score (i.e., COMPASS 31).³³

Studies assessing symptoms related to the cardiovascular system are also emerging, but none that used clustering methods were identified.^{34,35} Future research validating cardiovascular and neurologic biomarkers or functional impairment could complement approaches for assessing organ-specific subtypes, as well.³⁶⁻³⁹

Previously Characterized Conditions May Manifest in Some People With Post-COVID-19 Condition

Many of the symptoms associated with post-COVID-19 condition are similar to other established conditions. As such, there is emerging work comparing and contrasting people with post-COVID-19 condition to those other conditions. Treatment and care approaches used for established conditions may help inform appropriate care for people with subtypes or clinical manifestations of post-COVID-19 condition.

One narrative review examined the literature base on post-COVID-19 condition and proposed that the different subtypes are clinical manifestations of those other health conditions.⁴⁰ Some of these subtypes are distinct health conditions that have been characterized before the COVID-19 pandemic, but it is currently uncertain whether they present with similar clinical features only or also share a similar pathophysiology. Based on 43 studies identified by the narrative review, authors described the following subtypes:

- **Pulmonary fibrosis sequelae or fibrosis** – This refers to damage or scarring of lung tissue following acute illness that may be identifiable with radiological imaging.⁴⁰ Although mechanisms of fibrosis among people with COVID-19 is not yet well understood, several hypotheses include dysregulated inflammation response, co-infections, and clotting that leads to vascular damage.⁴¹ A systematic review that compared patients who had post-COVID-19 and developed fibrosis to those who had post-COVID-19 and did not

develop fibrosis, reported a higher rate of fatigue, muscle pain, chest pain, and shortness of breath.⁴¹

- **Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)** – This is a complex condition marked by severe tiredness that does not recover after rest, as well as muscle pains, headaches, disrupted sleep, and many other symptoms that can affect a person’s physical and mental well-being.⁴⁰ Certain neurologic symptoms may be able to predict the likelihood of developing of ME/CFS.⁴² A systematic review comparing post–COVID-19 condition with ME/CFS reported that while many of the symptoms show overlap, a limited number of studies of people with post–COVID-19 condition have followed participants for at least 6 months, which is one of the diagnostic criteria for ME/CFS.⁴³ Authors of the systematic review also remarked that if even 10% of people with COVID-19 meet the definition of ME/CFS, that would equate to a substantial number of chronic cases.⁴³
- **Postural orthostatic tachycardia syndrome (POTS)** – This is a health condition in which a person’s heart rate increases substantially after standing up and is linked with dysfunction of the autonomic nervous system.^{40,44} The condition may be associated with fatigue, headaches, sleep disturbance, nausea, and other debilitating symptoms that can affect a person’s functional abilities and QoL.⁴⁴ A review by a clinical autonomic society has suggested that, based on preliminary data from some autonomic clinics, the incidence of POTS may have increased since the COVID-19 pandemic, and that there is a need to further assess whether there are distinct features of people with post–COVID-19 condition who experience POTS.⁴⁵
- **Post-intensive care syndrome (PICS)** – Some people who developed severe acute illness of COVID-19 and required hospitalization may not have had complete recovery.⁴⁰ They may experience long-term symptoms affecting their cognitive ability along with effects to the mental and physical health.⁴⁰ A prospective cohort study that compared people after admission to intensive care with and without COVID-19, 6 months after their admission, reported that there were no significant differences between those in both groups who developed PICS.⁴⁶ The narrative review that discussed this subtype also suggested that pharmaceutical and rehabilitation interventions used for PICS may be tested and considered for post–COVID-19 condition.⁴⁰
- **Non-severe COVID-19 multi-organ sequelae** – This refers to people with mild initial COVID-19 who may develop a variety of symptoms that affect multiple organs.⁴⁰ Due to the heterogeneity of symptoms, the authors of the narrative review indicated that a holistic treatment approach and personalized management would likely need to be considered.⁴⁰

In addition to the previously mentioned subtypes, the narrative review reported that some studies have hypothesized that COVID-19 may have revealed other underlying conditions that may not have been previously apparent.⁴⁰ In some cases, COVID-19 may have exacerbated existing chronic conditions or led to new symptoms with new diagnoses. The review reported that among some people, such medical or clinical sequelae could qualify as a post–COVID-19 condition subtype, but this requires further research.⁴⁰

Multisystem inflammatory syndrome (MIS) is a rare and emerging condition associated with COVID-19 that may affect children or adults.⁴⁷ Among children, it can present with several gastrointestinal symptoms, respiratory symptoms, and clinical features that resemble Kawasaki disease.⁴⁸ There is increasing attention and research being conducted to characterize the condition’s prevalence, risk factors, clinical manifestations, and treatment options.⁴⁹⁻⁵² However, as health authorities are considering that MIS may be a unique condition, distinct from post–COVID-19 condition, potentially with its own subtypes, we did not extensively review the literature base of MIS for this report.^{47,48,53-55}

Association Between Different Variants and Subtypes of Post-COVID-19 Condition

Emerging research is beginning to assess whether different variants of SARS-CoV-2 or particular waves of the pandemic may be associated with post-COVID-19 condition and potentially different subtypes (Table 4). Studies have used either variant testing with polymerase chain reaction (PCR) or different time periods (i.e., pandemic waves) as a proxy for different variants.

One preprint prospective cohort study from Norway used data from a national registry to compare people (more than 35,000 individuals) with confirmed diagnoses (genomic testing) of the Delta and Omicron variants.⁵⁶ The study reported that people with either variant more commonly reported fatigue and shortness of breath compared to people who were not infected with COVID-19.⁵⁶ However, between both variants, the study did not find any significant differences in the type or frequency of common post-COVID-19 symptoms reported.⁵⁶

A case-control study using data from the Covid Symptoms Study⁵⁷ compared the odds of developing long COVID (defined as new or ongoing symptoms for at least 4 weeks) between 2 COVID-19 waves. Researchers selected 2 time periods where more than 70% of cases could be attributed to either the Delta or Omicron variant, respectively.⁵⁸ The study reported that people likely infected by the Omicron variant were less likely to experience long COVID compared to people infected by the Delta variant, with an odds ratio ranging from 0.24 to 0.50 (statistical P values not reported).⁵⁸ While the study did not assess whether the clinical features of people who developed long COVID differed between 2 variants, the study suggested that different variants may be associated with different risk profiles.

A subsequent preprint study from UK also using data from the COVID Symptoms Study and specifically aimed to examine whether variants were associated with different symptoms clustering patterns.⁵⁹ This study compared clinical manifestations of long COVID (symptoms lasting for more than 4 weeks) or post-COVID-19 (symptoms lasting for more than 12 weeks), which are the definitions used by the National Institute for Health and Care Excellence.² Clustering analysis revealed a differing number of symptoms clusters across the wild-type, Alpha, and Delta variants. These clusters affected a range of different organ systems and had varying severities.⁵⁹ However, among all variants examined, the 3 most common clusters were the central neurologic cluster (most prominent in Alpha and Delta variants), the cardiorespiratory cluster (most prominent in the wild-type variant), and the systemic/inflammatory cluster (prevalent across all variants but at a lower frequency).⁵⁹ A Spanish study examining hospital survivors who were infected with the same 3 variants similarly reported that people with the Delta variant were more likely to report neurologic symptoms (e.g., headache, anosmia, and ageusia).⁶⁰ Authors of the UK preprint study reported that this early evidence suggests that post-COVID-19 may have different subtypes that could, in part, be associated with the variant of infection; however, further research would need to assess the biologic mechanisms.⁵⁹

Table 4: Summary of Studies Examining Subtypes or Different Manifestations of Post–COVID-19 Condition Between Different Variants of Infection

Author (year), country	Study population and variants assessed	Major findings
Antonelli et al. (2022), ⁵⁸ UK	n = 56,003 people with likely Omicron and n = 41,361 people with likely Delta infection. Participants were identified from COVID-19 symptoms study and had positive PCR test during time periods (proxy for variant) and at least 4 weeks of follow-up time.	Among people who likely had Omicron infection, 4.5% reported long COVID; among Delta cases, 10.8% reported long COVID. The odds ratio of experiencing long COVID for Omicron compared to Delta was 0.24 to 0.50 (statistical P values not reported). Specific symptoms differences between variants were not assessed.
Canas et al. (2022), ⁵⁹ UK	n = 9,323 people from the COVID Symptoms Study who experienced symptoms for at least 4 weeks after infection. Wild-type, Alpha, and Delta variants were assessed based on a predominant strain during time of infection (proxy for variant).	Among wild-type cases, there were 4 clusters; among Alpha cases, there were 7 clusters; among Delta cases, there were 5 clusters. Between variants, the central neurologic symptoms cluster was most prominent among Alpha and wild-type cases, while the cardiorespiratory symptoms cluster was most prominent among Delta cases. The wild type variant was associated with the highest risk of severe illness.
Fernández-de-las-Peñas et al. (2022), ⁶⁰ Spain	n = 614 participants randomly recruited from people previously hospitalized (approximately 6 month prior) with COVID-19. Wild-type (also called Wuhan), Alpha, and Delta variants were assessed with PCR testing.	There may be significant differences in symptoms prevalence between variants. Neurologic symptoms were more prevalent among Delta cases and gastrointestinal symptoms were more prevalent among wild-type cases. Delta cases were more likely to report loss of sense of taste and smell.
Magnusson et al. (2022), ⁵⁶ Norway	n = 13,028 Omicron cases, n = 23,368 Delta cases, and n = 105,196 cases negative for SARS-CoV-2 from the Norwegian registry were analyzed. Variant assessment was confirmed with PCR testing.	No significant differences between Omicron and Delta cases for the overall risk of post–COVID-19 condition and its associated symptoms were identified.

PCR = -polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Limitations

This report provides a narrative overview of the emerging evidence examining different subtypes of post–COVID-19 condition, but did not quantify or qualify the strength of evidence about subtypes. We focused primarily on subtypes related to symptoms presentation and did not examine other disease features (e.g., biomarkers) or patient-level factors (e.g., demographics, sex, age, health status, vaccination status) that could affect people’s varying experiences with the long-term effects of COVID-19, or how post–COVID-19 condition may manifest differently among subgroups of people. Patient-level factors are an important aspect of understanding the condition, but given the complexity of analysis required, were outside the scope of this review.

Although effort was made to capture the expansive nature of the evidence, this report focused on the major approaches being used to propose or develop subtypes. It was not an exhaustive search of all subtypes, and other subtypes may not have been identified. The emerging approaches and subtypes presented in the report are not validated and would

require further study to guide clinical care. Given the emerging nature of the evidence, and limited understanding of SARS-CoV-2 and its long-term effects, other approaches that examine the molecular underpinning of the virus may reveal different subtypes of post-COVID-19 condition. We found limited research from Canada or limited studies using data from people in Canada. As such, the findings may not be generalized to all settings or patients across Canadian health systems.

Regarding research question 2, there may be limitations in sampling approaches, access to testing at different time periods, and study designs that make assessing the relationship between variants and subtypes of post-COVID-19 condition complex. Preprint studies were also included to address this question due to limited published evidence. Overall, the report is not a systematic review and it did not involve critical appraisal, assessment of the quality of evidence, or provide a detailed summary of study findings.

Conclusions and Implications for Health Systems

In our overview of the emerging evidence, we found studies using several different approaches to group together or characterize post-COVID-19 condition's varied and diverse symptoms. Previous research has noted that beginning to group together symptoms and the diversity of clinical presentations of post-COVID-19 condition could help develop more tailored approaches for diagnosis and treatment.⁸ Our review explores the early approaches being considered to develop or propose subtypes based on clinical presentation of post-COVID-19 condition.

We identified at least 25 studies that are beginning to reveal that the condition may present in distinct patterns based on groups of symptoms, severity of symptoms, and certain organ systems. While specific symptoms groups range across different studies, there are common groupings related to the occurrence of some symptoms. For example, we identified at least 6 studies that proposed clusters of cardiorespiratory and neurologic symptoms.^{10,20,25,27,35,61} We also found 4 studies suggesting that a minority of people may experience symptoms that have more severe impacts to people's health and well-being.¹⁸⁻²¹ While the evidence seems to be in the early stages of exploring statistical associations, future work assessing and prospectively validating these potential subtypes could be helpful for designing and optimizing treatments, and tailoring models of care.

At the time of editing this report, a prospective cohort study that examined hospitalized patients 12 months after their initial diagnosis was identified.⁶² The study reported that symptoms clusters among their cohort also mapped to therapy clusters. For example, people within the symptoms cluster that reported shortness of breath and cognitive symptoms were more likely to receive physical and occupational therapy, while the cluster of those who reported higher anxiety and depression symptoms were more likely to receive anti-depressants, anti-anxiety, and psychological therapy interventions.⁶² It is likely that future studies will continue to identify other ways that assessing and identifying subtypes may guide health systems planning for delivering appropriate interventions.

Characterizing potential subtypes may help improve care pathways because having a better understanding of the condition's varied clinical manifestations may help improve diagnostic criteria and refine existing tools used to assess people suspected of having post-COVID-19

condition. Identifying biomarkers or specific clinical features of subtypes may help reduce the challenges faced by some people in accessing appropriate care, including relevant specialists, and could inform prognosis.^{36-39,42} Understanding the extent of symptoms affecting different organ systems may also provide health care decision-makers with foresight into the potential needs for specialists' care.^{10,27} Given that there may be a spectrum of needs across more than a million⁷ people who may be affected in Canada, health systems would need to ensure that the subset of people with the highest and most complex multisystem needs are provided enhanced treatment supports, while most people are provided with resources and access to their specific care needs. A growing body of evidence is also exploring whether some people may be developing previously established or recognized conditions, such as ME/CFS, pulmonary fibrosis, or post-intensive care syndrome.^{40,43,46} People who develop those subtype conditions may be able to benefit from similar treatments known to be effective for those conditions.⁴⁰ Certain people who require hospitalization for acute illness may also need enhanced monitoring to ensure the presence of certain subtype conditions can be detected early and guide their care.⁴⁶ Moreover, determining appropriate classification criteria will be important as many proposed subtypes identified in the literature base show substantial overlap with each other and with other conditions.

Across the literature base, we found at least 4 studies examining whether different variants of infection may be associated with subtypes, or a differential risk of post-COVID-19 condition.^{56,58-60} It is possible that, in part, particular symptoms patterns of post-COVID-19 condition may be associated different variants of infection; however, the evidence at this time remains uncertain. If these associations are validated with more rigorous study designs, it may further highlight the importance of continued testing of acute infections to help inform prognosis and long-term treatment approaches.

Although we did not explore the demographic, socioeconomic, and health-related factors of people with post-COVID-19 condition in this review, such factors could be associated with different subtypes.²⁰ Future research exploring the pathophysiology of the condition and its subtypes would need to consider these factors when providing accessible and equitable care. As many of the identified studies are at an exploratory stage, and as the evidence matures and proposed subtypes are validated, it will be important to continue to engage with patient partners and clinical experts to help inform care.

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