COVID-19 Scientific Advisory Group
Rapid Evidence Report

Key Research Questions:

1. **After a diagnosis of COVID-19, which symptoms are commonly noted after 30 days, and what is the usual duration of these chronic symptoms?**
2. **Which patients with COVID-19 are at highest risk of developing these chronic symptoms?**
3. **What mechanisms are likely to be responsible for chronic symptoms?**

Context

- There is growing recognition that a subset of patients recovering from COVID-19 experience symptomatology beyond the acute infection period. These “long haulers” are thought to experience a “Long Covid”, which are two hashtags increasingly prominent in social media. News media outlets are increasingly describing some of these patients’ plights, such as Nature (Marshall, 2020), Bloomberg (Gale, 2020), and CTV News (Neustaeter, 2020). Continuing medical education strategies have begun to describe and consider the long-term symptoms of COVID-19 survivors (Burak et al., 2020).
- The Post-COVID Rehabilitation Taskforce received Alberta Health Services’ leadership support on October 29, 2020 to begin implementation of a longitudinal strategy to better support patients with the post-acute symptoms of COVID-19, particularly their rehabilitation needs. This strategy includes a directive to prospectively follow-up patients recovering from COVID-19 to determine persistent symptoms and rehabilitation needs.
- To inform this initiative, and clinicians caring for patients post-COVID, in this report, we sought to determine the current best evidence regarding the nature, frequency, duration, risk factors and mechanism of these persistent, long-term, post-COVID-19 symptoms.

Key Messages from the Evidence Summary

- Although structured definitions of chronic symptoms are not yet standardized, this review found 46 unique chronic symptoms described after acute COVID-19 infection.
- The chronic symptoms noted most frequently across studies included dyspnea, fatigue, cough, headache, loss of smell (anosmia), cognitive impairment, loss of taste (ageusia), and muscle/joint pain (myalgia) (Table 1a, Figure 1). Less frequently noted was chronicity of sleep impairments, chest pain, tachycardia, GI upset, muscle weakness and anxiety.
- Based on the median [range] prevalence noted across more than one study, the three most prevalent chronic symptoms post-COVID19 at 4 to 6 weeks post-diagnosis are fatigue (55% [16.4-73%], headache (37.8%, [15-50%]), and dyspnea (33% [1.53-56%]). Based on the median [range] prevalence noted across more than one study, the three most prevalent chronic symptoms post-COVID19 at 8 to 12 weeks post-diagnosis are fatigue (42% [9.5-62%], dyspnea (39% [1.53-48%]), and sleep impairments (30.8% [10-39%]).
- The nascent nature of the illness and corresponding literature limits generalizations on the prevalence and duration of chronic symptoms. The included studies followed patients for on average 6.82 (+/- 3.16) weeks, and follow-up was often limited to a one-time follow-up, so the natural history of post COVID symptoms remains unclear. Mode of follow-up varied from rigourous, objective assessments to self-report or social media analyses, which carry a greater risk of bias.
- Of importance, the data is limited due to lack of standardized definitions of chronicity, symptomatology post-COVID-19, and an over-reliance on subjective self-report without comparator populations or objective tools.
- Given that we have only 11 months of experience with COVID 19, we do not yet understand the true duration of chronic post-COVID-19 symptoms. Few studies followed patients until complete resolution of symptoms for the majority of patients, and where such studies did, the sample sizes were quite limited.

- Current literature suggests that chronic symptoms can result in myriad symptoms and multiple functional impairments.
- Some studies have assessed risk factors for developing chronic symptoms:
    - Having dyspnea (shortness of breath) in the acute phase of the illness (defined as day 7 after symptom onset), or having a history of asthma or chronic lung disease, is associated with a higher risk for prolonged or chronic dyspnea (Carvalho-Schneider et al., 2020; Cellai & O'Keefe, 2020).
    - Younger age, being of female gender, or previous diagnosis of a psychiatric disorder (De Lorenzo et al., 2020; Halpin et al., 2020; Mazza et al., 2020; Taquet, Luciano, Geddes, & Harrison, 2020) are associated with a higher risk of persistent psychiatric symptoms, particularly PTSD.
- There is little data on long term symptoms in pediatric populations. A single study (n=25) on pediatric patients found that they did not experience chronic symptoms or laboratory abnormalities.
- The severity of the acute COVID-19 illness is associated with a higher risk of chronic post-COVID19 symptoms (Carvalho-Schneider et al., 2020), but conversely some studies find hospitalization protective (particularly against psychiatric symptoms) (De Lorenzo et al., 2020) or found no difference with respect to chronic symptoms of Intensive Care Unit (ICU) and non-ICU hospitalized patients (Garrigues et al., 2020).
- The mechanisms that may be responsible for chronic symptoms remain uncertain. The theories proposed currently describe potential pathophysiologic aspects of SARS-CoV-2 infection, including direct viral, immune and inflammatory manifestations. This includes causing 'cytokine storm,' highly inflammatory states; passing through the olfactory bulb to affect the senses; and how these may lead to both acute complications (e.g. stroke, encephalitis); and possibly transition into the experience of chronic symptoms post-acute COVID-19. Current literature focuses primarily on neurological manifestations and mechanisms although other areas are evolving and emerging in the literature.

Table 1a. Most Common Symptoms and Range of Prevalence Noted by Included Studies.

System	Symptom	# of STUDIES	Median [Range] Prevalence Range (4-6 week f/u studies)	Median [Range] Prevalence Range (8, 12 or more week f/u studies)
Respiratory	**Shortness of breath (dyspnea)**	18	**33%** [1.53% - 56%] (5 studies; 2 unclear)	**39%** [1.53% - 48%] (9 studies; 4 unclear)
	Cough	13	**18.3%** [7%-33%] (5 studies, 3 unclear)	**7.7%** [1.81% - 27%] (4 studies, 2 unclear)
	Chest pain	7	**18.0%** [n/a] (1 study, 3 unclear)	**17.1%** [13%-31%] (4 studies, 2 unclear)
Neurological	**Fatigue**	15	**55%** [16.4%-73%] (6 studies, 2 unclear)	**42%** [9.5%- 62%] (7 studies, 1 unclear)
	Headache	12	**37.8%** [15%-50%] (3 studies, 4 unclear)	**18.2%** [7%-22%] (3 studies, 2 unclear)
	Loss of smell (anosmia)	11	**12%** [5%-36%] (5 studies, 2 unclear)	**12%** [9.7%-39%] (5 studies, 1 unclear)
	Cognitive impairment	9	**18%** [12%-25.4%] (3 studies, 4 unclear)	**20%** [12%-28%] (2 studies, 2 unclear)
	Loss of taste (ageusia)	8	**28%** [9%-32%] (3 studies, 4 unclear)	**12.1%** [1.17%-23%] (2 studies, 1 unclear)
Musculoskeletal	**Muscle/joint pain**	8	**9.8%** [5%-15%] (3 studies, 3 unclear)	**16.3%** [6%-28%] (3 studies)
Mental health	**Sleep impairments**	7	**40%** [n/a] (1 study, 3 unclear)	**30.8%** [10%-39%] (3 studies)

Committee Discussion

The review was discussed by the Scientific Advisory Committee on November 18, 2020. The committee reached consensus on the following recommendations and research gaps. It was acknowledged that there was a great breadth of literature on the post-COVID-19 chronic symptoms, but that many research gaps remain. Gaps remaining include standardization of the definition of chronicity and the best methodology to study chronic symptoms post-COVID-19. The included studies were of moderate quality without any high quality studies at low risk of bias; most of the studies were observational, focused on self-report, lacked comparators and lacked objective assessments. A concern was raised that a focus on self-report and a lack of comparator or objective assessments may be as a result of paitents somaticizing their symptoms, though definitive conclusions can not be made this early in a pandemic.

While there was a focus on moderate to high quality studies, there is still a wide range on the prevalence of symptoms across the studies. There is recognition that a significant portion of COVID-19 survivors will have chronic symptoms, but less clarity on which symptoms those will be. Given the range of jurisdictions from where studies were conducted, there remain questions on whether jurisdictional or genetic differences impact chronic symptomatology. There was discussion about the importance to raise awareness on the breadth of possible long-term symptoms for patients recovering from COVID-19 amidst care providers, particularly primary care, nursing and allied health professionals. There was discussion on the importance of generating high-quality data in Alberta to inform decision-making and care planning. The related recommendation should tie to current or planned work, particularly that of the Provincial Post-COVID Rehabilitation Taskforce. The need to include hospitalized and community-only COVID-19 survivors was noted.

Recommendations

1. Strategies to support patients recovering from COVID-19 should be multidisciplinary, and should involve options for decentralized care through collaboration with primary care physicians as well as nursing and allied health professionals.
   Rationale:
   The duration and diversity of chronic symptoms post COVID-19 makes longitudinal follow-up vital to identify and support the specific needs of individual patients. Post-COVID long-term symptoms should be assessed in a systematic fashion using standard definitions, and appropriate treatment and monitoring established to support the patient.

2. For patients recovering from COVID-19 who are identified at higher risk of chronic symptoms, increased attention should be made to their general health in their long-term recovery. Particular attention should be given to patients at higher risk of mental health symptoms (current risk factors include female, younger adults, or with a history of psychiatric diagnoses) and patients at higher risk for respiratory symptoms (current risk factors include existing chronic lung disease, and/or dyspnea in the acute phase).
   Rationale:
   Patients recovering from COVID-19 should be followed clinically in a structured fashion to document incidence and duration of chronic symptoms in our population. Optimally patients may be randomized into a community-based structured care versus an intensified follow-up care stream to elucidate whether additional testing and follow-up impacts the post COVID illness experiences. In addition, assessment of therapeutic options for chronic symptoms should be preferentially offered and followed within the context of trial protocols, whether patients are in an intensive follow-up cohort or community-based cohort.

3. There should be a systematic approach, including the use of standard definitions, to monitoring and studying the chronic symptoms of Albertans with COVID-19, so that the health system can understand the local context of symptomatology and epidemiology better. It may be useful to also consider data collection in a control population (perhaps also recovering from another viral illness, or another population within primary care).
   Rationale:
   In October 2020, Alberta Health Services approved a proposed strategy by the Provincial Post-COVID Rehabilitation Taskforce (Alberta Health Services, 2020). *Part of the proposed strategy centres on*

completing longitudinal follow-up with persons recovering from COVID19, whether hospitalized or community-only experience. This follow-up should aim to ensure care continuity for patients with persistent post-COVID19 symptoms, and to provide much-needed clarity on the exact epidemiology, particularly prevalence, of chronic symptoms post-COVID-19 in Alberta. Any follow-up should consider the chronic needs of patients recovering from COVID-19 post-hospitalization as well as the needs of patients who were not admitted to hospital (for whom less information is available).

Pragmatic Considerations

Developing a care pathway focused on chronic symptoms is beyond the scope of this review, but is likely essential to support patients in their long-term recovery from COVID-19. The current Presumed/Confirmed COVID19 Positive Primary Care Pathway may represent an existing tool to update with the knowledge generated in this rapid evidence review. In particular, there may be a need to refine the current pathway to include some of these chronic symptoms. Primary care input will be needed to determine what is feasible and what support is needed.

Research Gaps

While this rapid evidence review includes 54 articles, the quality of these articles is neither abysmal nor excellent. The studies are informative and of moderate to high quality. There remain gaps in the literature that must be addressed. These include the following:

- As noted in the literature, greater clarity is required on the exact definition of chronicity in the context of COVID-19.
- The included studies varied in data collection, some studies used self-report apps, others had clinicians use de novo (or occasionally validated) surveys with patients to capture self-report, and others involved more objective physical assessments and laboratory testing to complement self-report. The committee notes a significant research gap relates to the need for a set of standard definitions on the symptomatology that is objectively chronic post-COVID-19 and for the gold standard tools to measure such symptoms.

Strength of Evidence

The body of evidence is moderate to strong. Most of the included studies were peer-reviewed (14 of the 54 studies were preprints). The risk of selection bias for forming cohorts was difficult to assess, while some studies described seeking consecutively admitted COVID-19 patients, others used social media or convenience sampling without insight on the process. Qualitative comparisons suggest that the app-based assessments (Banda et al, 2020) listed fatigue more often than other smaller clinic-based studies that mentioned mental health and dyspnea more frequently. The systematic reviews were limited but of very high quality, while the numerous observational cohorts were of moderate to high quality. None of the observational cohorts fell into the low-quality area, and all have very reasonable sample sizes. However, none of the observational cohorts stood out as of exceptionally high quality with limit risk of bias.

Limitations of this review

Chronicity of symptoms is implied to be at 30 days or longer. This was viewed as a benchmark, not a hard limit. Many studies that met the “spirit” of the research questions used a different definition for long-term follow-up or chronic post-COVID-19 symptoms (i.e. long COVID). These different definitions included using a weekly timeline that went to 4 weeks (i.e. 28 days). These studies were included to ensure comprehensive coverage. One study was highly cited (particularly by the World Health Organization), focused on long-term symptoms, but used a 2 to 3 week follow-up period (14-21 days): this study was included for Research Question 1 only (Tenforde et al., 2020). As recognized in Amenta et al. (2020), “there is no universally accepted time period that defines the beginning of the post-acute period.” But Amenta et al. (2020) suggest that chronic COVID-19 includes “… persistent symptomatology extending beyond 12 weeks after initial symptoms.”

This review limited itself to the direct language of the Research Questions, which spoke to symptoms not complications or sequelae. While the search strategy included all terms such as complications, sequelae and symptoms, the resulting studies screened did not include literature that clarified acute complications in hospital or

sought associations between particular sequelae and chronic symptoms. The symptomatology assessed in these studies considered hospitalized, non-hospitalized or both types of patients, but the detailed experiences in hospital were not discussed. A future review search strategy may be required to fully elucidate the correlation between acute complications and chronic symptoms.

The rapid turnaround time of this review introduced challenges and related workarounds, as follows:

- The second part of Research Question 2 seeks information on the duration of chronic symptoms. The included studies can only speak to duration relative to the timeline of their study, which was on average 6.93 (+/- 3.15) weeks post-diagnosis with the longest follow-up period being 15.8 weeks in one study. This evidence review cannot confirm the decisive duration of chronic post-COVID-19 symptoms. Few studies followed patients until complete resolution of symptoms for the majority of patients, and where such studies did the sample sizes were quite limited.
- The literature on the mechanism of chronic symptoms is nascent and highly hypothetical.
    - Articles were excluded if the discussion on the mechanisms focused on chronic complications that could not yet manifest given the emerging nature of this pandemic. Examples include studies that hypothesized on the pathology of neurological complications, which could lead to neurodegenerative disorders such as Alzheimer's disease, Parkinsons' disease, or cancer.
    - Articles were excluded if the discussion on mechanisms focused on acute symptomatology. Articles were included, however, if the discussion on acute symptomatology implied acute complications with long-term symptom implications. These were included for a high-level discussion (not detailed analysis). Such studies hypothesize on acute complications such as encephalitis, stroke or Guillain-Barre Syndrome.
    - Articles were included for extraction and analysis to address Research Question 3 if they approached, hypothetically or empirically, the potential mechanisms of chronic post-COVID-19 symptoms.
- The focus of this narrative review was limited to the incidence, duration and risk factors of patient symptoms or outcomes experienced post-COVID-19, and not that of medical conditions or complications which could arise as a complication of COVID-19. The former included a range of symptoms such as cough, fatigue, PTSD, and dyspnea (shortness of breath), while the latter included a range of complications such as stroke, myocardial infarction, sepsis, and post-ICU syndrome. This limit was verified by the 26 observational cohort studies that attempted to follow-up COVID-19 survivors and determine their experience. These studies measured symptoms, through self-report, lab tests or physical assessments, but did not detail patient complications or conditions.

Given the emerging nature of the pandemic and timeline since the introduction of the virus, the recommendations rely on preprints and peer-reviewed articles in equal stead. This review should be read as a rapid, emerging evidence summary, rather than a rapid evidence review.

Databases were searched for English-language evidence published in 2020, thus, evidence from outbreaks in jurisdictions where English is not common has not been included in this review.

Summary of Evidence

Literature for this review was collected from a database search covering OVID MEDLINE, CINAHL, LitCovid, PubMed, TRIP PRO, WHO COVID-19 Database, Centre for Evidence Based Medicine (CEBM), Google and Google Scholar. The search was limited by the following parameters: COVID-19, SARS-CoV-2 virus, long-term follow-up, outcomes, post-discharge, post-diagnosis, and mechanism.

One hundred and sixty-five articles (peer-reviewed and pre-prints) were identified in the initial search, alongside with citation tracking and snowball searching amongst the KRS librarian and review writers. After a title, abstract and paper review where each paper was assessed by two writers independently, 54 published articles (including 14 pre-prints) were included, based on consensus. A total of four writers were involved in screening and extraction.

The search was limited by the parameters of the questions: determining the nature, duration, risk factors and potential mechanisms for symptoms that remain with COVID-19 survivors after the acute infection stage of COVID-19. The search was limited to English articles published 2020-current. Articles were not excluded based on population. While the research questions framed chronicity as at 30 days or beyond the date of diagnosis, as discussed above, we did not limit the search strategy by specific date and sought articles that examined or considered symptoms in the non-acute infection period of COVID-19.

The majority of the included studies were observational cohorts (n=26) and unstructured review (n=11), while other studies included editorials (n=6), cross-sectional surveys (n=5), systematic reviews (n=4), case-control study (n=1) and case report (n=1). The editorials primarily described potential mechanisms, while the surveys and cohorts informed chronic symptoms prevalence and duration. The jurisdictional distribution of the studies was as follows: USA (n=19), UK (n=9), Italy (n=7), International teams (n=4), China (n=3), France (n=3), Austria (n=2), and one each from Belgium, Finland, Iran, Israel, Japan, Spain, and Switzerland.

Research Question 1: After a diagnosis of COVID-19, which symptoms are commonly noted after 30 days, and what is the usual duration of these chronic symptoms?

Evidence from secondary and grey literature

Any secondary and grey literature that was identified that addressed this question included citations to primary literature or original research. This review limited its analysis and discussion to primary literature or original research (including preprints).

Evidence from the primary literature

This synthesis is based on 38 studies that explicitly considered the nature or frequency of chronic symptoms post-COVID-19. These included 25 observational cohorts, 5 cross-sectional survey studies, 3 reviews, 3 editorials, and 1 case report. Table 3a in the Appendix section contains the information extracted from each document.

From the studies that completed follow-up, the average (standard deviation) number of weeks of follow-up was 6.82 (+/- 3.16), while the minimum and maximum follow-up periods were 2 weeks (Tenforde et al., 2020) and 15.8 weeks (Garrigues et al., 2020). Nineteen studies only included 1 time-point for follow-up, with the maximum number of follow-ups being 7 times. The included studies speak to follow-up at 30 or less days (14 studies), 42 days (11 studies), 60 days (10 studies), 90 days (6 studies), while 8 studies were unclear. Conservatively, these studies can generalize to the nature of chronic symptoms post-COVID-19 experienced by patients up to the mean of nearly 7 weeks from diagnosis. The longer-term manifestation of chronic symptoms, especially by a more formalized definition of chronic COVID-19 at 12 weeks or beyond diagnosis is unclear from the studies in this review.

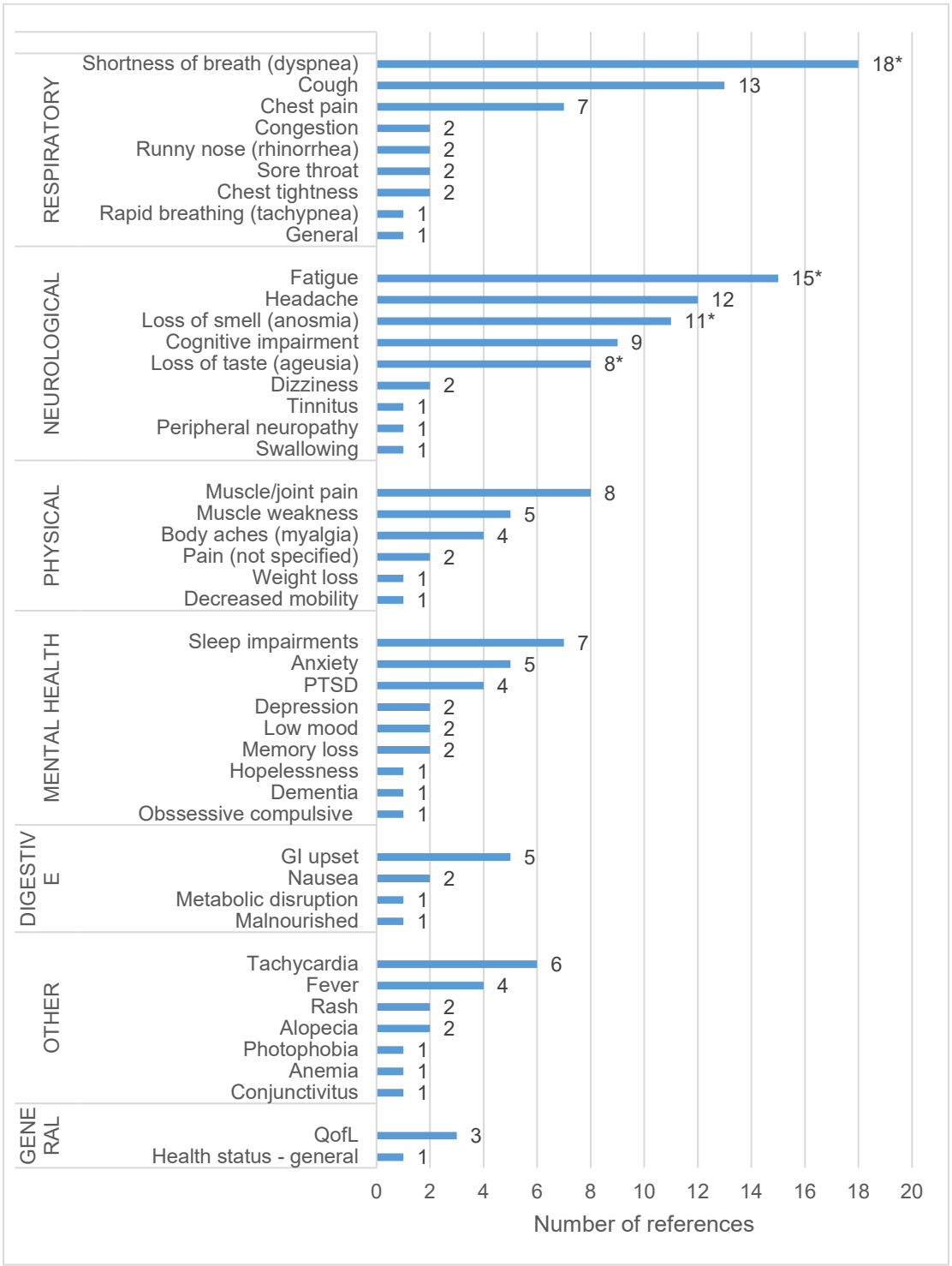
The sample size of the observational cohorts and surveys were noteworthy and wide ranging. The maximum participant sample size was 84,285 (Hampshire et al., 2020), while it is unclear how many participants took part in the Banda et al. (2020) study wherein 144,600 social media posts were analyzed. Due to outliers, the mean (SD) sample size is unclear at 4837.2 (+/- 18194.0). The median sample size for the studies was 119, while the 25th and 75th percentiles were 57 and 224, respectively. This suggest robust sample sizes, although there is less clarity on the recruitment tactics to minimize selection bias.

These studies noted that persons recovering from COVID-19 developed 46 unique chronic symptoms (Figure 1; Table 1b). The chronic symptoms noted most frequently across the included references include dyspnea (18 references), fatigue (15 references), cough (13 references), headache (12 references), loss of smell (anosmia) (11 references), cognitive impairment (11 references), myalgia (muscle/joint pain) (8 references), sleep impairments (7 references), chest pain (7 references), tachycardia (6 references), GI upset (5 references), muscle weakness (5 references) and anxiety (5 references). Based on the median [range] prevalence noted across more than one study, the five most prevalent chronic symptoms post-COVID19 at 4 to 6 weeks post-diagnosis are fatigue (55% [16.4-73%], headache (37.8%, [15-50%]), dyspnea (33% [1.53-56%]), loss of taste (ageusia) (28% [9-32%]), and cough (18.3% [7-33%]). Based on the median [range] prevalence noted across more than one study, the five most prevalent chronic symptoms post-COVID19 at 8 to 12 weeks post-diagnosis are fatigue (42%

[9.5-62%], dyspnea (39% [1.53-48%]), sleep impairments (30.8% [10-39%]), cognitive impairment (20% [12-28%]), and headache (18.2% [7-22%]).

We examined whether studies focused their aims and methods on a broad or narrow range of systems. Across the 38 studies that considered chronic symptoms, whether empirically or theoretically, 10 (26.3%) articles focused on only one system or type of symptoms (e.g. neurological, cardiovascular), while 28 (75.7%) articles took a broader approach to include more than one system. Based on the categorization of the four writers, some of the included studies had methodologies that considered neurological symptoms (64.2%), respiratory symptoms (64.2%), sensory symptoms (50.9%), functional symptoms (41.5%), cardiovascular symptoms (37.7%), fatigue-specific symptoms (45.3%), musculoskeletal symptoms (26.0%), psychiatric symptoms (26.4%), immunological and inflammatory symptoms (24.5%), and quality-of-life-related symptoms (17.3%). In most cases, the studies that assess quality of life used validated surveys, but for the other categories of symptoms the studies varied greatly on the use of validated instruments, clinical assessments or patient self-report using novel surveys.

Figure 1. Chronic Post-COVID-19 Symptoms Identified in the Primary Literature



Due to heterogeneity and time constraints, we were unable to pool studies to obtain point estimates on the frequency and duration of chronic symptoms after 30 days of diagnosis with COVID-19. Some studies were more illuminating that others in this regard. This information supplements Table 1a above:

- One study found that 43.4% of COVID-19+ cases have symptoms lasting longer than 30 days, and 24.1% still have at least one symptom after 90 days (Cirulli et al., 2020).
- Another study found that only 18 (12.6%) of participants were completely free of COVID-19-related symptoms around 8.6 weeks from diagnosis (Carfì, Bernabei, & Landi, 2020). Carfi, Bernabei & Landi (2020) also found that at follow-up, 32% of participants had 1 or 2 symptoms, and 55% had 3 or more chronic symptoms.
- At 6 weeks follow-up, a study focused on headache found it persisted for 37.8% of patients post-COVID-19, including 60.7% (17) having daily constant headache (Caronna et al., 2020).
- Cellai et al. (2020) noted that 69.2% of patients reported at least 4 concurrent symptoms at 30-day follow-up.
- Charlotte et al. (2020) found that the 30-day post-diagnosis time-point, 63% (73) patients reported persistent symptoms.
- The frequently cited, but shorter duration, study by Tenforde et al. (2020), found that 34% (59 of 175) respondents had one or more COVID-19-related chronic symptoms at follow-up.

These studies that noted symptom persistence did not distinguish on symptom severity. Few studies discussed re-hospitalization, and those that did were not explicit on which chronic symptomatology or complication caused the re-hospitalization.

Taken together, these studies suggest that a minority of patients will be without chronic symptoms at the 30-day (or 4 week) mark after COVID-19 diagnosis. However, there appears to be jurisdictional variation in the propensity for some of these symptoms.

Importantly, only one study found that no patients had clinical symptoms or laboratory test abnormalities 4-months after the study (Denina et al., 2020). Denina et al. (2020) followed 25 hospitalized children in Italy. This study may suggest that pediatric patients with COVID-19 may be less likely to experience chronic symptoms, but the small sample size and lack of corroboration limits the generalizability of this suggestion. Most of the studies included in this rapid evidence review focused on adult patients.

Table 1b. Chronic Symptoms Experienced by Patients Recovering from COVID-19.

System	Symptom	# of Studies	References
Respiratory	Shortness of breath (dyspnea)	18	Arnold DT *et al.,* 2020; Banda JM *et al*., 2020; Carfi A *et al*., 2020; Carvalho-Schneider C *et al.,* 2020; Cellai & O'Keefe, 2020; Cirulli ET *et al.*, 2020; Daher A *et al*., 2020; De Lorenzo et al., 2020; Garrigues E *et al*., 2020; Greenhalgh *et al*., 2020; Halpin SJ *et al*., 2020; Miyazato Y *et al*., 2020; Morley JE 2020; O'Keefe JB *et al*., 2020; Rogliani P *et al*., 2020; Sollini M *et al*., 2020; Wang X *et al*., 2020; Zhao YM et al., 2020
	Cough	13	Bakhoum MF *et al*., 2020; Banda JM *et al*., 2020; Blair PW *et al*., 2020; Cellai & O'Keefe, 2020; Daher A *et al*., 2020; Greenhalgh *et al*., 2020; Halpin SJ *et al*., 2020; Miyazato Y *et al*., 2020; Morley JE 2020; Klein H *et al*., 2020; O'Keefe JB *et al*., 2020; Wang X *et al*., 2020; Zhao YM et al., 2020
	Chest pain	7	Banda JM *et al*., 2020; Carfi A *et al*., 2020; Carvalho-Schneider C *et al.,* 2020; Cirulli ET *et al.*, 2020; Greenhalgh *et al*., 2020; Morley JE 2020; Sollini M *et al*., 2020
	Congestion	2	Cellai & O'Keefe, 2020; O'Keefe JB *et al*., 2020
	Runny nose (rhinorrhea)	2	Carvalho-Schneider C *et al.,* 2020; Daher A *et al*., 2020
	Sore throat	2	Daher A *et al*., 2020; Wang X *et al*., 2020
	Chest tightness	2	Cellai & O'Keefe, 2020; Wang X *et al*., 2020
	Rapid breathing (tachypnea)	1	De Lorenzo *et al*., 2020
	General	1	Charlotte P *et al*., 2020

Neurological	Fatigue	15	Arnold DT *et al.,* 2020; Banda JM *et al*., 2020; Carfi A *et al*., 2020; Cellai & O'Keefe, 2020; Charlotte P *et al*., 2020; Daher A *et al*., 2020; Garrigues E *et al*., 2020; Greenhalgh *et al*., 2020; Halpin SJ *et al*., 2020; Miyazato Y *et al*., 2020; Morley JE 2020; Savarraj JP *et al*., 2020; Sollini M *et al*., 2020; Sudre CH et al., 2020; Zhao YM et al., 2020
	Headache	12	Bakhoum MF *et al*., 2020; Banda JM *et al*., 2020; Caronna E *et al*., 2020; Cellai & O'Keefe, 2020; Cirulli ET *et al*., 2020; Daher A *et al*., 2020; Greenhalgh *et al*., 2020; Morley JE 2020; Sollini M *et al*., 2020; Sudre CH et al., 2020; Zhao YM et al., 2020; Zubair AS *et al*., 2020
	Loss of smell (anosmia)	11	Carvalho-Schneider C *et al.,* 2020; Charlotte P *et al*., 2020; Cirulli ET *et al*., 2020; Daher A *et al*., 2020; Miyazato Y *et al*., 2020; Morley JE 2020; Klein H *et al*., 2020; O'Keefe JB *et al*., 2020; Sollini M *et al*., 2020; Sudre CH et al., 2020; Zubair AS *et al*., 2020
	Cognitive impairment	9	Cirulli ET *et al*., 2020; Daher A *et al*., 2020; De Lorenzo *et al*., 2020; Garrigues E *et al*., 2020; Greenhalgh *et al*., 2020; Hamphire A *et al*., 2020; Morley JE 2020; Savarraj JP *et al*., 2020; Sudre CH et al., 2020
	Loss of taste (ageusia)	8	Carvalho-Schneider C *et al.,* 2020; Cirulli ET *et al*., 2020; Daher A *et al*., 2020; Miyazato Y *et al*., 2020; Morley JE 2020; Klein H *et al*., 2020; Sollini M *et al*., 2020; Zubair AS *et al*., 2020
	Dizziness	2	Cirulli ET *et al*., 2020; Greenhalgh *et al*., 2020
	Tinnitus	1	Sudre CH et al., 2020
	Peripheral neuropathy	1	Sudre CH et al., 2020
	Swallowing	1	Greenhalgh *et al*., 2020
Physical	Muscle/joint pain	8	Banda JM *et al*., 2020; Carfi A *et al*., 2020; Carvalho-Schneider C *et al.,* 2020; Daher A *et al*., 2020; Greenhalgh *et al*., 2020; Morley JE 2020; O'Keefe JB *et al*., 2020; Sollini M *et al*., 2020
	Muscle weakness	5	Bakhoum MF *et al*., 2020; Blair PW *et al*., 2020; Charlotte P *et al*., 2020; Greenhalgh *et al*., 2020; Morley JE 2020
	Body aches (myalgia)	4	Arnold DT *et al.,* 2020; Carvalho-Schneider C *et al.,* 2020; O'Keefe JB *et al*., 2020; Miyazato Y *et al*., 2020
	Pain (not specified)	2	Banda JM *et al*., 2020; Savarraj JP *et al*., 2020
	Weight loss	1	Carvalho-Schneider C *et al.,* 2020
	Decreased mobility	1	Morley JE 2020
Mental Health	Sleep impairments	7	Arnold DT *et al.,* 2020; Banda JM *et al*., 2020; De Lorenzo *et al*., 2020; Garrigues E *et al*., 2020; Greenhalgh *et al*., 2020; Mazza MG *et al*., 2020; Taquet M *et al*., 2020
	Anxiety	5	Daher A *et al*., 2020; De Lorenzo *et al*., 2020; Greenhalgh *et al*., 2020; Mazza MG *et al*., 2020; Taquet M *et al*., 2020
	PTSD	4	De Lorenzo *et al*., 2020; Halpin SJ *et al*., 2020; Mazza MG *et al*., 2020; Savarraj JP *et al*., 2020
	Depression	2	Daher A *et al*., 2020; Mazza MG *et al*., 2020
	Low mood	2	Greenhalgh *et al*., 2020; Taquet M *et al*., 2020
	Memory loss	2	Cirulli ET *et al*., 2020; Garrigues E *et al*., 2020
	Hopelessness	1	Greenhalgh *et al*., 2020
	Dementia	1	Taquet M *et al*., 2020
	Obsessive compulsive	1	Mazza MG *et al*., 2020
Digestive	GI upset	5	Carvalho-Schneider C *et al.,* 2020; Cellai & O'Keefe, 2020; Daher A *et al*., 2020; Greenhalgh *et al*., 2020; Zhao YM et al., 2020
	Nausea	2	Daher A *et al*., 2020; Wang X *et al*., 2020
	Metabolic disruption	1	Greenhalgh *et al*., 2020
	Malnourished	1	De Lorenzo *et al*., 2020
Other	Tachycardia	6	Banda JM *et al*., 2020; Carvalho-Schneider C *et al.,* 2020; Cellai & O'Keefe, 2020; Cirulli ET *et al*., 2020; Morley JE 2020; Sudre CH et al., 2020
	Fever	4	Banda JM *et al*., 2020; Carvalho-Schneider C *et al.,* 2020; Daher A *et al*., 2020; Greenhalgh *et al*., 2020
	Rash	2	Carvalho-Schneider C *et al.,* 2020; Greenhalgh *et al*., 2020

	Alopecia	2	Garrigues E *et al*., 2020; Miyazato Y *et al*., 2020
	Photophobia	1	Bakhoum MF *et al*., 2020
	Anemia	1	Sonnweber T *et al*., 2020
	Conjunctivitis	1	Morley JE 2020
General	QofL	3	Arnold DT *et al.,* 2020; Carfi A *et al*., 2020; Halpin SJ *et al*., 2020
	Health status - general	1	Arnold DT *et al.,* 2020

Research Question 2: Which patients with COVID19 are at highest risk of developing these chronic symptoms?

Evidence from secondary and grey literature

Any secondary and grey literature that was identified that addressed this question included citations to primary literature or original research. This review limited its analysis and discussion to primary literature or original research (including preprints).

Evidence from the primary literature

This synthesis related to risk factors is based on 17 primary articles (7 preprints, and 10 peer-reviewed articles), including 13 observational cohorts, 3 cross-sectional surveys, and 1 editorial. Table 2a one overviews the key takeaways from these articles on the risk factors for chronic symptoms post-COVID19, while Table 3a in the Appendix section contains the information extracted from each document.

There are only a few clear findings related to the types of patients with COVID19 who are at highest risk of developing certain chronic symptoms.

- First, it appears that those at higher risk of psychiatric chronic symptoms, particularly PTSD, include those:
    - of younger age (about 40-60 years) (OR 1.033 [95%CI 1.003-1.067], p=0.037, De Lorenzo et al., 2020),
    - of female gender (OR 1.76 [95% CI 0.94-3.37], p=0.085, De Lorenzo et al., 2020), (76.9% females vs. 38.5% males in ICU, Halpin et al. 2020), (2.9:1 Female: Male ratio, χ^2=54.98, p<0.001 for clinical PTSD and 3:1 M:F (χ^2=15.13, p<0.001 for clinical depression), Mazza et al. 2020).
    - with previous diagnosis of a psychiatric disorder (RR 1.65 [95% CI 1.59-1.71], p<0.001, Taquet et al. 2020)

Second, there is some support that patients with dyspnea (shortness of breath) in the acute phase, or who have a history of asthma or chronic lung disease, may be at higher risk for a chronic experience of dyspnea (OR 2.4 [1.0-5.3 95%CI, p=0.02) (Carvalho-Schneider et al., 2020; Cellai & O'Keefe, 2020). It should be noted that dyspnea is somewhat mixed as a symptom: some patients develop chronic dyspnea without any evidence of having developed a chronic lung disease, while those with prolonged COVID-19 pneumonia may have dyspnea due, in part, because they have developed a complication of the pneumonia (i.e. chronic fibrotic lung disease).

Third, the severity of the acute COVID-19 experience may lead to higher risk of chronic post-COVID19 symptoms (OR 2.8 [1.2-6.2 95% CI, p=0.017) (Carvalho-Schneider et al., 2020), but this is not irrefutable. There are studies that suggest no difference in the outcomes of ICU and non-ICU patients (Garrigues et al., 2020), while another study found hospitalization a protective factor for chronic symptoms (particularly psychiatric symptoms) (OR 1.081[95% CI 0.57-2.02], p=0.81 (De Lorenzo et al., 2020). Two of these studies are more theoretical in their attribution of severity in acute COVID-19 to chronic symptoms (Bakhoum et al., 2020; Weerahandi et al., 2020).

The remaining studies herein attempt to inform the risk factors for chronic symptoms post-COVID-19, but they do not have corroboration from other studies. For example, Pizzini et al. (2020) found that low Vitamin D was not related to chronic symptoms (no OR provided; p=0.116); Klein et al. (2020) found that severity of the olfactory change was related to chronic sensory symptoms (correlation 0.34, p=0.003); and Sonnweber et al. (2020) found that hyperferritinemia was associated with decreased 6-minute walking distance (~200m yes to hyperferritnemai versus ~400m, p=0.011).

Table 2a. Summary of Articles Informing Risk Factors for Chronic Symptoms.

Author	Study Design	Type of Article	Type of COVID patients	Noted Risk Factor	Noted Chronic Symptom
(Bakhoum et al., 2020)	Observational Cohort	Preprint	All	-Post viral inflammation	Generic[1]
(Blair et al., n.d.)	Observational Cohort	Preprint	All	-While the majority 63.7% of participant had no symptoms or only had mild symptoms during the first week of illness a substantial proportion continued to have mild or moderate symptoms for over one month.	Generic
(Caronna et al., 2020)	Observational Cohort	Peer-reviewed	All	-There were no statistically significant differences with regard to the demographic variables in patients that were not followed up.	Generic
(Carvalho-Schneider et al., 2020)	Observational Cohort	Preprint	All	-These prolonged symptoms were significantly associated with **age** 40 to 60 years old, **hospital** admission at symptom onset, **severe** COVID-19, and **dyspnea** or abnormal auscultation.	Generic
(Cellai & O'Keefe, 2020)	Observational Cohort	Peer-reviewed	Non-hospitalized	**-Asthma and chronic lung disease** (prospectively coded at intake visit) appeared more frequently in the patients identified in the persistent symptom cohort for this study.	Respiratory chronic symptoms (e.g. dyspnea, chest pain)
(Cirulli et al., 2020)	Cross-sectional Survey	Preprint	All	-We additionally observe that individuals who had an initial symptom of **dyspnea** are significantly more likely to develop long-term symptoms. -Only five factors maintained a nominal association (uncorrected $p<0.05$) with long-term symptoms in COVID-19+ cases: the initial symptoms of **dyspnea and chest pain,** and **blood type A** as well as blood **type A+** (but not blood type A-, which	Generic

[1] Generic reference to chronic symptom means articles attributes risk factor to having some type of chronic symptom, but does not specific exactly which symptom. Often the risk factor analysis focused on presence or absence (or number of) symptoms, versus type of symptoms.

				is rarer) were associated with increased risk	
(De Lorenzo et al., 2020)	Observational Cohort	Peer-reviewed	Hospitalized	-Hospitalization, instead, emerged as protective factor. -PTSD: **Decreasing age**, **female gender** and **positive psychiatric history** were significantly associated with the risk of developing PTSD after COVID-19.	Mental Health
(Garrigues et al., 2020)	Observational Cohort	Peer-reviewed	Hospitalized	No difference in persistent symptoms between ICU and non-ICU/ward groups	Generic
(Halpin et al., 2020)	Cross-sectional Survey	Peer-reviewed	Hospitalized	-Moderate or severe fatigue (rated 4 + /10) was reported more frequently by **female** patients than male patients in both groups. -PTSD symptoms were reported by a much higher proportion of **females** (10/13; 76.9%) than males (5/19; 38.5%) in the ICU, whereas in the ward group these proportions were similar (22.9% of males and 24.2% of females). -In both groups, those reporting PTSD symptoms were **younger**.	-Fatigue (for gender) -PTSD (for age, gender)
(Hampshire et al., 2020)	Observational Cohort	Preprint	All	-The observed deficits varied in scale with respiratory symptom severity, related to positive biological verification of having had the virus even amongst milder cases, could not be explained by differences in age, education or other demographic and socioeconomic variables, remained in those who had no other residual symptoms and was of greater scale than common pre-existing conditions that are associated with virus susceptibility and cognitive problems	Cognitive deficits

(Klein et al., 2020)	Cross-sectional Survey	Preprint	All	-The **severity** of **olfactory change** is associated with its recovery time.	-Loss of taste -Loss of smell
(Mazza et al., 2020)	Observational Cohort	Peer-reviewed	Hospitalized	-Despite significantly lower levels of baseline inflammatory markers, **females suffered more for both anxiety and depression**. -Patients with a **positive previous psychiatric diagnosis** showed increased scores on most psychopathological measures, with similar baseline inflammation. -**Baseline systemic immune-inflammation index (SII)** was positively associated with scores of depression and anxiety at follow-up. -**Younger patients** showed higher levels of depression and sleep disturbances	Mental Health
(Morley, 2020)	Editorial	Peer-reviewed	All	-Elevated d-dimer levels are prognostic of poor lung function at 3 months; potential for chronic sub-clinical inflammation	Respiratory symptoms
(Pizzini et al., 2020)	Observational Cohort	Peer-reviewed	Hospitalized	-Low VitD levels at disease onset or at 8-week follow up were not related to persistent symptom burden, lung function impairment, ongoing inflammation	-Generic -Respiratory symptoms
(Sonnweber et al., 2020)	Observational Cohort	Peer-reviewed	All	-Hyperferritinemia was associated with decreased 6-minute walking distance (~200m yes to hyperferritinemia versus ~400m, p=0.011).	Mobility/function
(Taquet, Luciano, Geddes, & Harrison, 2020)	Observational Cohort	Peer-reviewed	All	-Having a **diagnosis of psychiatric disorder** in the year before the COVID-19 outbreak was associated with a 65% increased risk of COVID-19 (RR 1·65, 95% CI 1·59–1·71; p<0·0001) compared with a cohort matched for established physical risk factors for	Mental Health

				COVID-19 but without a psychiatric diagnosis.	
(Weerahandi et al., 2020)	Observational Cohort	Preprint	Hospitalized	-**Increased intensive care or mechanical ventilation**, likely explaining the higher prevalence of persistent dyspnea in our study.	Dyspnea

Research Question 3: What mechanisms are likely to be responsible for chronic symptoms?

Evidence from secondary and grey literature

Any secondary and grey literature that was identified that addressed this question included citations to primary literature or original research. This review limited its analysis and discussion to primary literature or original research (including preprints).

Evidence from the primary literature

Twenty-six articles touched upon the potential mechanisms responsible for the chronic post-COVID-19 symptoms for patients. Nineteen of these articles were more hypothetical on mechanisms, and their discussion centered on mechanisms responsible for acute symptomatology or acute-phase complications (Table 2b). Seven studies were more specific in their elaboration on potential mechanisms for long-term, chronic symptoms experienced post-COVID-19 (Table 2c). The implications for chronic symptoms in Table 2b studies is more implied, while the chronic implications of proposed mechanisms are explicit in Table 2c.

The broadly hypothetical discussions speak to mechanisms involving cardiovascular, neurological, immune, gastrointestinal, and multiple systems. Often these proposed mechanisms focused on acute complications due to organ injury (especially in cardiovascular, gastrointestinal, neurological and respiratory systems), which the reader then interpreted as causing long-term consequences including chronic symptoms for that organ or system at issue. These significant complications include encephalitis, necrotizing encephalopathy, fibrotic lung disease, Guillain-Barre syndrome, hemorrhages, hepatic injury, post-infectious neurological complications, and stroke.

Two major themes from Table 2b from the 19 articles with hypothetical mechanisms are (a) hyper-inflammatory responses or heightened immune responses to the virus were proposed as manifesting in acute complications and/or chronic symptoms; and (b) the neurological activity and implications of SARS-CoV-2 is the most commonly discussed and agreed upon in theory. Chronic neurological symptoms could result from nervous system invasion by SARS-CoV-2; cytokine storms that manifest into neural injury; brain expression of SARS-CoV-2-receptors and related proteins; various routes of brain entry (including olfactory route, blood-brain barrier, and infiltration of infected immune cells); indirect brain effects from systemic factors; and a hypercoaguable state.

Table 2b. Articles Detailing Highly Hypothetical, or More Acute, Mechanisms That May Contribute to Post-COVID-19 Chronic Symptoms.

System of Focus	High-Level Summary of Proposed Mechanisms	Implicated Chronic Symptoms[2]	# Studies	Citations of Studies Included
Cardiovascular System	• Describes potential metabolic, lipid and vascular mechanisms that increase risks of SARS-CoV-2 infection susceptibility and severity, related to the role in regulation of immunity and inflammation.	-Fatigue -Chest Pain -Tachycardia -Muscle weakness -Myalgia	1	(Becker, 2020)

[2] Many of these papers were high-level and hypothetical. Often, they did not elaborate the specific chronic symptoms that would follow from these hypothetical mechanisms. This list provides potential chronic symptoms that could be implicated, but we limit to ascribing only the most-frequently cited chronic symptoms.

Neurological System	• Potential mechanisms responsible for neurological symptoms in COVID-19 infection (acute and chronic): 1) Hyperinflammatory state in some patients ('cytokine storm') that manifests into neural injury (which can lead to other potential mechanisms listed herein) 2) Nervous system invasion by SARS-CoV-2 3) Brain expression of SARS-CoV-2-receptors and related proteins 4) Various routes of brain entry (olfactory route (cribiform plate and olfactory bulb), blood-brain barrier, infiltration of infected immune cells) 5) Indirect brain effects from systemic factors 6) Hypercoaguable state	-Loss of taste (ageusia) -Loss of smell (anosmia) -Fatigue -Sleep impairments -Cognitive impairment -Anxiety -Headache	13	(Ahmed et al., 2020; Amenta et al., 2020; Caronna et al., 2020; De Lorenzo et al., 2020; Fiani, Covarrubias, Desai, Sekhon, & Jarrah, 2020; Iadecola, Anrather, & Kamel, 2020; Mazza et al., 2020; Mohammadi, Moosaie, & Aarabi, 2020; Najjar et al., 2020; Taquet, Luciano, Geddes, & Harrison, 2020; Vonck et al., 2020; F. Wang, Kream, & Stefano, 2020; Whittaker, Anson, & Harky, 2020)
Immune System	• Describe the potential link between Western diets and obesity, chronic inflammation and alveolar damage in COVID-19 pathology. Suggest the inflammation will lead to long-term symptoms, but not specific on the type of symptom.	-Unclear	1	(Butler & Barrientos, 2020)
Gastrointestinal System	• Potential mechanisms to acute liver injury in COVID-19 infection, which could lead to chronic symptoms. Includes injury due to virus, treatment, or pre-existing hepatitis.	-GI upset	1	(Kunutsor & Laukkanen, 2020)
Multiple Systems	• Activated immune response to virus may lead to neurological complications (e.g. Guillain-Barre Syndrome), hematological complications (e.g. antiphospholipid syndrome), cardiovascular complications (e.g. haemorrhagic and ischaemic stroke), and respiratory complications (e.g. lung fibrosis). These complications can lead to chronic symptoms for	-Dyspnea -Fatigue -Cough -Headache -Loss of smell (anosmia) -Cognitive impairment -Loss of taste (ageusia)	3	(Daher et al., 2020; Leung et al., 2020; Lopez, Bell, Annaswamy, Juengst, & Ifejika, 2020)

	patients (e.g. fatigue, mobility issues, chest pain, and dyspnea).	-Muscle/joint pain (myalgia) -Sleep impairments -Chest pain -Tachycardia -GI upset -Muscle weakness -Anxiety		

Seven studies more clearly, or empirically, considered the mechanisms responsible for chronic symptoms post-COVID-19 focused on the immune, respiratory or multiple systems. There is, albeit limited, empirical evidence of patients with chronic symptoms having markers of prolonged inflammation or fibrotic abnormalities in their lungs. These studies are very limited due to sample size, lack of comparison, and lack of randomization. In a review by Morley (2020), a number of mechanistic possibilities for chronic COVID-19 are postulated. These symptoms include fatigue, cough, dyspnea, loss of smell and taste, muscle weakness and chest pain. Proposed mechanisms include post-viral syndrome, and neurological and immunological mechanisms proposed for acute complications.

Table 2c. Articles Specifically Approaching Potential Mechanisms Responsible for Post-COVID-19 Chronic Symptoms

System of Focus	High-Level Summary of Proposed Mechanisms	Implicated Chronic Symptoms[3]	# Studies	Citations of Studies Included
Immune System	• Quasi-histological evidence that neuro-inflammation is present in persons who recovered from COVID19, particularly inflammatory cells in the vitreous cavity. Persons who felt that their recovery was incomplete had more inflammatory cells, which likely suggests residual inflammation elsewhere. • Vitamin D levels not associated with COVID-19 disease outcomes. • Empirical study using diagnostic imaging of patients with unexplained, persisting symptoms more than 30 days from COVID-19 diagnosis had persistent vascular inflammation.	Unclear	4	(Bakhoum et al., 2020; Galeotti & Bayry, 2020; Pizzini et al., 2020; Sollini et al., 2020)
Multiple Systems	• Connects chronic symptoms of “long COVID” to proposed hypothetical mechanisms. Symptoms recognized include fatigue, cough, dyspnea, loss of taste and smell, muscle weakness, muscle and joint pain, headache, confusion, conjunctivitis,	-Dyspnea -Fatigue -Cough -Loss of smell (anosmia) -Cognitive impairment -Loss of taste (ageusia)	1	(Morley, 2020)

[3] Many of these papers were high-level and hypothetical. Often, they did not elaborate the specific chronic symptoms that would follow from these hypothetical mechanisms. This list provides potential chronic symptoms that could be implicated, but we limit to ascribing only the most-frequently cited chronic symptoms.

	chest pain, decreased mobility and falls. • Well-recognized that post-viral syndrome usually includes chronic fatigue, which can be aggravated by immobilization during hospitalization.	-Muscle/joint pain (myalgia) -Muscle weakness -Chest pain -Decreased Mobility -Conjunctivitis		
Respiratory System	• Hypothesize that fibrotic abnormalities of the lung due to COVID-19 will manifest in pulmonary abnormalities for patients. • Hyperferritinemia was present in 38% patients in the post-acute phase of COVID-19. This was associated with functional outcomes: a decreased walking distance.	-Dyspnea -Fatigue -Cough -Chest pain	2	(Raghu & Wilson, 2020; Sonnweber et al., 2020)

Evolving Evidence

There is a rapidly evolving evidence base on the long-term impact and symptomatology of COVID-19, as researchers from the earliest affected jurisdictions publish the findings from further along the COVID-19 trajectory. There will be a need to revisit the state of the literature and understanding on the chronic symptoms and rehabilitation needs of patients recovering from COVID-19. This reassessment may be appropriate in 3 or 6 months, as we near the 1-year mark since the calling of the global pandemic.

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(If applicable) Date of re-assessment:

Authorship and Committee Members

The review was written by Kiran Pohar Manhas, Ania Kania-Richmond, Ceara Cunningham, and Cyndie Koning. It was scientifically reviewed by Brandie Walker, Chester Ho (external reviewer), Kelly W. Burak (external reviewer), Frank MacMaster (external reviewer), and Kerry Alison McBrien (external reviewer). The full Scientific Advisory Group was involved in discussion and revision of the document: Braden Manns (co-chair), Lynora Saxinger (co-chair), John Conly, Alexander Doroshenko, Shelley Duggan, Nelson Lee, Elizabeth MacKay, Andrew McRae, Melissa Potestio, Jeremy Slobodan, James Talbot, Brandie Walker, and Nathan Zelyas.

COVID-19 Scientific Advisory Group
Rapid Evidence Report

Appendix

List of Abbreviations

AHS: Alberta Health Services

COVID-19: Coronavirus Disease-2019

ICU: Intensive Care Unit

KRS: Knowledge Resource Services

PTSD: Post-Traumatic Stress Disorder

SAG: Scientific Advisory Group

Expanded Evidence Synthesis

The following tables provide most of the detailed data extracted from the included studies.

Table 3a – Data extract from literature relevant to Research Questions 1 (After a diagnosis of COVID-19, which symptoms are commonly noted after 30 days, and what is the usual duration of these chronic symptoms?) and 2 (Which patients with COVID-19 are at highest risk of developing these chronic symptoms?

Author	Study Design	Type of COVID-19 patients	Details
(Amenta et al., 2020)	Review	All	• Review article on post-acute COVID-19 • Empirical studies included in this rapid evidence review. • Length of follow-up ranged from 3 to 12 weeks. • Suggests approach to classify different manifestations of post-acute COVID-19 syndrome
(Arnold et al., 2020)	Observational Cohort (n=163)	Hospitalized	• Consecutive hospitalized patients had outcomes recorded at baseline (admission), 28 days post, and invited for follow-up at 8-12 weeks. • Focus on symptoms, radiology and pulmonary function. • 74% reported at least one ongoing symptom since discharge home. Those hospitalized with moderate or severe illness, hand at least one symptom at 28-day follow-up (75% and 89%, respectively). • Severe disease patients more symptomatic in terms of breathlessness, fatigue, myalgia and insomnia. • Study reported on co-morbidity but did not speculate on risk factors for long-term symptoms.
(Bakhoum et al., 2020)	Observational Cohort (n=15)	All	• Use of spectral domain optical coherence tomography to detect presence of inflammatory cells in vitreous cavity in persons recovered from COVID-19. • Study completed on average 10.9 weeks from COVID-19 diagnosis (range 8.7-13 weeks) • Symptoms noted in patients included cough, headache, photophobia, lower extremity weakness/numbness, post-nasal drip, dry cough.

			• Persons who felt that their recovery was incomplete had more inflammatory cells present, which likely suggests residual inflammation elsewhere.
(Banda, Singh, Alser, & PRIETO-ALHAMBRA, 2020)	Observational Cohort (n=107)	All	• Mined and manually reviewed social media data from #longcovid and #chroniccovid to select tweets related to experiences of post-COVID Twitter users. Assessed number of symptoms per tweet and person. • The 10 most commonly mentioned symptoms were: malaise and fatigue (62%), dyspnea (19%), tachycardia/palpitations (13%), chest pain (13%), insomnia/sleep disorders (10%), cough (9%), headache (7%), and joint pain, fever, and unspecified pain by 6% each.
(Becker, 2020)	Review	All	• Review article. • Discussion mostly focused on "hypothetical" symptoms that could arise due to cardiovascular injury. Only included chronic symptoms where there was evidence to support. • Viral myocarditis (7-14 days post-COVID-19) was seen typically following more severe cases of COVID-19, and had chronic symptoms.
(Blair et al., n.d.)	Observational Cohort (n=118)	All	• Prospective outpatient cohort completed measurements for symptoms, SaO2, HR, and temp at intervals up to 4 weeks. • Up to 7 follow-up data collection points. • Participants returned to their usual health a median of 20 days (IQR, 37 13 to 38) from the symptom onset, and only 65.5% of respondents were at their usual health during the fourth week of illness. • Over 28 days, 10.9% presented to the emergency department and 7.6% required hospitalization. • Individuals at the same duration of illness had a 6.1 times increased adjusted odds of subsequent hospitalization per every percent decrease in home SaO2 (95% confidence interval [CI]: 1.41 to 31.23, p=0.02). • Baseline factors of age, sex, or comorbid conditions were not associated with a delay in return to health or to usual activities with unadjusted Cox proportional hazards regression (data not shown). Notably, while the majority 63.7% of participant had no symptoms or only had mild symptoms during the first week of illness a substantial proportion continued to have mild or moderate symptoms for over one month (Figure 3C-E). During the third and fourth week of illness, only 52.6% and 65.5% of respondents had returned to their usual health, respectively.
(Carfi, Bernabei, Landi, & Gemelli Against COVID-19 Post-Acute Care Study Group, 2020)	Observational Cohort (n=143)	Hospitalized	• Assess persistent symptoms in patients who were discharged from the hospital after recovery from COVID-19 via outpatient clinic. • Patients were offered a comprehensive medical assessment with detailed history and physical examination. Data on all clinical characteristics, including clinical and pharmacological history, lifestyle factors,

			vaccination status, and body measurements, were collected in a structured electronic data collection system. • Follow-up at 60.3 days (+/- 13.6 days). • Only 18 (12.6%) were completely free of any COVID-19–related symptom, while 32% had 1 or 2 symptoms and 55% had 3 or more. • None of the patients had fever or any signs or symptoms of acute illness. • Worsened quality of life was observed among 44.1% of patients. A high proportion of individuals still reported fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%) and chest pain (21.7%).
(Caronna et al., 2020)	Observational Cohort (n=100)	All	• This is a prospective study, comparing clinical data and inflammatory biomarkers of COVID-19 patients with and without headache, recruited at the Emergency Room/admitted to hospital. • Authors compared baseline with 6-week follow-up to evaluate disease evolution. • After 6 weeks, of the 74 headache patients, 37.8% (28/74) still had headache. Those patients whose headache had stopped had a mean duration of the symptom of 15.4-11.1 days. Then, we analyzed patients with ongoing headache after 6 weeks, observing that 50% of them (14/28) had never suffered from recurrent headache before. • A total of 60.7% of patients (17/28) had daily constant headache. • Response to acute treatment was insufficient both at baseline and follow-up, without statistically significant differences at the two time-points (32.1% vs. 28.6%; p ¼ 0.701). • RISK: There were no statistically significant differences with regard to the demographic variables in patients that were not followed up.
(Carvalho-Schneider et al., 2020)	Observational Cohort (n=150)	All	• Aimed to describe the clinical evolution and predictors of symptom persistence during 2-month follow-up in adults with non-critical COVID-19. • Patients were followed up at 7 days, 30 days and 60 days. • At D30 and D60, patients reported symptoms including dyspnea, chest pain, flu-like symptoms (aches, runny nose), digestive disorders (diarrhea), weight loss, palpitations, arthralgia, and cutaneous signs. • The most frequent symptom reported at D30 and D60 was anosmia/ageusia. • RISK: Those with prolonged symptoms were significantly associated with age 40 to 60 years old, hospital admission at symptom onset, severe COVID-19, and dyspnea or abnormal auscultation.
(Cavalagli et al., 2020)	Case Report (n=1)	Hospitalized	• This single case report expands knowledge about clinical picture about post-acute cranial nerves impairment after SARS-CoV-2 disease. • In-depth case study on one patient who presented acquired weakness and dysphagia with clinical cranial

			nerves impairment of lingual, IX, X and XII after SARS-CoV-2 infection, without electrophysiological alterations. • Speech therapy assessment showed oropharyngeal dysphagia with poor management of airway secretions with consequent persistent bubbling voice.
(Cellai & O'Keefe, 2020)	Observational Cohort (n=496)	Non-hospitalized	• Aim: To identify patients with COVID-19 in a telemedicine clinic who requested ongoing follow-up calls 6 weeks after symptom onset and assess persistent symptoms in patient population. • We identified 51 (9.4%) as receiving calls >6 weeks after symptom onset and arrived at a total of 26 (4.8%) "prolonged cases." • Respiratory symptoms were most common in week 6, and reported in 23 patients (88.5%), most frequently cough, shortness of breath with exertion, sinus congestion, and chest tightness. Other common symptoms include fatigue (17 patients, 65%) and headache (13 patients, 50%). Less commonly reported, 9 patients (34.6%) had persistent gastrointestinal symptoms, 6 patients (23%) complained of palpitations, and 3 had persistent low-grade fevers. • Of note, 18 (69.2%) reported at least 4 concurrent symptoms. Patients with persistent symptoms entered the telemedicine clinic a median (range) of 9.5 (4–39) days after symptom onset and were followed by the telemedicine clinic for a median (range) of 38 (21–49) days. The time from symptom onset to discharge from the telemedicine clinic was a median (range) of 47.5 (42–80) days. At telemedicine discharge, 24 (92.3%) patients reported significant improvement in symptoms, with only 7 (26.9%) reporting that they were at baseline health (symptom free). • RISK: Asthma and chronic lung disease (prospectively coded at intake visit) appeared more frequently in the patients identified in the persistent symptom cohort for this study.
(Charlotte et al., 2020)	Observational Cohort (n=196)	Hospitalized	• Retrospective cohort study included all inpatients hospitalized with microbiologically confirmed COVID-19 between 1 March and 12 April 2020 in the public hospital network of a Swiss area (Fribourg). Demographic data, comorbidities and outcomes were recorded. Rate of potential hospital-acquired infection, outcomes 30 days after onset of symptoms and in-hospital mortality are reported. • At D30, 73 patients (63%) reported persistent symptoms. Asthenia (67%), respiratory symptoms (56%) and anosmia/dysgeusia (10%) were the most frequently reported symptoms.
(Cirulli et al., 2020)	Cross-sectional Survey (n=233)	All	• Report the analysis of 32 self-reported short and long-term symptoms in a general adult population cohort comprised of 233 COVID-19+ cases, 3,652 SARS-CoV-2-negative controls, and 17,474 non-tested individuals. • Follow-up at 30, 60 and 90 days.

			• 43.4% of COVID-19+ cases have symptoms lasting longer than 30 days, and 24.1% still have at least one symptom after 90 days. These numbers are higher for COVID-19+ cases who were initially more ill, 59.4% at 30 days and 40.6% at 90 days, but even for very mild and initially asymptomatic cases, 14.3% have complications persist for 30 days or longer. • In contrast, only 8.6% of participants from the general untested population develop new symptoms lasting longer than 30 days due to any illness during the same study period. The long-term symptoms most enriched in those with COVID-19 are anosmia, ageusia, difficulty concentrating, dyspnea, memory loss, confusion, headache, heart palpitations, chest pain, and pain with deep breaths, dizziness, and tachycardia. • RISK: We additionally observe that individuals who had an initial symptom of dyspnea are significantly more likely to develop long-term symptoms. • RISK: After including the total number of initial symptoms as a covariate in the analysis, only five factors maintained a nominal association (uncorrected $p<0.05$) with long-term symptoms in COVID-19+ cases: the initial symptoms of dyspnea and chest pain, and blood type A as well as blood type A+ (but not blood type A-, which is rarer) were associated with increased risk.
(Daher et al., 2020)	Observational Cohort (n=33)	Hospitalized	• Hospitalized COVID-19 patients not requiring mechanical ventilation were included and followed 6 weeks after discharge to an outpatient unit. Body plethysmography, lung diffusion capacity (DLco), blood gas analysis (ABG), 6-min walk test (6MWT), echocardiography, and laboratory tests were performed. Quality of life (QoL), depression, and anxiety were assessed using validated questionnaires. • Although patients in this cohort had some respiratory symptoms, they had no significant ventilatory limitations in the PFTs and only a mild reduction in diffusing capacity of the lungs for carbon monoxide. Other Symptoms @ follow-up include: Fever 1 (3%); Cough 11 (33%); Dyspnea 11 (33%); Fatigue 15 (45%); Tiredness 15 (45%); Rhinorrhea 4 (12%); Sore throat 3 (9%); Angina pectoris 6 (18%); Myalgia 5 (15%); Headache 5 (15%); Cognitive disorders – 6 (18%); Loss of Smell 4 (12%); Loss of Taste 3 (9%); Gastrointestinal symptoms 3 (9%); Diarrhea 3 (9%); Nausea 2 (6%); Stomach pains 1 (3%). According to PHQ-9 and GAD-7 questionnaires, patients mostly suffered from mild depression and anxiety
(De Lorenzo et al., 2020)	Observational Cohort (n=185)	Hospitalized	• Setup a COVID-19 follow-up outpatient clinic to longitudinally follow patients recovered from COVID-19. Here, we report a first assessment of the information gathered on COVID-19 sequelae and propose strategies to identify patients who may benefit from continued monitoring in Milan, Italy. To investigate the relevance of

			the follow-up visit, we created a composite dichotomous outcome variable, i.e. need of follow-up, which identified patients requiring medical advice after COVID-19 recovery. • Follow-up at 4 weeks • At follow-up evaluation, 54 (29.2%) patients had shortness of breath or were tachypnoeic. 116 (62.7%) patients were malnourished or at risk for malnutrition, and approximately one quarter of patients achieved MoCA scores compatible with cognitive impairment, despite no known history of cognitive disorders. • Psychiatric disturbances including anxiety, insomnia, or PTSD were observed in 83 (44.9%) patients. • The need of follow-up, defined as the presence at follow-up evaluation of at least one among RR >20 breaths/min, uncontrolled blood pressure requiring therapeutic change, moderate to very severe dyspnea, malnutrition, or new-onset cognitive impairment, was present in 109 (58.9%) patients. • RISK: Decreasing age, female gender and positive psychiatric history were significantly associated with the risk of developing PTSD after COVID-19. • RISK: Hospitalization, instead, emerged as protective factor.
(Denina et al., 2020)	Observational Cohort (n=25)	Subpopulation	• Evaluation based - set up clinic to do follow up of discharge pediatric patients; reporting on the data they collected. • Follow-up at 35 days. • No symptom: "all of our patients showed a clinical and complete laboratory recovery about a month after discharge, without manifestation of any COVID-19-related sequelae 4 months later."
(Galeotti & Bayry, 2020)	Editorial	Subpopulation	• Discusses pediatric inflammatory multi-systemic syndrome in children with COVID19. Detailed investigations of some of these cases, including a study of 17 patients in Paris and a retrospective study of 35 patients across twelve French and one Swiss medical centre. • Revealed that in addition to gastrointestinal symptoms, skin rashes, cervical lymphadenopathy, cheilitis and high levels of inflammatory markers, myocardial involvement was common. • The increased incidence of myocarditis highlights that patients with KD-COVID-19 are more severely ill and are often hospitalized in intensive care.
(Garrigues et al., 2020)	Observational Cohort (n=120)	Hospitalized	• To assess post-discharge persistent symptoms and health-related quality of life (HRQoL) of patients hospitalized in a COVID-19 ward unit more than 100 days after their admission. • Follow-up average was 15.8 weeks (110.9 days). • The most frequently reported persistent symptoms were fatigue (55%), dyspnea (42%), loss of memory (34%),

			concentration and sleep disorders (28% and 30.8%, respectively). • Loss of hair was reported by 24 (20%) patients, including 20 women and 4 men. • Thirty-five (29%) patients had an mMRC grade ≥2 ("Walks slower than people of the same age because of dyspnea or has to stop for breath when walking at own pace"). • In both group, EQ-5D (mobility, self-care, pain, anxiety or depression, usual activity) was altered with a slight difference in pain in the ICU group. No statistical significance difference between the groups. • RISK: No difference in persistent symptoms between ICU and non-ICU/ward groups.
(Greenhalgh, Knight, A'Court, Buxton, & Husain, 2020)	Editorial	All	• Post-acute covid-19 symptoms vary widely. Even so-called mild covid-19 may be associated with long term symptoms, most commonly cough, low grade fever, and fatigue, all of which may relapse and remit. • Other reported symptoms include shortness of breath, chest pain, headaches, neurocognitive difficulties, muscle pains and weakness, gastrointestinal upset, rashes, metabolic disruption (such as poor control of diabetes), thromboembolic conditions, and depression and other mental health conditions. • Skin rashes can take many forms including vesicular, maculopapular, urticarial, or chilblain-like lesions on the extremities (so called COVID toe). • Around 10% of patients who have tested positive for SARS-CoV-2 virus remain unwell beyond three weeks.
(Halpin et al., 2020)	Cross-sectional Survey (n=100)	Hospitalized	• Used C19-YRS (Yorkshire Tool) • To examine the impact of COVID-19 on survivors discharged from hospital. This study reports the first systematic assessment (in the current literature) of post-discharge symptoms and rehabilitation needs in COVID-19 survivors after hospital discharge. • Extremely high levels of fatigue were reported. The severity of the impact of this fatigue was high, with a mean rating of 4.8 out of 10 across both groups. Moderate or severe fatigue (rated 4 + /10) was reported more frequently by female patients than male patients in both groups. • New or worsened breathlessness (when compared with pre-COVID illness) was a significant symptom even several weeks post-discharge, affecting over two-fifths of ward patients and two-thirds of ICU patients. • PTSD symptoms were reported by a much higher proportion of females (10/13; 76.9%) than males (5/19; 38.5%) in the ICU, whereas in the ward group these proportions were similar (22.9% of males and • 24.2% of females). In both groups, those reporting PTSD symptoms were younger. • Symptoms relating to communication, voice, swallow, and laryngeal sensitivity (including persistent cough) were

			more common in the ICU group (12.4%) than the ward group (5.9%). • Of the 22 ICU participants experiencing new problems in mobility, self-care or usual activities, 17 had new or worsened breathlessness and 19 had new fatigue. • RISK: Moderate or severe fatigue (rated 4 + /10) was reported more frequently by female patients than male patients in both groups. • RISK: PTSD symptoms were reported by a much higher proportion of females (10/13; 76.9%) than males (5/19; 38.5%) in the ICU, whereas in the ward group these proportions were similar (22.9% of males and 24.2% of females). • RISK: In both groups, those reporting PTSD symptoms were younger.
(Hampshire et al., 2020)	Observational Cohort (n=84,285)	All	• Aim: to examine the cognitive deficits of patients with suspected or confirmed COVID at the population level (and how this differs with respiratory symptom severity and hospitalization status). • RISK: The observed deficits varied in scale with respiratory symptom severity, related to positive biological verification of having had the virus even amongst milder cases, could not be explained by differences in age, education or other demographic and socioeconomic variables, remained in those who had no other residual symptoms and was of greater scale than common pre-existing conditions that are associated with virus susceptibility and cognitive problems.
(Klein et al., 2020)	Cross-sectional Survey (n=112)	All	• Aim: to address gaps in knowledge regarding the order of symptoms appearance and their durations in RT-PCR positive patients. • 6-week follow-up • Smell and taste changes were the longest-lasting symptoms (24.3 ± 22.9 days and 19.4 ± 19.1 (mean ± SD), respectively), with longer smell recovery correlated with smell change severity. • In one third of patients who reported cough, smell and taste changes, these symptoms persisted after recovery. • 36% of patients with smell change, 32% of patients with taste change, and 27% with dry or productive cough, still had these symptoms post recovery (defined as two consecutive negative RT-PCR-test results). • RISK: The severity of olfactory change is associated with its recovery time.
(Maxwell, 2020)	Review	All	• COVID-19 is not always a linear disease with an acute phase followed by recovery or a steady state rehabilitation. It can be cyclical disease, with symptoms moving round different body systems and fluctuating in severity. • There is a lack of understanding that people living with COVID-19 can suffer from a wide range of interconnected symptoms, and that even if not individually severe they

			can collectively leave people severely debilitated. This means many are relying on peer support through social media channels.
(Mazza et al., 2020)	Observational Cohort (n=402)	Hospitalized	• The present study aims to investigate the psychopathological impact of COVID-19 in survivors at one month follow up, also considering the effect of possible risk factors. • Follow-up 4 weeks. • A significant proportion of patients self-rated in the psychopathological range: 28% for PTSD, 31% for depression, 42% for anxiety, 20% for OC symptoms, and 40% for insomnia. • COVID-19 survivors presented a high prevalence of emergent psychiatric sequelae, with 55% of the sample presenting a pathological score for at least one disorder. • RISK: Despite significantly lower levels of baseline inflammatory markers, females suffered more for both anxiety and depression. • RISK: Patients with a positive previous psychiatric diagnosis showed increased scores on most psychopathological measures, with similar baseline inflammation. • RISK: Baseline systemic immune-inflammation index (SII) was positively associated with scores of depression and anxiety at follow-up. • RISK: Younger patients showed higher levels of depression and sleep disturbances.
(Miyake & Martin, 2020)	Observational Cohort	All	• Aim: To identify competing definitions of Covid-19 through quantitative and qualitative analyses of online Long COVID narratives in the UK; to map UK Long Haulers' experiences, emotions and practices as articulated online; to encourage further dialogue between patients, doctors and researchers to reassess existing definitions of Covid-19, with the collective aim of improving care and support for Long Haulers. • Analyzed social media data posts (n=144,637 posts). • There are 'officially' recognized symptoms that are used to (self)diagnose COVID-19: at the peak of the pandemic, the UK communicated these as a 'new and continuous cough' and 'high fever'; as from 18 May,16 'loss or change to your sense of smell or taste' was also included in the criteria, as well as other secondary symptoms (Flu-like with no fever; Flu-like with fever; Gastrointestinal; Fatigue (severe level one); Confusion (severe level two); Abdominal and respiratory (severe level three). • Long COVID sufferers report a whole other range of symptoms which do not officially fall under the Covid-19 criteria, something that has also been specifically observed and highlighted in the Covid-19 'Long Hauler' Symptoms Survey Report.

(Miyazato et al., 2020)	Cross-sectional Survey (n=63)	All	• To investigate the duration of persistent symptoms and late-onset symptoms including alopecia in patients discharged from NCGM after recovery from COVID-19. • Structured 1:1 interviews. • Follow-up 4-22 weeks post-discharge. • Distinguished between prolonged symptoms (6) at 60 and 120 days after symptom onset, and late onset symptoms (anosomia= smell (n=2)); alopecia (n=14), which started 30-92 days after symptom onset; see symptom table for full details on symptoms, proportion and duration.
(Morley, 2020)	Editorial	All	• RISK: Elevated d-dimer levels are prognostic of poor lung function at 3 months; potential for chronic sub-clinical inflammation.
(O'Keefe Tong, D. C., & O'Keefe, G. A. D, 2020)	Observational Cohort (n=273)	Non-hospitalized	• Follow-up 4 weeks • We hypothesized that risk factors for covid-19 complications severity (demographics, comorbidities, symptom severity) would predict symptom duration. • Symptoms were groups into systems: upper respiratory (cough, congestion, sore throat, loss of smell or taste), systemic (body aches, chills, dizziness, headache, joint pain), lower respiratory (shortness of breath with exertion, shortness of breath at rest, chest tightness) and gastrointestinal (nausea, abdominal pain, and diarrhea).
(Pizzini et al., 2020)	Observational Cohort (n=109)	Hospitalized	• Aim: Investigate association of VitD status to COVID-19 disease presentation. • 8-week follow-up • RISK: Low VitD levels at disease onset or at 8-week follow up were not related to persistent symptom burden, lung function impairment, and ongoing inflammation.
(Rogliani et al., 2020)	Observational Cohort (n=27)	Hospitalized	• Aim: Assess the real risk of developing post-COVID-19 pulmonary fibrosis. • Follow-up 5-7 weeks • This study provides the preliminary evidence that in hospitalized patients with prevalently mild-to-moderate forms of COVID-19 pulmonary opacity was completely recovered at follow-up, with no evidence of any fibrotic abnormality. Interestingly, at follow-up also lung function and exercise capacity were in the normal range. • These findings suggest that these patients are not at risk of developing post-COVID-19 pulmonary fibrosis. However, also considering that abnormal pulmonary function was detected in COVID-19 patients at time of hospital discharge [10], the results of this study have to be confirmed in larger and longer studies, and verified also in patients with severe COVID-19.
(Savarraj et al., 2020)	Observational Cohort (n=48)	Hospitalized	• Aim: To characterize long-term neurologic outcomes (functional, cognitive, and psychiatric symptoms) after COVID-19 in a cohort of hospitalized patients who were assessed at 3-months. • Follow-up 12 weeks • Main finding is that 71% of the patients still experienced neurological symptoms at 3 months

			• The most common symptoms being fatigue (42%) and PTSD (29%), pain symptoms (64%), and cognitive symptoms (12%).
(Sonnweber et al., 2020)	Observational Cohort (n=109)	All	• Aim: To analyze for persisting alterations of iron metabolism in survivors of COVID-19. • Follow-up at 8.5 weeks (average). • 60 days after disease onset, 30% of subjects still presented with iron deficiency and 9% had anemia, mostly categorized as anemia of inflammation. • RISK: Anemia was found in ten subjects (9.2%) and was more frequent in males (12%) than females (5%). Disease severity strongly correlated with the prevalence of anemia, as 90% of anemic patients previously had severe to critical COVID-19.
(Sudre et al., 2020)	Observational Cohort (n=4182)	All	• COVID 19 Symptom Study app. app, which collects data on personal characteristics and through prospective logging of symptoms, was launched in the UK, the US and Sweden between 24th March (UK) and 30th 331 April (Sweden), and rapidly reached over 4 million users. This study focuses on 4182 users who reported testing positive to SARS-CoV2 by PCR swab test and had a disease onset between 25th March 2020 and 30th June 2020, for whom onset date matched with date of test and duration of symptoms could be estimated. • Follow-up 4 weeks. • Fatigue (97.7%) and headache (91.2%) were the most reported symptoms in those with Long- COVID, followed by anosmia and lower respiratory symptoms. Notably, while fatigue was reported continuously, other symptoms such as headache are reported intermittently. Cardiac symptoms (palpitations, tachycardia) were over-represented in the LC28 112 group (6.1%) compared to in short-COVID (0.5%) ($p<0.0005$) as were concentration or memory issues (4.1% vs 0.2%) ($p<0.0005$), tinnitus and earache (3.6% vs 0.2% $p<0.0005$) and peripheral neuropathy symptoms (pins and needles and numbness) (2% vs 0.5%) ($p=0.004$). Most of these symptoms were reported for the first time 3-4 weeks post symptom onset.
(Taquet et al., 2020)	Observational Cohort (n=62,354)	All	• QUESTION: Whether a diagnosis of COVID-19 (compared with other health events) was associated with increased rates of subsequent psychiatric diagnoses, and whether patients with a history of psychiatric illness are at a higher risk of being diagnosed with COVID-19. • RISK: Having a diagnosis of psychiatric disorder in the year before the COVID-19 outbreak was associated with a 65% increased risk of COVID-19 (RR 1·65, 95% CI 1·59–1·71; $p<0·0001$) compared with a cohort matched for established physical risk factors for COVID-19 but without a psychiatric diagnosis.
(Tenforde et al., 2020)	Cross-sectional	Non-hospitalized	• Aim: To characterize return to baseline health among outpatients with milder COVID-19 illness • Follow-up **14-21 days.**

	Survey (n=292)		• Among the 274 symptomatic outpatients, the median number of symptoms was seven of 17 listed in the interview tool (IQR = 5–10), with fatigue (71%), cough (61%), and headache (61%) those most commonly reported. • Among respondents who reported fever and chills on the day of testing, these resolved in 97% and 96% of respondents, respectively. • Symptoms least likely to have resolved included cough (not resolved in 43% [71 of 166]) and fatigue (not resolved in 35% [68 of 192]); among 90 who reported shortness of breath at the time of testing, this symptom had not resolved in 26 (29%). • The median interval to symptom resolution among those who reported individual symptoms at the time of testing but not at the time of the interview ranged from 4 to 8 days from the test date, with the longest intervals reported for loss of smell (median = 8 days; IQR = 5–10.5 days) and loss of taste (median = 8 days; IQR = 4–10 days). • Among respondents who reported returning to their usual state of health, 34% (59 of 175) still reported one or more of the 17 queried COVID-related symptoms at the time of the interview.
(X. Wang et al., 2020)	Observational Cohort (n=131)	Hospitalized	• Aim: To investigate clinical outcomes, distribution of quarantine locations, and the infection status of the contacts of COVID-19 patients after discharge (up to 4 weeks). • Follow-up weekly to 4 weeks. • Observational follow up disclosed that during the first and the second week after discharge, 63 (48.09%) patients had one or more symptoms including cough (31.3%), fatigue (5.34%), expectoration (0.76%), chest tightness (6.11%), chest pain (3.05%), palpitation (2.29%), pharyngeal pain (1.53%), nausea (1.53%), inappetence (2.29%),vomiting (0.76%), diarrhea (0.76%), myalgia (0.76%) and rhinorrhea (0.76%). • Fever (8.4%), dyspnea (7.63%) and headache (3.82%) were newly occurred. In the third and the fourth week after discharge, only 18 (13.74%) patients had one or more symptoms with the incidence of cough (9.16%), chest tightness (0.76%), dyspnea (1.53%), pharyngeal pain (1.53%) and nausea (0.76%) (Table 2). • There was no statistical difference in the percentage of each symptom between severe and non-severe patients.
(Weerahandi et al., 2020)	Observational Cohort (n=152)	Hospitalized	• Aim: to characterize overall health status and the physical and mental health of patients discharged home after severe COVID-19 (up to 6.5 weeks). • Follow-up average 6.5 weeks. • At the time of survey, a total of 113 (74.3%) participants reported some shortness of breath (median score 3 out of 10, IQR 0-5), compared to only 47 (30.9%) pre-COVID-19 infection (0, IQR 0-1), $p<0.001$.

			• The PROMIS® Global Health-10 instrument scores indicated worse general health after COVID-19 illness (3 out of 5, IQR 2-4) compared to baseline (4, IQR 3-5). Before COVID-19, participants' summary t-scores in both the physical health and mental health domains were slightly above the United States mean of 50 (54.3, standard deviation 9.3; 54.3 SD 7.8, respectively). One month after COVID-19 infection, both scores were significantly lower (physical health: 43.8, SD 9.3; mental health 47.3, SD 9.3; p<0.001 for both). Patients also reported worsened ability to carry out social activities post COVID-19. • RISK: This cohort of patients experienced increased intensive care or mechanical ventilation, likely explaining the higher prevalence of persistent dyspnea in our study.
(Zhao et al., 2020)	Observational Cohort (n=55)	Hospitalized	• Aim: To investigate the relationship between clinical characteristics and pulmonary function or CT scores. • 12-week follow-up • At the 3 month follow up, presenting symptoms included: GI symptoms (30.91%); headache (18.18%); fatigue (16.36%); dyspnea (upon exertion) (14.55%); cough and sputum (1.81%); persistent decrease in sense of taste (4%).

Table for Research Question 3 – What mechanisms are likely to be responsible for chronic symptoms?

Table 3b. Articles Detailing Highly Hypothetical Mechanisms Responsible for Post-COVID-19 Chronic Symptoms.

System of Focus	High-Level Summary of Proposed Mechanisms	# Studies	Citations of Studies Included
Cardiovascular System	• Describes potential metabolic, lipid and vascular mechanisms that increase risks of SARS-CoV-2 infection susceptibility, severity of COVID-19 infection and organ damage, and related long-term recovery. Each relate to the role in regulation of immunity and inflammation. Vascular mechanisms may relate to diffuse alveolar damage.	1	(Becker, 2020)
Neurological System	• Post-ICU syndrome might contribute to patients with post-acute COVID-19 symptoms whose hospitalization included ICU care. • Potential mechanisms responsible for neurological symptoms in COVID-19 infection (acute and chronic): 1) Hyperinflammatory state in some patients ('cytokine storm') that manifests into neural injury (which can lead to other potential mechanisms listed herein) 2) Nervous system invasion by SARS-CoV-2 3) Brain expression of SARS-CoV-2-receptors and related proteins	13	(Ahmed et al., 2020; Amenta et al., 2020; Caronna et al., 2020; De Lorenzo et al., 2020; Fiani, Covarrubias, Desai, Sekhon, & Jarrah, 2020; Iadecola, Anrather, & Kamel, 2020; Mazza et al., 2020; Mohammadi, Moosaie, & Aarabi, 2020; Najjar et al., 2020; Taquet, Luciano, Geddes, & Harrison,

	4) Various routes of brain entry (olfactory route (cribiform plate and olfactory bulb), blood-brain barrier, infiltration of infected immune cells) 5) Indirect brain effects from systemic factors 6) Hypercoaguable state • Neurological disturbances impact sleep, senses, pain sensitivity, and energy.		2020; Vonck et al., 2020; F. Wang, Kream, & Stefano, 2020; Whittaker, Anson, & Harky, 2020)
Immune System	• Describe the potential link between Western diets and obesity, chronic activation of the innate immune system, as well as lung tissue inflammation and alveolar damage in COVID-19 pathology. • Not all human studies • Hypothesizing from non-COVID-19 literature.	1	(Butler & Barrientos, 2020)
Gastrointestinal System	• Potential mechanisms to acute liver injury in COVID-19 infection, which could lead to chronic symptoms. These potential mechanisms include: 1) drug-induced hepatic injury during treatment 2) direct injury due to COVID-19 hepatitis 3) COVID-19 induced myositis 4) biding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) positive rich cholangiocytes causing liver damage 5) hepatic congestion from mechanical ventilation 6) aggravation of pre-existing viral heptatis	1	(Kunutsor & Laukkanen, 2020)
Multiple Systems	• While cardiobiological biological mechanisms are less clear, neurological disturbances noted to impact sleep, senses, pain sensitivity, and energy. • Activated immune response to virus may lead to neurological complications (e.g. Guillain-Barre Syndrome), hematological complications (e.g. antiphospholipid syndrome), cardiovascular complications (e.g. haemorrhagic and ischaemic stroke), and respiratory complications (e.g. lung fibrosis). These complications can lead to chronic symptoms for patients (e.g. fatigue, mobility issues, chest pain, and dyspnea).	3	(Daher et al., 2020; Leung et al., 2020; Lopez, Bell, Annaswamy, Juengst, & Ifejika, 2020)

Table 3c. Articles Specifically Approaching Potential Mechanisms Responsible for Post-COVID-19 Chronic Symptoms

System of Focus	High-Level Summary of Proposed Mechanisms	# Studies	Citations of Studies Included
Immune System	• Quasi-histological evidence that neuroinflammation is present in persons who recovered from COVID19, particularly inflammatory cells in the vitreous cavity. Persons who felt that their recovery was incomplete had more inflammatory cells, which likely suggests residual inflammation elsewhere. • Specific to chronic symptoms, two possible mechanisms:	4	(Bakhoum et al., 2020; Galeotti & Bayry, 2020; Pizzini et al., 2020; Sollini et al., 2020)

	1) SARS-CoV-2 acts as direct trigger of autoimmune and/or autoinflammatory conditions 2) Immune responses following SARS-CoV-2 prompt other environmental insults. • Vitamin D levels show deficiency in COVID-19 patients, but not associated with COVID-19 disease outcomes. • Empirical study using diagnostic imaging of patients with unexplained, persisting symptoms more than 30 days from COVID-19 diagnosis revealed significantly higher target-to-blood pool ratios in three vascular regions, which indicate persistent vascular inflammation.		
Multiple Systems	• Connects chronic symptoms of "long COVID" to proposed hypothetical mechanisms. Symptoms recognized include fatigue, cough, dyspnea, loss of taste and smell, muscle weakness, muscle and joint pain, headache, confusion, conjunctivitis, chest pain, decreased mobility and falls. • Well-recognized that post-viral syndrome usually includes chronic fatigue, which can be aggravated by immobilization during hospitalization. • Coronavirus can invade myocardial cells and cause destruction of heart muscle. • Elevated D-dimer levels are prognostic of poor lung function. • Discusses neurological mechanisms due to micro-structural changes in brain post-COVID-19.	1	(Morley, 2020)
Respiratory System	• Hypothesize that fibrotic abnormalities of the lung due to COVID-19 will manifest in pulmonary abnormalities for patients, but that those with pre-existing lung disease will experience severity of COVID-19 disease concomitant to severity of the pre-existing lung disease. • Hyperferritinemia was present in 38% patients in the post-acute phase of COVID-19. This was associated with functional outcomes: a decreased walking distance. This may contribute to end-organ damage in COVID-19 and chronic symptoms therein.	2	(Raghu & Wilson, 2020; Sonnweber et al., 2020)

Methods

Literature Search

A literature search was conducted by Nicole Loroff from Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. KRS searched databases for articles published from 2020 and included: Ovid MEDLINE® and In-Process & Other Non-Indexed Citations and Daily, CINAHL, PubMed, TRIP Pro, Google Scholar, medRxiv, bioRxiv, LitCOVID, WHO Global Research on COVID-19 (database), Centre for Evidence Based Medicine (CEBM), and CADTH COVID-19 Evidence Portal. Briefly, the search strategy involved combinations of keywords and subject headings including:

- "COVID-19" OR coronavirus OR SARS-CoV-2 OR "severe acute respiratory syndrome cov 2" OR SARS-Cov-2019

- Long Term Adverse Effects OR Symptom Flare Up OR symptom* OR complicat* OR consequence* OR outcome* OR effect* OR manifest* OR sequela*
- Post-covid* OR discharge* OR post-discharge* OR post-acute OR post-hospitali?ation OR aftercare OR follow-up
- Patholog* OR mechanism* OR risk* OR predispose*
- Longitudinal study OR longitudinal studies OR follow-up study OR follow-up studies
- (Long covid OR longcovid* OR long hauler* OR longhauler*) AND (covid-19 OR coronavirus OR SARS-CoV-2)

The search strategy included these terms, complemented by citation tracking and snowball searching including resources noted by the review writers and reviewers. Where possible, PowerPoint presentations were hand-searched and the published articles that were cited, not the presentations themselves, were included. The search was limited to English articles published 2020-current. Articles were not excluded based on population.

Articles identified by KRS in their search were initially screened by title against the inclusion/exclusion criteria listed in Table 4a below.165 articles were identified by KRS with references and abstracts provided for further review. 111 were excluded from the review in accordance with the inclusion/exclusion criteria stated below. Title/abstract screening and full-text screening were completed by two independent reviewers, and discrepancies were determined by discussion and consensus. The final number of included articles was 54 published articles, 40 of which were peer-reviewed and 14 were pre-prints.

Table 4a. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
- COVID-19 - Post-diagnosis (and/or post-discharge) - Long-term (or chronic) symptoms or outcomes (i.e. post-diagnosis) - Risk factors for long-term (or chronic) symptoms - Mechanism for long-term (chronic) symptoms - All COVID-19 positive populations (i.e. no limit on age, hospitalization) - 2020 to present (focus on COVID-19 outbreak) - All research methods including empirical, review, case report, editorial - English language only - All publication status: pre-print, ahead of print, accepted, published, grey literature - Any jurisdiction	- Article is not from a credible source (author or publisher) - Non-COVID-19 conditions (e.g. SARS, MERS) - Focused on solely on acute symptoms or on mechanisms leading to acute symptoms. Acute was framed as during the infectious period or acuity of experience, not by number of days post-diagnosis - Focused on the complications or conditions that may follow SARS-CoV-2 infection - Presented data/evidence is not sufficient to address the research questions

Critical Evaluation of the Evidence

Exclusion criteria for study quality were adapted from the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). Potential articles were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. Preprints and non-peer-reviewed literature (such as commentaries and letters from credible journals) are not excluded out of hand due to the novelty of COVID-19 and the speed with which new evidence is available.

Table 4b below is a narrative summary of the body of evidence included in this review. The categories, format, and suggested information for inclusion were adapted from the Oxford Centre for Evidence-Based Medicine, the

Cochrane Library, and the AGREE Trust (Brouwers et al., 2010; Urwin, Gavinder, & Graziadio, 2020; Viswanathan et al., 2012; Wynants et al., 2020).

Table 4b. Narrative overview of the literature included in this review.

	Description
Volume	The articles examined in this narrative review included 4 systematic reviews, 11 reviews (without described methodology), 1 case-control study, 26 prospective observational cohort studies (11 were pre-review), 5 cross-sectional surveys (2 were pre-review), 1 case report (which was pre-review), and 6 editorials. The jurisdictional distribution of the studies was as follows: USA (n=19), UK (n=9), Italy (n=7), International teams (n=4), China (n=3), France (n=3), Austria (n=2), and one each from Belgium, Finland, Iran, Israel, Japan, Spain, and Switzerland. No grey literature was included in this review.
Quality	The quality of the studies was critiqued using the adapted MMAT. The four systematic reviews were generally of high quality, having undergone peer review and detailing clear research questions accompanied by relevant data. In contrast, the 11 review articles were of low to moderate quality. These articles were in stark contrast to the systematic reviews, with many lacking a clear research question (70%). Most of these review articles did not describe the methodology in collecting the data that formulated the review, and data relevance was questioned on most studies (70%). The 26 observational cohorts were of moderate to high quality. While 11 were preprints, the clarity of question and relevance of data were present in all but a minority of these articles (~15%, with 4 or 3 articles not meeting that criteria, respectively). While the MMAT permitted relatively high-quality scores, many of the observational cohort studies lacked a comparator group and relied on self-report. Their noted quality may not withstand closer scrutiny. For 24% of the studies with more than 1 follow-up data collection point, there is risk of attrition bias. While not the majority of studies, this directly influences the ability to inform the Research Question 1 interest in duration of chronic symptoms. The 5 cross-sectional survey studies were of moderate to high quality. Three of the 5 were peer-reviewed; four had clear questions; and four had relevant data. These cross-sectional surveys have methodological weaknesses inherent, particularly a reliance on subjective self-report. The sample size of the observational cohorts and surveys were noteworthy and wide ranging. The maximum participant sample size was 84285, while it is unclear how many participants took part in the Banda et al. (2020) study wherein 144,600 social media posts were analyzed. Due to outliers, the mean (SD) sample size is unclear at 4837.2 (+/- 18194.0). The median and mode sample size for the studies were 119 and 100, respectively. This suggests robust sample sizes, although no clarity on the randomization or selection of the samples. Finally, while the case-control and case report studies were of high quality according to the modified MMAT, the latter is of limited generalizability and the former lacks randomization and clarity on case matching.

Applicability	There are no Canadian (or Albertan) studies included in this review. The included primary studies were limited to the USA, Europe, and Asia. There is an over-representation of USA studies, which have had a significantly different experience in severity and mortality related to COVID-19, different COVID-19 response, and have a distinct healthcare system. The next most frequent studies from the UK and Italy have also experienced severe outbreaks, while there is more similarity in healthcare system infrastructure. This raises questions on the applicability to Alberta. Nevertheless, with respect to the Research Questions, the moderate-to-high-quality observational cohort and cross-sectional survey studies provide evidence directly applicable to the Research Questions 1 and 2 on chronic post-COVID-19 symptom nature and duration. These studies also touch upon Research Question 3 related to potential mechanisms responsible for the chronic symptoms. However, study evidence directly applicable to Research Question 3 also heavily relies on the lower-quality review articles.
Consistency	For Research Questions 1 and 2, there was consistency in some areas, particularly the most common chronic symptoms and a few of the key risk factors. However, in other areas, the findings from one study were unique and un-corroborated and should thus be considered with caution. For Research Question 3, there was relative consistency across the articles on the types and facets of the hypothesized mechanisms proposed as responsible for the chronic, post-COVID-19 symptoms.

Table 4c. Critical Quality Appraisal of Included Studies

Author	Study Design	Type of Article	Is there clear research question?	Data appropriate to research question?	Type of COVID patients
(Ahmed et al., 2020)	Systematic Review	Peer-reviewed	Yes	Yes	All
(Amenta et al., 2020)	Review	Peer-reviewed	No	No	All
(Arnold et al., 2020)	Observational Cohort	Preprint	Yes	Yes	Hospitalized
(Bakhoum et al., 2020)	Observational Cohort	Preprint	Yes	Yes	All
(Banda, Singh, Alser, & PRIETO-ALHAMBRA, 2020)	Observational Cohort	Preprint	Yes	Yes	All
(Becker, 2020)	Review	Peer-reviewed	Yes	Yes	All
(Blair et al., n.d.)	Observational Cohort	Preprint	Yes	Yes	All
(Butler & Barrientos, 2020)	Editorial	Peer-reviewed	No	No	All
(Carfi, Bernabei, Landi, & Gemelli Against COVID-19	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized

Post-Acute Care Study Group, 2020)					
(Caronna et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	All
(Carvalho-Schneider et al., 2020)	Observational Cohort	Preprint	Yes	Yes	All
(Cavalagli et al., 2020)	Case Report	Preprint	Yes	Yes	Hospitalized
(Cellai & O'Keefe, 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Non-hospitalized
(Charlotte et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(Cirulli et al., 2020)	Cross-sectional Survey	Preprint	Yes	Yes	All
(Daher et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(De Lorenzo et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(Del Rio, Collins, & Malani, 2020)	Review	Peer-reviewed	No	Yes	All
(Denina et al., 2020)	Observational Cohort	Peer-reviewed	No	No	Subpopulation
(Fiani et al., 2020)	Review	Peer-reviewed	Yes	No	All
(Galeotti & Bayry, 2020)	Editorial	Peer-reviewed	No	No	Subpopulation
(Garrigues et al., 2020)	Observational Cohort	Peer-reviewed	No	Yes	Hospitalized
(Greenhalgh, Knight, A'Court, Buxton, & Husain, 2020)	Editorial	Peer-reviewed	No	No	All
(Halpin et al., 2020)	Cross-sectional Survey	Peer-reviewed	Yes	Yes	Hospitalized
(Hampshire et al., 2020)	Observational Cohort	Preprint	Yes	Yes	All
(Iadecola et al., 2020)	Review	Peer-reviewed	Yes	No	All
(Klein et al., 2020)	Cross-sectional Survey	Preprint	No	No	All
(Kunutsor & Laukkanen, 2020)	Editorial	Peer-reviewed	Yes	Yes	All
(Leung et al., 2020)	Systematic Review	Peer-reviewed	Yes	Yes	All
(Lopez et al., 2020)	Review	Peer-reviewed	Yes	No	All
(Maxwell, 2020)	Review	Peer-reviewed	No	No	All
(Mazza et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(Miyake & Martin, 2020)	Observational Cohort	Preprint	Yes	Yes	All

(Miyazato et al., 2020)	Cross-sectional Survey	Peer-reviewed	Yes	Yes	All
(Mohammadi et al., 2020)	Review	Peer-reviewed	Yes	No	All
(Morley, 2020)	Editorial	Peer-reviewed	No	No	All
(Najjar et al., 2020)	Review	Peer-reviewed	Yes	No	All
(O'Keefe Tong, D. C., & O'Keefe, G. A. D, 2020)	Observational Cohort	Peer-reviewed	Yes	No	Non-hospitalized
(Pizzini et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(Raghu & Wilson, 2020)	Editorial	Peer-reviewed	No	No	All
(Rogliani et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(Savarraj et al., 2020)	Observational Cohort	Preprint	No	No	Hospitalized
(Sollini et al., 2020)	Case-Control	Peer-reviewed	Yes	Yes	All
(Sonnweber et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	All
(Sudre et al., 2020)	Observational Cohort	Preprint	No	Yes	All
(Taquet et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	All
(Tenforde et al., 2020)	Cross-sectional Survey	Peer-reviewed	Yes	Yes	Non-hospitalized
(Vonck et al., 2020)	Review	Peer-reviewed	Yes	No	All
(F. Wang et al., 2020)	Review	Peer-reviewed	Yes	No	All
(X. Wang et al., 2020)	Observational Cohort	Preprint	Yes	Yes	Hospitalized
(Weerahandi et al., 2020)	Observational Cohort	Preprint	Yes	Yes	Hospitalized
(Whittaker et al., 2020)	Systematic Review	Peer-reviewed	Yes	Yes	All
(Zhao et al., 2020)	Observational Cohort	Peer-reviewed	Yes	Yes	Hospitalized
(Zubair et al., 2020)	Systematic Review	Peer-reviewed	Yes	Yes	All

Search Strategy

Search Strategy

Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations and Daily 1946 to November 03, 2020

#	Searches	Results
1	exp Coronavirus/ or exp Coronavirus Infections/ or (covid or coronaviru* or corona viru* or ncov* or n-cov* or novel cov* or COVID-19 or COVID19 or COVID-2019 or COVID2019 or SARS-CoV-2 or SARSCoV-2 or	69722

	SARSCoV2 or SARSCoV19 or SARS-Cov-19 or SARSCov-19 or SARSCoV2019 or SARS-Cov-2019 or SARSCov-2019 or "severe acute respiratory syndrome cov 2" or 2019 ncov or 2019ncov).tw,kf.	
2	limit 1 to english language	66436
3	limit 2 to yr="2020 -Current"	49480
4	Long Term Adverse Effects/ or Recurrence/ or Symptom Flare Up/ or Symptom Assessment/	191000
5	((long-term or longterm or longitudinal* or chronic* or persist* or prolong* or ongoing or recurr* or lasting or long-lasting* or linger*) adj3 (symptom* or complicat* or consequence* or outcome* or effect* or manifest* or sequela*)).tw,kf.	361241
6	4 or 5	536001
7	3 and 6	742
8	Patient Discharge/ or exp Aftercare/ or Time Factors/ or Long-Term Care/ or Subacute Care/	1424418
9	(post-covid* or discharge* or post-discharge* or postdischarge* or post-acute or postacute or post-hospitali?ation or after hospitali?ation or recover* or aftercare or after care or survivor* or follow-up or duration or frequency or rehabilitat*).tw,kf.	3177887
10	8 or 9	4234711
11	7 and 10	239
12	exp Pathology/ or Risk Factors/	886026
13	(patholog* or mechanism* or risk* or predispos*).tw,kf.	5052951
14	12 or 13	5320157
15	7 and 14	311
16	exp "Signs and Symptoms"/	2088048
17	3 and 6 and 16	70
18	Longitudinal Studies/ or Follow-Up Studies/	773091
19	(longitudinal study or longitudinal studies or follow-up study or follow-up studies).tw,kf.	126939
20	18 or 19	826060
21	(symptom* or complicat* or consequence* or effect* or manifest* or sequela*).tw,kf.	9054248
22	3 and 20 and 21	230
22	(long covid* or longcovid* or long hauler* or long hauler*).tw,kf.	15
23	sequela*.tw,kf.	68653
24	3 and 23	169

CINAHL

#	Searches	Results
1	((MH "Coronavirus+") or coronavirus* or covid) AND (wuhan or beijing or shanghai)) OR (("novel coronavirus*" AND ((MH "China") or China)) OR TI coronavirus* OR (((MH pneumonia) or pneumonia) AND Wuhan) OR ((D614G or "Covid-19" or Covid19 or "2019-nCoV" or "SARS-CoV-2" or (MH Coronavirus Infections))))) AND ((MH "Coronavirus+") or coronavirus* or covid) AND (wuhan or beijing or shanghai)) OR (("novel coronavirus*" AND ((MH "China") or China)) OR TI coronavirus* OR (((MH pneumonia) or pneumonia) AND Wuhan) OR ((D614G or "Covid-19" or Covid19 or "2019-nCoV" or "SARS-CoV-2" or (MH Coronavirus Infections))))) AND DT 20191201-20300101)	26028
2	limit 1 to english language	25489
3	limit 2 to yr="2020 -Current"	25476
4	(MH “Recurrence”)	49130
5	TI ((long-term or longterm or longitudinal* or chronic* or persist* or prolong* or ongoing or recurr* or lasting or long-lasting* or linger*) n3 (symptom* or complicat* or consequence* or outcome* or effect* or manifest* or sequela*)) OR AB ((long-term or longterm or longitudinal* or chronic* or persist* or prolong* or ongoing or recurr* or lasting or long-lasting* or linger*) n3 (symptom* or complicat* or consequence* or outcome* or effect* or manifest* or sequela*))	100694
6	4 OR 5	144885

7	3 AND 6	234
8	(MH "Prospective Studies+")	453995
9	TI ((longitudinal study or longitudinal studies or follow-up study or follow-up studies)) OR AB ((longitudinal study or longitudinal studies or follow-up study or follow-up studies))	43202
10	8 OR 9	469736
11	TI ((symptom* or complicat* or consequence* or outcome* or effect* or manifest* or sequela*)) OR AB ((symptom* or complicat* or consequence* or outcome* or effect* or manifest* or sequela*))	1921345
12	3 AND 10 AND 11	304
13	TI ((long covid* or longcovid* or long hauler* or long hauler*)) OR AB ((long covid* or longcovid* or long hauler* or long hauler*))	8
14	TI sequela* OR AB sequela*	13760
15	3 AND 14	58

PubMed

#	Searches	Results
1	((Coronavirus[mh:noexp] OR Betacoronavirus[mh:noexp] OR Coronavirus Infections[mh:noexp]) AND (Disease Outbreaks[mh:noexp] OR Epidemics[mh:noexp] OR Pandemics[mh])) OR COVID-19 diagnostic testing [Supplementary Concept] OR COVID-19 drug treatment [Supplementary Concept] OR COVID-19 serotherapy [Supplementary Concept] OR COVID-19 vaccine [Supplementary Concept] OR spike glycoprotein, COVID-19 virus [Supplementary Concept] OR COVID-19 [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 [Supplementary Concept] OR nCoV[tiab] OR nCoV[tt] OR 2019nCoV[tiab] OR 2019nCoV[tt] OR 19nCoV[tiab] OR 19nCoV[tt] OR COVID19*[tiab] OR COVID19*[tt] OR COVID[tiab] OR COVID[tt] OR SARS-CoV-2[tiab] OR SARS-CoV-2[tt] OR SARSCOV-2[tiab] OR SARSCOV-2[tt] OR SARSCOV2[tiab] OR SARSCOV2[tt] OR Severe Acute Respiratory Syndrome Coronavirus 2[tiab] OR Severe Acute Respiratory Syndrome Coronavirus 2[tt] OR ((severe acute respiratory syndrome[tiab] OR severe acute respiratory syndrome[tt]) AND (corona virus 2[tiab] OR corona virus 2[tt])) OR new coronavirus[tiab] OR (new[tt] AND coronavirus[tt]) OR novel coronavirus[tiab] OR novel coronavirus[tt] OR novel corona virus[tiab] OR (novel[tt] AND corona virus[tt]) OR novel CoV[tiab] OR (novel[tt] AND CoV[tt]) OR novel HCoV[tiab] OR (novel[tt] AND HCoV[tt]) OR (("19"[tiab] OR "19"[tt] OR "2019"[tiab] OR "2019"[tt] OR Wuhan[tiab] OR Wuhan[tt] OR Hubei[tiab] OR Hubei[tt]) AND (coronavirus*[tiab] OR coronavirus*[tt] OR corona virus*[tiab] OR corona virus*[tt] OR CoV[tiab] OR CoV[tt] OR HCoV[tiab] OR HCoV[tt])) OR ((coronavirus*[tiab] OR coronavirus*[tt] OR corona virus*[tiab] OR corona virus*[tt] OR betacoronavirus*[tiab] OR betacoronavirus*[tt]) AND (outbreak*[tiab] OR outbreak*[tt] OR epidemic*[tiab] OR epidemic*[tt] OR pandemic*[tiab] OR pandemic*[tt] OR crisis[tiab] OR crisis[tt])) OR ((Wuhan[tiab] OR Wuhan[tt] OR Hubei[tiab] OR Hubei[tt]) AND (pneumonia[tiab] OR pneumonia[tt]))	73536
2	limit 1 to english language	70804
3	limit 2 to yr="2020 -Current"	68041
4	"long term adverse effects"[MeSH Terms] OR "recurrence"[MeSH Terms] OR "symptom flare up"[MeSH Terms] OR "symptom assessment"[MeSH Terms]	191090
5	"symptom*"[Title] OR "complicat*"[Title] OR "consequence*"[Title] OR "outcome*"[Title] OR "effect*"[Title] OR "manifest*"[Title] OR "sequela*"[Title]	2743001
6	"long-term"[Title] OR "longterm"[Title] OR "longitudinal*"[Title] OR "chronic*"[Title] OR "persist*"[Title] OR "prolong*"[Title] OR "ongoing"[Title] OR "recurr*"[Title] OR "lasting"[Title] OR "long lasting*"[Title] OR "linger*"[Title]	953857
7	5 and 6	141815
8	4 or 7	326254
9	3 and 8	443
10	"longitudinal studies"[MeSH Terms] OR "follow up studies"[MeSH Terms]	773544
11	“longitudinal study”[Title/Abstract] OR “longitudinal studies”[Title/Abstract] OR “follow-up study”[Title/Abstract] OR “follow-up studies”[Title/Abstract]	130122
12	10 or 11	829460

13	"symptom*"[Title/Abstract] OR "complicat*"[Title/Abstract] OR "consequence*"[Title/Abstract] OR "outcome*"[Title/Abstract] OR "effect*"[Title/Abstract] OR "manifest*"[Title/Abstract] OR "sequela*"[Title/Abstract]	10059315
14	3 and 12 and 13	312
15	"long covid*"[Title/Abstract] OR "longcovid*"[Title/Abstract] OR "long hauler*"[Title/Abstract] OR "long hauler*"[Title/Abstract]	6
16	"sequela*"[Title/Abstract]	69855
17	3 and 16	252

TRIP Pro/Google Scholar/medRxiv & bioRxiv

((long-term or longterm or longitudinal* or chronic* or persist* or prolong* or ongoing or recurr* or lasting or long-lasting or linger*) AND (symptom* or complication* or consequence* or outcome* or effect* or manifest* or sequela*)) AND (covid-19 or coronavirus or SARS-CoV-2)

(long covid or longcovid* or long hauler* or longhauler*) AND (covid-19 or coronavirus or SARS-CoV-2)

LitCOVID/WHO Global research on COVID-19 (database)/Centre for Evidence Based Medicine (CEBM)/CADTH COVID-19 Evidence Portal

((long-term or longterm or longitudinal or chronic or persist or prolong or ongoing or recurring or lasting or long-lasting or linger) adj (symptom or complication or consequence or outcome or effect or manifest or sequela or sequelae))

(long covid or longcovid* or long hauler* or longhauler*)

* The proximity string is used to demonstrate that each combination or terms was searched separately, e.g. “long-term symptom”, “long-term complication”, or “chronic symptom”, “chronic complication”, etc.).

**Citation tracking and snowball searching of key articles was conducted via Google Scholar.

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