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RAPID REVIEW

Post-Acute COVID-19 Syndrome (PACS) in Adults

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Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory coronavirus 2 (SARS-CoV-2).

This rapid review concentrates on results from systematic reviews and meta-analyses, updating the evidence on the prevalence of PACS, PACS symptoms by organ system and risk factors for developing PACS. The update includes more meta-analyses and primary research with larger sample sizes and includes a new section reporting on the impacts of PACS on daily living. This rapid review replaces *Persistent Symptoms and Post-Acute COVID-19 in Adults – What We Know So Far* (April 9, 2021).[1]

Key Messages

- The definition of and diagnostic criteria for post-acute COVID-19 syndrome (PACS) are not yet well established. This rapid review considered PACS as persistent or new sequelae present 3 or more weeks after severe, mildly symptomatic or asymptomatic SARS-CoV-2 infection.
- Pooled mean prevalence results for any experience of PACS, extracted from nine systematic reviews, ranged from 51%–80%.
- Pooled mean prevalence results for specific PACS symptoms were extracted, when available, from 32 systematic reviews. Symptoms and prevalence results varied widely across reviews, however some of the most commonly reported symptoms included fatigue; shortness of breath; anxiety; depression; sleep disorder; cognitive and memory impairments; and negative impacts on quality of life (QoL). The most commonly reported risk factors for developing PACS were increased disease severity during acute SARS-CoV-2 infection and female sex.
- Few included studies used control groups of individuals not infected with SARS-CoV-2 (e.g., healthy controls, patients with alternative diagnoses). These studies consistently found overall greater rates or risk of persistent symptoms consistent with PACS among patients with COVID-19 compared to symptoms in those without COVID-19. Further case-control studies would help disentangle the impact of public health measures, other confounders and SARS-CoV-2 infection on symptoms consistent with PACS.
- Results across reviews and studies with multiple follow up periods did not consistently indicate if prevalence of PACS or PACS sequelae increased, decreased or remained stable over time.
- Overall, while ongoing research is needed to better characterize PACS characteristics and prevalence, this body of evidence indicates PACS is a condition experienced by a substantial number of individuals with previous SARS-CoV-2 infection. Care for patients with PACS will likely place added stresses on health care and social support systems, including increased emergency department visits, outpatient care, inpatient care and rehabilitation involving multidisciplinary teams.

Contents

Background

There are ongoing discussions and research into what constitutes PACS and how to define this condition. There are also a number of names used to refer to persistent symptoms after the acute phase of a SARS-CoV-2 infection, including "long COVID," "post-COVID syndrome," "post-acute COVID-19 syndrome," and "post-acute sequelae of SARS-CoV-2 infection";[2] the term PACS will used throughout this document. Nalbandian et al. (2021) described PACS as persistent symptoms and/or delayed symptoms of SARS-CoV-2 infection beyond 4 weeks from symptom onset.[3] PACS has been defined elsewhere as signs and symptoms that develop during or after SARS-CoV-2 infection, continue for more than 12 weeks, and are not explained by an alternative diagnosis.[4-6] The Ontario COVID-19 Science Advisory Table (2021) have reported that while a consistent case definition has not been established, PACS encompasses many potential sequelae of infection with SARS-CoV-2 which may persist for weeks to months, and can develop after severe, mildly symptomatic or asymptomatic SARS-CoV-2 infections.[7] To ensure a broad assessment of PACS and PACS sequelae, we will consider PACS as persistent or new symptoms or sequelae present 3 weeks or more after SARS-CoV-2 infection.

In a science brief by the Ontario COVID-19 Science Advisory Table (September, 2021), the authors estimated that 57,000 to 78,000 people in Ontario have experienced PACS, noting this estimate could vary widely depending on what case definition is applied.[7] In order to plan for a potential increase in use of health care resources post-COVID-19, the health care system needs to understand PACS in recovering patients. Knowledge of the risk factors associated with the development of PACS may be able to assist with following individuals at risk of further morbidity and direct resources appropriately.

The purpose of this document is to examine the prevalence of PACS symptoms and sequelae and explore risk factors for developing PACS.

Methods and Scope

In considering feasibility, scope, and a need for responsiveness, we chose a rapid review as an appropriate approach to understanding the persistent symptoms of PACS. A rapid review is a knowledge synthesis where certain steps of the systematic review process are omitted (e.g., duplicate screening, quality assessment) in order to be timely.[8]

PHO Library Services conducted updated literature searches in MEDLINE (February 11, 2022), National Institutes of Health COVID-19 Portfolio (Preprints) (February 11, 2022), Embase (February 15, 2022) and Global Health/Scopus (February 15, 2022). The search was informed by the previous search strategy, with the addition of updated SARS-CoV-2 variant of concern (VOC) terms and COVID-19 vaccination terms to ensure up-to-date concepts were captured (search strategies available upon request). We searched PubMed on March 15, 2022 for additional articles of interest.

English-language peer-reviewed and non-peer-reviewed studies that described persistent symptoms after the acute phase of SARS-CoV-2 infection were included. Studies did not have to specify if cases of SARS-CoV-2 were test-confirmed to be included, and did not need to specify if cases were symptomatic, asymptomatic, hospitalized or not hospitalized. We restricted the search to articles published after the previous search (March 1, 2021). This rapid review concentrated on evidence from systematic reviews and meta-analyses, supplemented by primary literature where appropriate.

Where prevalence data were reported for multiple end-points after SARS-CoV-2 infection, we reported prevalence for the latest follow-up period. Pooled prevalence estimates for PACS or PACS sequelae were extracted from systematic reviews. We did not check for overlap of primary studies across reviews, therefore some studies may have contributed to more than one included review. We excluded

systematic reviews that conducted their literature searches before 2021. Due to the substantial increase in available literature since the last version of this synthesis, and to limit the volume of primary studies included, we only included primary studies with at least 10,000 participants. Unless otherwise stated and to limit the number of relatively rare symptoms, we only included symptoms reported in at least 10% of patients in a study. Studies were restricted to those with adult patients greater than 17 years of age. Several symptoms were potentially associated with multiple organ systems; however, we reported these symptoms with the organ system where they were most often reported in the literature (e.g., chest pain in cardiovascular section). While signs (e.g., diagnostic tests and biomarkers) were not strictly scoped out, the focus of this synthesis was to describe symptoms and patient-important sequelae after the acute phase of SARS-CoV-2 infection.

This document does not report on the indirect impacts of pandemic public health measures on long-term sequelae; e.g., impact of social distancing on mental health or the consequences of deferred health care on chronic disease management. The impact of seeking health care/use of health care resources as a result of PACS symptoms was not in scope of this review. In addition, this synthesis does not address the management of patients with long-term sequelae, the underlying mechanisms for the emergence of sequelae, or sequelae related to treatment of SARS-CoV-2 infection (e.g., post-intensive care unit [ICU] admission, invasive mechanical ventilation, therapeutics). For information on post-acute COVID-19 in children, please see PHO's *Post-Acute COVID-19 and Multisystem Inflammatory Syndrome in Children (MIS-C) – What We Know So Far* (update in progress).[9] Finally, the impact of vaccination on PACS is not in scope of this synthesis, however is addressed in PHO's *Impact of Vaccination on Post-Acute COVID-19 Syndrome (PACS) – What We Know So Far*.[10]

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

Search Findings

We screened 7,263 articles identified from updated database searches: MEDLINE (n=2,893 articles), Embase and Global Health (n=3,223), Scopus (n=756), and National Institutes of Health COVID-19 Portfolio (Preprints) (n=391). After screening, full-text review, and re-assessment of the previously included evidence with updated inclusion criteria, we included 32 systematic reviews and meta-analyses, and 18 primary research articles. Nine of the 50 (18%) total articles were non-peer-reviewed preprints.

Over half (19/32) of the included systematic reviews conducted meta-analyses, and approximately one third (11/32) reported on multiple follow-up periods. In terms of settings during the acute phase of COVID-19 illness, most reviews examined a mix of inpatients and outpatients (27/32), few examined only inpatients (3/32) or outpatients (1/32), and one did not report the acute illness setting. No reviews limited inclusion to studies with non-COVID-19 control groups, making it challenging to attribute PACS symptoms only to previous SARS-CoV-2 infection. Five of 32 included reviews were non-peer reviewed preprints.[11-15]

Primary studies were conducted in the United States (US) (11/18), the United Kingdom (UK) (3/18), Denmark (2/18), France (1/18) or included multiple countries (1/18). Most studies included a mix of participants who were inpatients or outpatients during acute COVID-19 (12/18), three assessed only outpatients, one assessed only inpatients and two did not report the setting. Fourteen of 18 studies assessed symptoms consistent with PACS among patient with COVID-19 and among comparator groups of patients without COVID-19 infection, however the types of control patients varied across studies (e.g., healthy controls, patients with influenza). Four of 18 primary studies were non-peer-reviewed preprints.[16-19]

Please refer to Appendix A, Table 1 and Table 2 for additional characteristics of included studies.

It is important to note the considerable heterogeneity across included studies. Studies used different follow-up periods and different time points to determine follow-up periods; e.g., time from hospital discharge, time from positive SARS-CoV-2 test, and time from symptom onset in acute stage of disease. Reported symptoms, outcome measures/criteria, and populations (e.g., severity of illness during acute SARS-CoV-2 infection) also varied widely across studies. As noted above, the definition, diagnostic criteria and official name for this new condition are not yet established. Due to this significant heterogeneity and the evolving nature of this condition, determining exact prevalence estimates for PACS and PACS sequelae (i.e., through meta-analysis) was not considered appropriate for this rapid review or this body of evidence. We aimed to provide an overall understanding of the breadth of PACS sequelae, identify common sequelae and possible PACS risk factors.

Thus, to summarize the mean/median pooled estimates extracted from heterogeneous systematic reviews, we first reported the range of all identified pooled mean/median prevalence results (e.g., 5%–75%). Then, for each outcome we identified the interquartile range of (IQR) of all pooled mean/median prevalence results, along with the number of systematic reviews informing that outcome. This descriptive approach was used to demonstrate the wide range of results in the available literature related to this topic, along with a central range (i.e., IQR) to describe a more focused range of available results.

Prevalence of PACS

Reviews

Results ranged widely across 12 systematic reviews that reported on the pooled mean prevalence of any PACS symptoms.[11-13,20-28] All reviews except one (i.e., van Kessel et al., 2022 assessed only outpatients)[28] included both hospitalized and non-hospitalized patients during acute COVID-19 illness. Most reviews specified minimum follow-up times of 3–4 weeks post-acute SARS-CoV-2 infection; however, several reported on longer follow-up periods.

- Nine reviews reported a pooled mean prevalence (range of follow-up period) for one or more PACS symptom(s): 80% (14–110 days),[24] 56% (≥21 days),[13] 56% (30–180 days),[27] 73% (>30 days),[25] 53% (>84 days),[12] 62% (>84 days),[23] 59% (>90 days),[26] 51% (120 days)[11] and 54% (180 days).[22] Of these nine results, the range of pooled prevalence estimates was 51%–80% and the IQR was 54%–64.75%.

- Three reviews reported a range of mean prevalence results from included primary studies but no pooled result: 5%–80% (>21 days),[20] 10%–35% (>21 days)[28] and 16%–87% (>21 days).[21]

Four systematic reviews reported on PACS prevalence at multiple follow-up points.[11,12,22,23] Evidence across reviews is insufficient to determine if prevalence consistently increased, decreased or remained stable over time.

- Chen et al. (2021) (preprint) reported a pooled mean prevalence for any PACS symptom(s) at least 28 days after acute infection, and at four follow-up periods (pooled mean prevalence, 95% confidence interval [CI]): overall (43%, 35–63), 30 days (36%, 25–48), 60 days (24%, 13–39), 90 days (29%, 12–57) and 120 days (51%, 42–59).[11]

- Reyes Domingo et al. (2021) (preprint) reported on PACS prevalence at two follow-up periods (pooled mean prevalence, 95% CI): 4–12 weeks (61%, 44–76) and >12 weeks (53%, 41–65).[12]

- Jennings et al. (2021) reported on PACS prevalence at two follow-up periods: 4–12 weeks (59%, range: 14–87) and >12 weeks (62%, range: 18–89).[23]

- Groff et al. (2021) reported on PACS prevalence at three follow-up periods (pooled median prevalence, IQR): 1 month (54%, 45–69), 2–5 months (55%, 34.8–65.5) and 6 months (54%, 31–67).[22]

Primary Literature

Three primary studies reported on the overall prevalence of PACS symptoms and sequelae in adults, which were largely in agreement with the included systematic reviews and meta-analyses, also demonstrating a considerable range of prevalence estimates.[18,29,30] A UK study by Whitaker et al. (2021) (preprint) included 508,707 participants and 19% of those self-reported previous COVID-19 illness; 38% reported one or more symptoms persisting beyond 12 weeks and 15% experienced at least three symptoms beyond 12 weeks.[18] Taquet et al. (2021a) conducted a study of 273,618 COVID-19 survivors in the US and found 37% experienced at least one PACS symptom 3–6 months after diagnosis, and that patients with COVID-19 were at significantly greater risk of persistent symptoms compared to patients with influenza (hazard ratio [HR]: 1.7, 95% CI: 1.62–1.67).[30] Chevinski et al. (2021) reported that at 31–120 days follow-up among 27,284 inpatients with COVID-19, 7% newly experienced at least one of five identified PACS conditions/groups of conditions: respiratory (e.g., shortness of breath), nervous system (e.g., altered mental status), urinary tract infection, cardiovascular (e.g., tachycardia) and nonspecific chest pain.[29] Similarly, among 44,489 outpatients with COVID-19, 7.7% newly experienced at least one of 10 identified PACS conditions/groups of conditions: respiratory symptoms, abdominal pain and other digestive/abdominal symptoms, nonspecific chest pain, nervous system symptoms, headache (including migraine), circulatory symptoms, fluid and electrolyte disorders, malaise and fatigue, nausea and vomiting, and urinary tract infections.

An additional study by Matta et al. (2022) investigated associations between self-reported COVID-19 illness (i.e., belief that one was previously infected) and persistent PACS symptoms at least 8 weeks after infection, as well as between test-confirmed SARS-CoV-2 infection and persistent symptoms.[31] The study included 26,823 participants of the general population in France. Belief in a previous infection (n=914) was significantly positively associated with 15 of 18 persistent physical symptoms (odds ratios [ORs] ranged 1.4–16.6), whereas test-confirmed SARS-CoV-2 infection (n=1,091) was only positively associated with one persistent symptom (anosmia OR: 2.6).

Prevalence of PACS Symptoms by Organ System

Across the included reviews, authors addressed a variety of PACS symptoms and outcomes. To maintain focus on more common outcomes, we reported on symptoms that appear in at least 10% of participants and in at least 25% of the reviews addressing the relevant organ system. In some cases, prevalence under 10% were reported for symptoms in individual reviews when that symptom appeared frequently across most included reviews. Please refer to Appendix A, Tables 1 and 2 for characteristics of included studies, and to Appendix B, Tables 3–7 for symptom prevalence details for all organ systems described in this rapid review.

Neurological and Mental Health Outcomes

REVIEWS

The total range of pooled mean/median prevalence results extracted from systematic reviews for the most commonly reported neurological sequelae are described below, followed by the IQR. A total of 26 included reviews reported prevalence results for neurological sequelae, the numbers of reviews that contributed results to specific sequelae (i.e., number of extracted pooled mean/median prevalence results) are listed following the range and IQR:

- **Memory impairment**: range: 11%–57%, IQR: 16%–27%, 17 reviews
- **Cognitive impairment**: range: 29%–57%, IQR: 15%–25.5%, 12 reviews
- **Concentration impairment**: range: 3%–85%, IQR; 12%–24%, 17 reviews
- **Smell dysfunction**: range: 6%–27%, IQR: 11%–18.5%, 23 reviews
- **Headache**: range: 4%–44%, IQR: 9%–19.5%, 22 reviews
- **Taste dysfunction**: range: 4%–23%, IQR: 8%– 14%, 21 reviews

A total of 22 included systematic reviews reported pooled mean/median prevalence results for mental health PACS sequelae:

- **Anxiety:** range: 11%–34%, IQR: 19%– 28.75%, 22 reviews
- **Depression:** range: 8%–33%, IQR: 19%– 28.75%, 22 reviews
- **Sleep disorder:** range: 11%–53%, IQR: 18.5%–34%, 21 reviews
- **Post-traumatic stress disorder (PTSD):** range: 1%–57%, IQR: 12.25%–18.75%, 14 reviews

We included eight key systematic reviews that had relatively large total sample sizes (n > 20,000) and/or that specifically investigated neurological or mental health outcomes:

- Chen et al. (2021) (preprint) conducted a systematic review and meta-analysis (searched to August 12, 2021) examining PACS symptoms at least 28 days after acute illness across 40 studies and 886,388 patients.[11] Common neurological symptoms (pooled mean prevalence, 95% CI) were memory problems (13%, 1–18), concentration and confusion (9%, 5–17), loss of smell (8%, 5–12) loss of taste (8%, 4–13) and headache (5%, 3–8). Common mental health symptoms were sleep problems (13%, 6–28), anxiety (10%, 6–16) and depression (10%, 5–21).

- A systematic review and meta-analysis (searched to October 2021) conducted by Alkodaymi et al. (2022) included 63 studies and 257,348 patients.[32] Neurological symptoms were reported at 3–6 months, 6–9 months, 9–12 months and >12 months after acute SARS-CoV-2 infection. Estimates were not reported (NR) at all follow-up periods for all symptoms. Estimated prevalence of PACS symptoms were (pooled mean prevalence [95% CI]): difficulty concentrating (22% [15–31], 22% [8–40], NR, NR), cognitive disorder (14% [3–31], 15% [6–27], NR, NR), headache (12% [5–20], 14% [7–23], 10% [4–17], NR), loss of smell (9% [4–7], 15% [10–22], 12% [1–30], NR) and loss of taste (8% [3–15], 13% [8–18], 6% [1–13], NR). Mental health symptoms included sleep disorder (24% [8–44], 29% [15–45]; NR; 30% [13–50]), anxiety (21% [6–43]; 23% [13–33]; NR; NR) and depression (14% [2–33]; 23% [21–26]; NR; NR).

- A systematic review and meta-analysis by Premraj et al. (2022) (searched to August 1, 2021) examined neuropsychiatric sequelae in patients with COVID-19, and included 19 studies and 11,324 patients.[33] Neurological symptoms included (pooled mean prevalence, 95% CI) brain fog (32%, 9–55), memory issues (27%, 18–36), attention disorder (22%, 20–34), loss of smell (12%, 7–17), taste dysfunction (11%, 4–17) and headache (10%, 1–21). Mental health symptoms included sleep disturbances (31%, 18–43), anxiety (23%, 13–33) and depression (14%, 7–21). The authors investigated the duration of PACS neuropsychiatric symptoms and found loss of smell, taste dysfunction and cognitive dysfunction did not change significantly from the mid-term (3–6 months) to the long-term (>6 months) follow-up. However, anxiety and depression increased substantially in the long-term compared to mid-term follow-up.

- Ceban et al. (2022) conducted a systematic review (searched to June 8, 2021) and meta-analysis examining fatigue and cognitive impairment in patients after acute COVID-19 infection, follow-up periods ranged from 2.8 to 11.2 months.[34] The systematic review included 81 studies; the meta-analysis for cognitive impairment included 13,232 patients. The pooled prevalence of cognitive impairment 12 weeks post-acute infection was 22% (95% CI: 17–28).

- Fernández-de-las-Peñas et al. (2021) conducted a systematic review and meta-analysis (searched to May 21, 2021) of 35 studies and 28,438 patients.[35] The authors examined headache as an acute COVID-19 symptom and as a PACS symptom at 30, 60, 90 and $\geq$180 days after acute infection. The pooled mean prevalence (95% CI) of headache after COVID-19 infection was 10% (5.4–18.5) at 30 days, 16.5% (5.6–39.7) at 60 days, 10.6% (4.7–22.3) at 90 days, and 8.4% (4.6–14.8) ≥180 days. There was no significant difference in headache between hospitalized and non-hospitalized patients. Regardless of hospitalization status, time had a significant effect, with headache prevalence gradually decreasing over time (the slight increase at 60 days was not found to be significant).

- In a systematic review (searched to March 2021) of 57 studies and 250,351 participants, Groff et al. (2021) assessed PACS symptoms at least 30 days after acute infection.[22] The most common neurocognitive symptoms were (pooled median frequency, IQR) difficulty concentrating (23.8%, 20.4–25.9), memory deficits (18.6%, 17.3–22.9), cognitive impairment (17.1%, 14.1–30.5), distorted taste (11.2%, 6.7–18.9) and loss of smell (13.4%, 7.9–19.0). Common mental health outcomes included generalized anxiety (29.6%, 14.0–44.0), sleep disorder (27.0%, 19.2–30.3), depression (20.4%, 19.2–21.5) and PTSD (13.3%, 7.3–25.1).

- A systematic review and meta-analysis (searched to February 20, 2021) by Badenoch et al. (2022) investigated persistent neuropsychiatric PACS symptoms across 51 studies and 18,917 patients assessed at least 20 days after acute COVID-19 infection.[36] Common neurological symptoms were (pooled mean prevalence, 95% CI) cognitive dysfunction (20.2%, 10.3–35.7), smell dysfunction (11.4%, 8.2–15.6), taste dysfunction (7.4%, 4.7–11.4) and headache (6.6%, 3.6–12.0). Common mental health outcomes were sleep problems (27.4%, 21.4–34.4), anxiety (19.1%, 13.3–26.8), PTSD (15.7%, 9.9–24.1) and depression (12.9%, 7.5–21.5).

- In a systematic review and meta-analysis (searched to January 1, 2021) of 15 articles and 47,910 patients, Lopez-Leon et al. (2021) reported on the long-term effects of COVID-19 14–110 days after acute infection.[24] The most common neurological symptoms were (pooled mean prevalence, 95% CI) headache (44%, 13–78), attention disorder (27%, 19–36), taste dysfunction (23%, 14–33), smell dysfunction (21%, 12–32), memory loss (16%, 0–0.55), and hearing loss/tinnitus (15%, 10–20). The most common mental health outcomes were anxiety (13%, 3–26), depression (12%, 3–23) and sleep disorder (11%, 3–24).

Details of the pooled mean/median prevalence measures reported in additional included reviews can be found in Appendix B, Table 3 and Table 4.

PRIMARY LITERATURE

Eleven large observational primary studies (n > 10,000 participants) examined neurological or mental health PACS symptoms and sequelae, which were in agreement with the included systematic reviews and meta-analyses. Nine studies used non-COVID-19 infected comparator groups and two assessed symptoms only in patients with COVID-19.

Seven of the studies that used non-COVID-19 comparator groups also examined symptoms consistent with PACS over multiple follow-up periods.[16,17,19,29,30,37,38] These studies found patients with COVID-19 experienced some neurological or mental health sequelae to a greater degree than patients without COVID-19; however, these differences tended to decrease over longer follow-up periods. For example, Coleman et al. (2021) (preprint) examined new onset mental illness among 638,121 patients with COVID-19 and 87,969 patients without COVID-19 diagnosed with either another respiratory tract infection, bone fracture or urolithiasis.[17] Follow-up periods were 21–120 days and 121–365 days after infection/illness. COVID-19 patients had greater overall incidence (%) and significantly greater risk (HR) of any psychiatric illness (3.8%, HR: 1.3, 95% CI: 1.2–1.4) and anxiety (2%, HR: 1.3, 95% CI: 1.1–1.4) in the 21–120 day follow-up period compared to patients without COVID-19 (incidence of 3% and 1.6%, respectively). In the 121–365 day follow-up period, patients with COVID-19 were not at significantly higher risk of any mental disorder, mood disorder or anxiety disorder compared to control patients without COVID-19. Chevinski et al. (2021) did not find significant differences between COVID-19 patients and controls for anxiety, depression or PTSD at the longest follow-up period (90–120 days).[29] They found that patients with COVID-19 remained at higher risk (OR, 95% CI) of neurocognitive disorders (2.5, 1.4–4.5) and other specified nervous system disorders (1.7, 1.1–2.6) compared to controls at 90–120 days follow-up. Five other observational studies similarly found increased rates of neurological or mental health outcomes among patients with COVID-19 compared to controls in shorter follow-up periods, but less often for longer follow-up periods of up to 12 months.[16,19,30,37,38]

Two studies with non-COVID-19 comparison groups examined non-hospitalised participants and follow-up times were approximately 6 months post-infection, these had contrasting results.[39,40] Al-Aly et al. (2021) investigated symptoms consistent with PACS among users of the US Veterans Health Administration and found those with COVID-19 (n = 73,435) to have excess burden of illness compared to patients without COVID-19 (n = 4,990,835) for the outcomes: sleep-wake disorders, nervous system signs and symptoms, trauma/stress-related disorders, anxiety and fear-related disorders, nervous system disorders, headache and neurocognitive disorders.[39] A study in Denmark by Lund et al. (2021) found patients with COVID-19 (n = 10,498) were not at a significantly increased risk of anosmia, headache, neurological disease, neuropathies, psychiatric illness, depression, anxiety or prescription antipsychotics, compared to those without COVID-19 (n = 80,894).[40]

Taquet et al. (2021b) and Wang et al. (2022) assessed symptoms only in patients with COVID-19 at follow-up periods of 168 days and 50–110 days, respectively.[41,42] Taquet et al. (2021b) found approximately a third of patients had a neuropsychiatric diagnosis (33.6%; 95% CI: 33.2–34.1) at follow-up and 12.8% (95% CI: 12.4–13.3) received a neuropsychiatric diagnosis for the first time. Mood, anxiety or psychotic disorder were reported for the first time in 8.6% (95% CI: 8.3–9.0) of patients.[41] Prevalence estimates for common neurological or mental health outcomes reported by Wang et al. (2022) generally fell within the prevalence ranges from review evidence described above, for example headache (20%), confusion (5%), problems with smell or taste (5%), anxiety (25%), depression (24%) and insomnia (11%).[42]

Respiratory

REVIEWS

A total of 21 systematic reviews reported pooled mean/median prevalence results for common respiratory sequelae. The number of reviews that reported results for specific symptoms are listed following the range and IQR.

- **Dyspnea (shortness of breath):** range: 14%–71%, IQR: 25%–36%, 21 reviews
- **Cough:** range: 6%–59%, IQR: 11%–19%, 21 reviews
- **Nasal congestion:** range: 1%–20%, IQR: 6.5%–16.5%, 7 reviews
- **Sputum:** range: 1%–59%, IQR: 5.75%–12.25%, 12 reviews

Six key systematic reviews included relatively large sample sizes (n > 20,000) and/or specifically investigated the respiratory system:

- Chen et al. (2021) (preprint) conducted a systematic review and meta-analysis (searched to August 12, 2021) examining PACS symptoms at least 28 days after acute illness across 40 studies and 886,388 patients.[11] Dyspnea was the only common (i.e., prevalence >10%) respiratory symptom (13%, 95% CI: 9–19), cough occurred less commonly (7%, 95% CI: 5–9).
- Alkodaymi et al. (2022) included 63 studies and 257,348 patients in their systematic review and meta-analysis, and reported common respiratory PACS symptoms at 3–6 months, 6–9 months, 9–12 months and >12 months after acute COVID-19 infection (pooled mean prevalence [95% CI]): dyspnea (25% [17–34], 25% [20–30], 21% [14–28], 31% [17–47], respectively) and cough (15% [10–21], 12% [6–20], 6% [1–12], NR, respectively).[32]
- Long et al. (2021) conducted a systematic review and meta-analysis of 16 studies and 4,478 patients with COVID-19 to investigate persistent symptoms and pulmonary function at least 30 days after discharge from hospital.[43] Common persistent respiratory symptoms included dyspnea (33%, 22–43) and cough (17%, 11–22).
- So et al. (2021) conducted a systematic review and meta-analysis of 15 studies and 3,066 patients followed up between 1 and 6 months post-SARS-CoV-2 infection.[27] The authors investigated radiological and functional lung outcomes. The pooled mean prevalence (95% CI) of any computerized tomography (CT) abnormality was 55.7% (41.2–70.1), and of any pulmonary function test abnormality was 44.3% (32.2–56.4).
- In a systematic review of 57 studies and 250,351 participants assessed at least 30 days after acute COVID-19, Groff et al. (2021) examined various PACS symptoms.[22] Common respiratory signs and symptoms included (pooled median frequency, IQR) dyspnea (29.7%, 14.2–37.0), cough (13.1%, 5.3–22.6), increased oxygen requirement (65.0%, 39.3–76.1), pulmonary diffusion abnormalities (30.3%, 22.1–38.5), ground glass opacification (23.1%, 19.7–43.0) and restrictive patterns on spirometry (10.0%, 6.1–24.1).
- In a systematic review and meta-analysis of 15 articles and 47,910 patients, Lopez-Leon et al. (2021) reported on the long-term effects of COVID-19 (mean follow-up: 14–110 days).[24] Common respiratory PACS symptoms were (pooled mean prevalence, 95% CI) dyspnea (24%, 14–36) and cough (19%, 7–34).

Details of the pooled mean/median prevalence measures reported in additional included reviews can be found in Appendix B, Table 5.

PRIMARY LITERATURE

Eight primary observational studies examined respiratory PACS symptoms and sequelae, seven used non-COVID-19 comparison groups and one assessed symptoms only in patients with COVID-19. The primary studies were in agreement with the included systematic reviews and meta-analyses.

Four studies used non-COVID-19 comparator groups and examined respiratory symptoms consistent with PACS over multiple follow-up periods.[19,29,30,37] All four suggested greater respiratory symptom prevalence in patients who had COVID-19 compared to those who did not, at some point during follow-up. Three studies indicated attenuation of respiratory symptom risk or prevalence over time and one found the risk of dyspnea did not reduce over time. Chevinski et al. (2021) examined symptoms consistent with PACS at four follow-up periods: 1–30, 31–60, 61–90 and 90–120 days.[29] Patients who had COVID-19 had significantly increased odds of having general respiratory signs and symptoms (OR: 1.4, 95% CI: 1.0–1.8) at the longest follow-up period compared to comparators who did not have COVID-19. There were more significant differences between patients with COVID-19 and control patients for respiratory outcomes in earlier follow-up periods (e.g., pneumonia), however these were not significantly different from the controls by the final follow-up. Taquet et al. (2021a) examined 273,618 COVID-19 survivors and a matched cohort of 114,449 influenza patients in the US.[30] One respiratory outcome was reported at 1–180 days follow-up in patients with COVID-19 and influenza, respectively (prevalence, 95% CI, HR): abnormal breathing (18.4%, 18.0–18.9 versus 9.7%, 9.5–10.0, HR: 2.0). When results were limited to 90–180 days follow-up (i.e., excluding any outcomes from the acute infection period), the prevalence of abnormal breathing reduced overall, but remained a greater risk for patients with COVID-19 relative to patients with influenza (9.1%, 8.6–9.5 versus 4.7%, 4.5–4.9, HR: 2.0). Sørensen et al. (2022) (preprint) assessed symptoms consistent with PACS at 6, 9 and 12 months after SARS-CoV-2 test.[19] Those who tested positive were at greater risk for dyspnea across all follow-up periods than those who tested negative, however overall prevalence (%) of dyspnea and risk difference (RD) in COVID-19 versus controls appeared to gradually decline over time: 6 months (6%, RD: 5.7), 9 months (5.4%, RD: 4.9) and 12 months (4.8%, RD: 4.2). Estiri et al. (2021) conducted a retrospective cohort study involving 96,025 non-hospitalized patient records, 22,475 of those (23.4%) had positive SARS-CoV-2 test results.[37] Respiratory outcomes significantly associated with a previous SARS-CoV-2 infection included (OR, 95% CI) dyspnea (3–6 months: 1.4, 1.22–1.64; 6–9 months: 1.5, 1.09–1.93) and pneumonia (3–6 months: 1.7, 1.28–2.16; 6–9 months: NR).

Three studies with non-COVID-19 comparator groups assessed respiratory symptoms consistent with PACS after acute infection but not at multiple follow-up periods.[39,40,44] At follow-up, patients with COVID-19 tended to experience more respiratory symptoms than patients without COVID-19. Al-Aly et al. (2021) and Ayoubkhani et al. (2021) reported any respiratory signs/symptoms and any respiratory disease, respectively, occurred at higher rates in patients with COVID-19 compared to patients without COVID-19.[39,44] Lund et al. (2021) found patients with COVID-19 were not at significantly increased risk of pulmonary disease or cough compared to patients without COVID-19, but were at significantly increased risk (relative risk [RR], 95% CI) of dyspnea (2.0, 1.62–2.48), use of bronchodilating medications (1.2, 1.01–1.48) and use of short-acting β2-agonists (1.3, 1.09–1.60).[40]

Wang et al. (2022) assessed symptoms in patients with COVID-19 at 50–110 days follow-up, from 23,505 patients and 299,140 clinical notes.[42] The prevalence of common respiratory symptoms generally aligned with the ranges from review evidence described above: dyspnea (20.8%), cough (17.5%) and wheezing (11.9%). Less common symptoms were nasal congestion (7.1%) and sore throat (6.4%).

Cardiovascular

REVIEWS

A total of 21 systematic reviews reported pooled mean/median prevalence results for common cardiovascular sequelae:

- **Pericardial effusion:** range: 9%–27%, IQR: 12%–18%, 4 reviews
- **Palpitations:** range: 5%–62%, IQR: 9.7%–14%, 13 reviews
- **Chest pain**: range: 5%–89%, IQR: 8%–16%, 21 reviews

Five key reviews included sample sizes greater than 20,000 participants and/or specifically assessed the cardiovascular system:

- A systematic review and meta-analysis (searched to October 2021) by Alkodaymi et al. (2022) included 63 studies and 257,348 patients with COVID-19.[32] Cardiovascular PACS symptoms are listed in order of pooled mean prevalence [95% CI] at 3–6 months, 6–9 months, 9–12 months and >12 months after acute SARS-CoV-2 infection: effort intolerance (19% [7–35], 45% [26–67], NA, NA), palpitations (14% [5–25], 14% [8–21], NA, NA) and chest pain (11% [6–16], 12% [8–18], 8% [5–11], NA).
- Chen et al. (2021) (preprint) conducted a systematic review and meta-analysis (searched to August 12, 2021) examining PACS symptoms at least 28 days after acute illness across 40 studies and 886,388 patients.[11] Cardiovasuclar symptoms such as tachycardia (7%, 95% CI: 3–18) and chest pain (5%, 95% CI: 4–7) were prevalent in less than 10% of patients.
- Ramadan et al. (2021) investigated cardiac sequelae of COVID-19 in a systematic review (searched to February 12, 2021) of 35 studies and 52,605 patients.[45] Median follow-up time was 28 days, results were synthesized qualitatively.. The pooled mean prevalence of all reported clinical diagnoses (e.g., myocarditis, myopericarditis, pericarditis, myocaridal infarction) were less than 10%. The median prevalence of chest pain was 17.5% (range: 0–73).
- In a systematic review of 57 studies and 250,351 participants assessed at least 30 days after acute COVID-19, Groff et al. (2021) examined various PACS symptoms.[22] Common cardiovascular symptoms were (pooled median, IQR) chest pain (13.3%, 8.8–17.8) and palpitations (9.3%, 6.0–10.8).
- In a systematic review and meta-analysis of 15 articles and 47,910 patients, Lopez-Leon et al. (2021) reported on the long-term effects of COVID-19 (mean follow-up: 14–110 days).[24] Common cardiovascular symptoms were (pooled mean prevalence, 95% CI): chest pain (16%, 10–22), tachycardia (11%, 9–14) and palpitations (11%, 6–17). Myocarditis was reported in 1% (0–4) of patients with PACS.

Details of the pooled mean/median prevalence measures reported in additional included reviews can be found in Appendix B, Table 6.

PRIMARY LITERATURE

Eight primary observational studies examined cardiovascular symptoms consistent with PACS, seven used non-COVID-19 comparison groups and one assessed symptoms only in patients with COVID-19. The primary studies were in agreement with the included systematic reviews and meta-analyses.

Two studies used non-COVID-19 comparator groups and examined cardiovascular sequelae over multiple follow-up periods.[19,29] Chevinski et al. (2021) examined 27,589 hospitalized matched pairs and 46,857 non-hospitalized matched pairs at 1–30, 31–60, 61–90 and 90–120 days follow-up. Patients with COVID-19, compared to those without COVID-19, had significantly increased odds of developing acute pulmonary embolism (OR: 2.3, 95% CI: 1.1–4.8) at the longest available follow-up time. In earlier follow-up periods, there were increased risks of other cardiovascular outcomes (e.g., chest pain, hypertension, and myocarditis) in patients with COVID-19; however, these were not significantly different at the final follow-up period. Sørensen et al. (2022) (preprint) examined 61,002 SARS-CoV-2-positive patients and 91,878 SARS-CoV-2-negative patients at 6, 9 and 12 months follow-up in Denmark.[19] Chest pain was the only cardiovascular symptom reported, and prevalence (%) among patients with COVID-19 was not very high, but there was greater risk (RD) among patients with COVID-19 compared to patients without COVID-19: 6 months (3.1%, RD: 2.1), 9 months (2.7%, RD: 1.8) and 12 months (2.7%, RD: 1.7).

Five studies with non-COVID-19 comparator groups assessed cardiovascular symptoms consistent with PACS but did not do so at multiple follow-up periods.[37,39,40,44,46] Most results across these studies indicated greater risk among patients with COVID-19 than those without COVID-19 for developing cardiovascular symptoms over various follow-up periods. For example, Ayoubkhani et al. (2021) conducted a retrospective cohort study of 47,780 patients discharged from hospital and 47,780 matched controls.[44] Mean follow-up time was 140 days. The rate of a major adverse cardiovascular event being diagnosed was 3.0 times (95% CI: 2.7–3.2) greater in patients with COVID-19 versus patients without COVID-19. Estiri et al. (2021) reported cardiovascular outcomes at 3–6 months follow-up that were significantly associated with a previous COVID-19 infection included (OR, 95% CI): chest pain (1.3, 1.09–1.48) and palpitations (1.4, 1.22–1.64).[37] Lund et al. (2021) found SARS-CoV-2-positive individuals were at significantly increased risk of venous thromboembolism (RR: 1.8, 95% CI: 1.09–2.86), but were not at a significantly increased risk of heart failure, stroke/transient ischemic attack or cardiovascular disease, compared to SARS-CoV-2-negative individuals.[40]

One study assessed symptoms only in patients with COVID-19. Wang et al. (2022) examined 23,505 patients with COVID-19 and 299,140 clinical notes from 50–110 days after their positive SARS-CoV-2 test, to develop a lexicon of PACS symptoms.[42] Common cardiovascular PACS symptoms included chest pain (12.5%) and palpitations (10.3%), which align relatively closely with the prevalence ranges from review evidence described above.

Other Symptoms

REVIEWS

A total of 25 systematic reviews reported pooled mean/median prevalence results for other common PACS sequelae:

- **Fatigue**: range: 23%–87%, IQR: 32%–48.25%, 25 reviews
- **Arthralgia (joint pain):** range: 9%–55%, IQR: 13%–22.5%, 17 reviews
- **Hair loss:** range: 7%–29%, IQR: 11%–20.75%, 15 reviews
- **Myalgia (muscle pain):** range: 6%–51%, IQR: 11%–23.5%, 16 reviews
- **Decreased appetite and weight loss:** range: 5%–31%, IQR: 7.5%–13.75%, 11 reviews

Five key reviews included large sample sizes and/or specifically investigated select organ systems:

- Chen et al. (2021) (preprint) conducted a systematic review and meta-analysis (searched to August 12, 2021) examining PACS symptoms at least 28 days after acute illness across 40 studies and 886,388 patients.[11] Common PACS symptoms (pooled mean prevalence, 95% CI) were fatigue (23%, 12–38) and joint pain (13%, 5–29). The pooled prevalence results for myalgia, hair loss, decreased appetite, diarrhea and fever did not exceed 10%.
- A systematic review and meta-analysis (searched to October 2021) by Alkodaymi et al. (2022) included 63 studies and 257,348 patients with COVID-19.[32] Common symptoms at 3–6 months, 6–9 months, 9–-12 months and >12 months after acute infection were (pooled mean prevalence, 95% CI) fatigue (32%, 22–44], 36% [27-46], 37% [16–62]), joint pain (14% [4–27], 23% [15–31], 15% [8–23], NA), myalgia (12% [4–22], 19% [7–35], 8% [3–14], 22% [6–46]), diarrhea (10% [2–21], 5% [2–11], NA, NA) and hair loss (9% [2–20], 10% [2–22], NA, 12% [3–24]).
- Groff et al (2021) conducted a systematic review of 57 studies and 250,351 survivors of COVID-19 who were assessed at least 30 days after acute SARS-CoV-2 infection.[22] Common PACS signs and symptoms included (pooled median frequency, IQR) fatigue or muscle weakness (37.5%, 25.4–54.5), general pain (32.4%, 22.3–38.4), hair loss (20.8%, 17.4–23.4), myalgia (12.7%, 5.6–21.3), flu-like symptoms (10.3%, 4.5–19.2) and joint pain (10.0%, 6.1–19.0).
- Ceban et al. (2022) conducted a systematic review (searched to June 8 2021) and meta-analysis examining fatigue and cognitive impairment in patients after acute COVID-19, follow-up periods ranged from 2.8 to 11.2 months.[34] 81 studies were included in the systematic review and the meta-analysis for fatigue included 25,268 patients. The proportion of fatigue at 12 weeks post-acute infection was 0.32 (95% CI: 0.27-0.37).
- In a systematic review of 15 articles and 47,910 patients, Lopez-Leon et al. (2021) reported on the long-term effects of COVID-19 (mean follow-up: 14–110 days).[24] The most common persistent symptoms for other organ systems were (pooled mean prevalence, 95% CI) fatigue (58%, 42–73), hair loss (25%, CI: 17–43), arthralgia (19%, CI: 7–34), sweats (17%, 6–30), nausea/vomiting (16%, 10–23), digestive disorders (12%, 7–18), weight loss (12%, 7–18), skin problems (12%, 7–18), general pain (11%, 7–18) and fever (11%, 8–15).

Details of the pooled mean/median prevalence measures reported in additional included reviews can be found in Appendix B, Table 7.

PRIMARY LITERATURE

Nine primary studies examined other symptoms consistent with PACS, eight used non-COVID-19 comparison groups and one assessed symptoms only in patients with COVID-19. Due to widely varying symptoms and outcomes measures, results are reported for each study. The primary studies were generally in agreement with the included systematic reviews and meta-analyses.

Four studies used non-COVID-19 comparator groups and examined symptoms and outcomes consistent with PACS over multiple follow-up periods.

- Chevinski et al. (2021) examined PACS symptoms at four follow-up periods (1–30, 31–60, 61–90 and 90–120 days) among 27,589 hospitalized matched pairs and 46,857 non-hospitalized matched pairs.[29] Non-hospitalized patients with COVID-19 had significantly increased odds (OR, 95% CI) of developing malnutrition (2.0, 1.1–3.5), bacterial infection (1.6, 1.1–2.2), septicemia (1.9, 1.2–2.9), urinary tract infection (1.4, 1.0–1.8), pressure ulcer (3.0, 1.5–6.1) and gout (2.2, 1.1–4.5) at the longest available follow-up compared to non-hospitalized patients without COVID-19. There were significant differences between patients with COVID-19 and those without COVID-19 for other outcomes in earlier follow-up periods (e.g. nausea/vomiting, diabetes mellitus with complication, fever, fatigue); however, these were not significantly different from the matched comparators by the final follow-up.

- Estiri et al. (2021) examined 22,475 non-hospitalized patient records. Outcomes were assessed at 3–6 and 6–9 months after acute infection.[37] Chronic fatigue syndrome was significantly associated with a previous COVID-19 infection at both follow-up times (OR, 95% CI): 3–6-months (2.6, 1.22– 2.10) and 6–9-month (2.0, 1.31–3.11). Type 2 diabetes mellitus was significantly associated with previous SARS-CoV-2 infection at 3–6 months follow-up (1.4, 1.22–1.64), no results were reported for 6–9 months follow-up.

- Sørensen et al. (2022) (preprint) examined 61,002 SARS-CoV-2-positive patients and 91,878 SARS-CoV-2-negative patients at 6, 9 and 12 months follow-up in Denmark.[19] Symptom prevalence (%) among patients with COVID-19 and RD compared to controls were reported for fatigue/exhaustion (6 months: 12.3%, RD: 9.8; 9 months: 11.2%, RD: 8.5; 12 months: 9.9%, RD: 7.0) and reduced strength in arms/legs (6 months: 6%, RD: 5.2; 9 months: 5.6%, RD: 4.7; 12 months: 5%, RD: 4.0).

- Taquet et al. (2021a) conducted a cohort study in the US with 273,618 patients with COVID-19 and a matched cohort of 114,449 patients diagnosed with influenza who were followed up to 6 months after infection.[30]

    - Including results from 1–180 days follow-up (i.e., including the acute infection period), prevalence of other outcomes in those with COVID-19 and influenza, respectively, were (prevalence, 95% CI, HR): abdominal symptoms (17.3%, 16.8–17.8 versus 11.4%, 11.2–11.7, HR: 1.6), fatigue (12.6%, 12.2–13.0 versus 6.8%, 6.6–7.0, HR: 1.9), general pain (12.1%, 11.7–12.5 versus 8.3%, 8.1–8.6, HR: 1.5) and myalgia (3.7%, 3.4–3.9 versus 2.2%, 2.1–2.4, HR: 1.7).

    - Outcomes reported in the 90–180 day follow-up period (i.e., excluding the acute infection period) in patients with COVID-19 and influenza, respectively, were (prevalence, 95% CI, HR): abdominal symptoms (10.7%, 10.16–11.22 versus 6.8%, 6.64–7.06, HR: 1.6), fatigue (6.4%, 5.99–6.79 versus 3.7%, 3.58–3.89, HR: 1.8), general pain (8.5%, 8.06–9.00 versus 5.5%, 5.33–5.72, HR: 1.5) and myalgia (2.1%, 1.82–2.28 versus 1.3%, 1.17–1.36, HR: 1.7).

Four studies used non-COVID-19 comparator groups but did not assess outcomes consistent with PACS over multiple follow-up periods.

- Al-Aly et al. (2021) investigated symptoms among users of the US Veterans Health Administration including 73,435 patients with COVID-19 and 4,990,835 patients without COVID-19.[39] The authors reported several outcomes at 30 days post-infection associated with COVID-19 infection compared to no COVID-19 infection, measured as excess burden per 1,000 persons (95% CI): musculoskeletal pain (13.9, 9.89–17.71), fatigue (12.6, 11.24–13.93), disorders of lipid metabolism (12.3, 8.18–16.24), diabetes mellitus (8.2, 6.36–9.95), obesity (9.5, 7.55–11.37), esophageal disorders (6.9, 4.58–9.07), abdominal pain (5.7, 3.7–7.62), muscle disorders (5.7, 4.60–6.74), anemia (4.8, 3.53–5.93), gastrointestinal disorders (3.6, 2.15–4.88) and dysphagia (2.8, 1.79–3.76).

- Ayoubkhani et al. (2021) conducted a retrospective cohort study of 47,780 patients with COVID-19 discharged from hospital and 47,780 matched controls with no COVID-19 infection.[44] Mean follow-up time was 140 days. The rate (95% CI) of being diagnosed with chronic liver disease, chronic kidney disease, and diabetes were 2.8 (2.0–4.0), 1.9 (1.7–2.1) and 1.5 (1.4–1.6) times greater, respectively, in patients with COVID-19 than in patients without COVID-19.

- Bowe et al. (2021) investigated kidney outcomes among 89,216 survivors of COVID-19 (5.2%) and 1,637,467 non-infected controls (94.8%).[47] Median follow-up times were 164 days for patients with COVID-19 and 172 days for those without COVID-19. Patients with COVID-19 were found to be at higher risk of all measured renal outcomes compared to controls, including (HR, 95% CI) acute kidney injury (1.9, 1.86–2.04), estimated glomerular filtration rate decline (eGFR) $\geq$30% (1.3, 1.14–1.37), eGFR decline $\geq$40% (1.4, 1.37–1.51), eGFR decline $\geq$50% (1.6, 1.51–1.74), end-stage kidney disease (3.0, 2.49–3.51) and major adverse kidney events (1.7, 1.58–1.74).

- A cohort study by Lund et al. (2021) conducted in Denmark included 10,498 non-hospitalized SARS-CoV-2-positive patients and 80,894 SARS-CoV-2-negative controls.[40] Follow-up ranged from 2 weeks to 6 months. Patients with COVID-19 were not found to be at significantly higher risk of developing acute kidney disease, diabetes mellitus, fatigue or non-specific pain compared to those without COVID-19.

One study assessed symptoms only in patients with COVID-19. Wang et al. (2022) examined records from patients in the US, focusing on clinical notes from 50–110 days after their positive SARS-CoV-2 test, to develop a lexicon of PACS symptoms.[42] In total, 23,505 patients with COVID-19 and 299,140 clinical notes were used to calculate the frequency of PACS symptoms. Common (>10% prevalence) symptoms included pain (43.1%), joint pain (21%), nausea/vomiting (19.9%), myalgia (19%), gastroesophageal reflux (18.6%), back pain (16.9%), fever (14.7%), swelling (14.7%), bleeding (14.7%), weight loss (14.2%), abdominal pain (14.1%), dizziness (14%), weakness (12.3%), constipation (11.9%), skin lesion (11.95) and rash (11.4%).

Impacts of PACS on Daily Living

Reviews

A total of 14 systematic reviews reported pooled mean/median prevalence results estimating the impacts of PACS on daily living:

- **Decreased quality of life (QoL):** range: 30%–59%, IQR: 40.5%–57%, 6 reviews
- **General pain and discomfort:** range: 13%–66%, IQR: 28%–37.25%, 9 reviews
- **Impaired activity and function:** range: 17%–63%, IQR: 27.75%–47%, 8 reviews
- **Mobility decline:** range: 7%–68%, IQR: 18.75%–34%, 8 reviews
- **Difficulty with self-care:** range: 6%–68%, IQR: 8%–29.75%, 5 reviews

Three key reviews included large total sample sizes and/or investigated daily living or QoL outcomes across studies that used a validated tool (e.g., EQ-5D-5L, EQ-VAS):

- Groff et al. (2021) conducted a systematic review of 57 studies and 250,351 survivors assessed at least 30 days after acute infection.[22] Common daily impairments related to PACS included (pooled median frequency, IQR): impairment in general functioning (44.0%, 23.4–62.6), mobility decline (20.2%, 14.9–30.6%) and reduced exercise tolerance (14.7%, 10.6–18.8).

- Jennings et al. (2021) conducted a systematic review (searched to April 2021) of 39 studies to examine PACS symptoms and impacts on QoL at two follow-up periods, 4–12 weeks and >12 weeks after initial infection.[23] The pooled mean prevalence of QoL impacts, measured with the EQ-5D-5L tool, were decreased QoL (4–12 weeks: 40%, >12 weeks: 57%), decrease in usual activities (4–12 weeks: NA, >12 weeks: 23%), mobility issues (4–12 weeks: 51%, >12 weeks: 32%), pain or discomfort (4–12 weeks: NA, >12 weeks: 36%) and issues with self-care (4–12 weeks: NA, >12 weeks: 10%).

- Malik et al. (2022) conducted a systematic review and meta-analysis to examine symptoms of PACS and impacts of PACS on function across 12 studies and 4,828 patients, follow-up times ranged from 30–180 days.[48] An overall pooled mean prevalence result was reported for poor QoL measured by the EQ-VAS questionnaire where higher scores represent better subjective health: 59% (95% CI: 42–75). Additionally, authors pooled prevalence results of individual factors in the EQ-5D-5L questionnaire (higher scores represent more problems with the specified factor): mobility (36%, 10–67), personal care (8%, 1–21), usual activities (28%, 2–65), pain/discomfort (42%, 28–55) and anxiety/depression (38%, 19–58).

Details of the pooled mean/median prevalence measures reported in additional included reviews can be found in Appendix C, Table 8.

Primary Literature

None of the included primary studies reported on daily functioning or QoL outcomes related to PACS.

Risk Factors Associated with PACS

From three meta-analyses and eight primary studies, the most commonly reported risk factors for developing PACS, where over 50% of the studies found a significant result, were:

- **Increased disease severity during acute infection**: 8/11 studies with significant findings
- **Female sex**: 6/11 studies with significant findings

Aspects of age, co-morbidities, pre-existing conditions and race were less commonly associated with predicting the occurrence of PACS.

Reviews

Three systematic reviews performed meta-analyses on potential risk factors for developing PACS.[33,43,49] Two of these meta-analyses noted an increased risk of PACS for those with increased disease severity during the acute phase of disease (2/3 studies) followed by female sex (1/3 studies). In a systematic review and meta-analysis by Premraj et al. (2022) (searched to August 1, 2021) examined neuropsychiatric sequelae at mid-term (3–6 months) and long-term (>6 months) follow-up, and included 19 studies with 11,324 patients.[33] In contrast to the other two reviews, results showed patients who were hospitalized during acute infection were less likely than non-hospitalized patients to develop loss of smell, anxiety, depression, taste dysfunction, fatigue, headache, myalgia and sleep disturbances at the 3–6 month follow-up, however hospitalization was significantly associated with increased post-acute memory issues. Cohorts with >20% of patients admitted to the ICU had a higher prevalence of anxiety and depression compared to cohorts with <20% of patients admitted to the ICU.

Five systematic reviews addressed potential risk factors associated with developing PACS; however, these systematic reviews did not perform meta-analyses.[11,20,34,50,51] These systematic reviews highlighted primary literature studies that identified several risk factors, including older age, female sex, hospitalization during acute illness, dyspnea during acute illness, symptom load during acute illness and comorbidities. These systematic reviews additionally highlighted inconsistency in factors that contribute to increased risk of PACS. In a publication by the Ontario COVID-19 Science Table, the primary risk factors for developing PACS were increased acute-disease severity, high body mass index, female sex and increasing age.[7]

Primary Literature

In eight primary studies investigating the risk factors associated with developing PACS, the main risk factors identified were increased disease severity during the acute phase of disease (6/8), female sex (5/8) and having pre-existing conditions or co-morbidities (4/8).[18,19,29,30,37,38,52,53] Indications of increased disease severity included measures of hospital admission, ICU admission, mechanical ventilation, need for supplemental oxygen, and the number and types of symptoms during acute infection. In a cohort study, using the US Department of Veterans Affairs database, Xie et al. (2021) investigated PACS in 181,384 people who had COVID-19 compared to 4,397,509 non-infected controls.[53] The risk of developing at least one PACS symptom increased with disease severity (care-setting during acute phase used as a proxy for disease severity) after 6 months: non-hospitalized (41 per 1,000 patients; 95% CI: 38.8–42.3), hospitalized (158/1,000; 95% CI: 153–164) and ICU (227/1,000; 216–239). The most prevalent PACS symptoms were shortness of breath, sleep disorder and chest pain. The median age of patients was 67.1 years (IQR: 53.1–74.5), 90.5% were male and 76.6% were white.

Please refer to Appendix D, Table 9 for all risk factors reported in the studies described above.

Limitations

We acknowledge that 18% of the research articles in this rapid review were non-peer-reviewed, preprint articles. Considering the rapid emergence and dynamic nature of the COVID-19 pandemic, the volume of preprint research is expected given the need for rapid dissemination of data. Studies used different follow-up periods and used different time points for determining follow-up periods; e.g., time from hospital discharge, time from negative test, and time from symptom onset in acute stage of disease. In addition, as the follow-up period increased, the sample size of patients generally decreased; therefore, we likely over-represent relatively short-term sequelae.

The expected limitations associated with systematic reviews and meta-analyses apply to our rapid review as well. First, we did not include non-English studies and we possibly missed additional articles of interest in other languages. Second, we did not check systematic reviews for overlap of included primary studies, therefore primary studies may have appeared in more than one included review. Thirdly, the high levels of heterogeneity in systematic reviews and meta-analyses made it difficult to compare findings between studies, and likely the result of primary studies being mostly observational in nature with variable follow-up periods. Fourth, systematic reviews and meta-analyses did not always include overall demographics of study population, including mean/median age of patients, sex proportions and ethnic/race information.

A limitation of this rapid review is that symptoms, conditions, and levels of function at baseline or before SARS-CoV-2 infection were often unknown. Without pre-COVID-19 clinical assessments and control groups, it is difficult to attribute PACS symptoms solely to COVID-19. There was no consistent definition of "PACS", and we accepted authors' definitions of post-acute symptoms. In most studies, it was not possible to determine the proportion of cases that had PACS symptoms or sequelae (but who had completely recovered), in contrast to those with ongoing symptoms from a lack of complete recovery from infection (patients with continued SARS-CoV-2 present in the blood). The impact of seeking health care/use of health care resources as a result of PACS symptoms was not in scope of this review, however would be useful to investigate in future work. Few studies examined PACS symptoms over several follow-up periods, making it difficult to understand how long specific PACS symptoms last. Among systematic reviews and meta-analyses, along with primary studies, there was no standardization of symptom definitions and diagnostic criteria (e.g., validated self-reported questionnaires versus clinical assessments). Included studies were likely biased towards studies where patients were tested by RT-PCR for SARS-CoV-2 infection. A bias towards positive test subjects means underrepresentation of those without access to testing, those with asymptomatic infection or mild infection, and those with barriers to accessing healthcare. Most systematic reviews and meta-analyses, along with primary studies, used subjective assessments of symptoms, which may be affected by recall bias.

Few studies included non-COVID-19 comparator groups, and among those studies the comparator groups were heterogeneous (e.g., healthy controls, patients with influenza or other non-COVID-19 diagnoses). It remains unclear the extent to which some persistent symptoms are due to public health measures (lockdowns, physical distancing), pre-existing condition, perceived infection or other potential confounding factors, rather than SARS-CoV-2 infection itself; further case-control studies would help disentangle the contribution of public health measures and infection to symptoms consistent with PACS. In addition to public health measures, ICU admission, invasive mechanical ventilation, corticosteroids, and other medical treatments may contribute to outcomes consistent with PACS, and not necessarily due to the infection itself. In addition, the majority of patients with COVID-19 who were studied were hospitalized and likely had more severe disease, leading to higher prevalence of PACS symptoms. The prevalence estimates reported in this review may not be generalizable to all patients with COVID-19.

Conclusions and Public Health Implications

The literature identified that approximately 50% of patients with COVID-19 may experience PACS. The most commonly reported sequelae affected multiple organ groups, negative effects on mental health were also among commonly reported sequelae, and contributed to a decreased quality of life, noting that the results were highly heterogeneous. Impacts on mental health, respiratory function and quality of life have been observed following other viral diseases. For example, following historical influenza pandemics, Severe Acute Respiratory Syndrome (SARS, caused by SARS-CoV-1) and Middle East Respiratory Syndrome (MERS, MERS-CoV), common long-term consequences included fatigue, shortness of breath, decreased quality of life and anxiety.[54-56] In a systematic review and meta-analysis of 28 studies of hospitalized patients with SARS or MERS (3 months after admission, 2 months after discharge), Ahmed et al. (2020) reported that over 25% of patients experienced reduced lung function, reduced capacity to exercise, PTSD, depression and anxiety.[57]

Care for patients with PACS will likely place added stresses on the health care and social support systems, including increased emergency department visits, outpatient care, inpatient care and rehabilitation involving multidisciplinary teams.[58-61] Given the wide variety of persistent symptoms and sequelae associated with PACS highlights the need for multi-disciplinary care, guidance is currently being developed for the assessment and management of patients with PACS, but there will need to be ongoing research and study to further characterize PACS.[3,62-67] Funding will be necessary to support multidisciplinary models of care for the large number of patients with PACS in Ontario.

Further longitudinal, standardized, case-control and large prospective cohort studies are needed to characterize the prevalence of PACS, PACS symptoms and the risk factors for developing PACS. Some of the research needs include:

- Refining and developing a standardized definition of PACS
- Developing standardized definitions of PACS symptoms and respective diagnostic criteria
- Further research into the risk factors associated with developing PACS
- Comparison of PACS and the sequelae of other respiratory infections
- Determining baseline, pre-infection comorbidities
- Determining the duration of PACS and PACS symptoms
- Determining the biological and physiological processes contributing to PACS
- Determining the impact of medical treatments on PACS
- Determining if PACS and PACS symptoms differ among variants of concern (VOCs)
- Determining if vaccination status has an impact on the development of PACS

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Appendix A. Characteristics of Included Studies

Table 1. Characteristics of included systematic reviews (n=32)

First author	Last search (2021)	Acute illness setting	Number of included studies (n patients)	PACS prevalence %	Proportion female patients %	Patient age (years)	Minimum follow-up (day)	Objective to assess at >1 follow-up time?	Meta-analysis?	Limited to studies with control groups?
Aiyegbusi[50]	Feb 8	Mixed	27 (total patients NR)	NR	NR	NR	28	No	Yes	No
Alkodaymi[32]	Oct	Mixed	63 (257,348)	NR	NR	NR	84	Yes: 3-6, 6-9, 9-12, and >12 months	Yes	No
Anaya[68]	May 8	Mixed	40 (11,196)	NR	50	Mean: 50.2 95% CI: 47-53.5 *from 34 studies	Mean: 105.9 95% CI: 89.1–122.7 *from 7 studies	No	Yes	No
Badenoch[36]	Feb 20	Mixed	51 (18,917)	NR	66.8	Mean: 50.9 SD: 9.4	28	No	Yes	No
Cabrera Martimbianco[20]	Feb 1	Mixed	25 (5,440)	Range: 4.7–80.0	NR	NR	21	No	No	No
Ceban[34]	Jun 8	Mixed	81 studies Fatigue meta-analysis n = 25,268 Cognitive impairment meta-	NR	NR	NR	84	No	Yes	No

First author	Last search (2021)	Acute illness setting	Number of included studies (n patients)	PACS prevalence %	Proportion female patients %	Patient age (years)	Minimum follow-up (day)	Objective to assess at >1 follow-up time?	Meta-analysis?	Limited to studies with control groups?
			analysis n = 13,232							
Chen[11] (preprint)	Aug 12	Mixed	40 (886,388)	51 (95% CI: 42–59)	NR	Median: ≈60	28	Yes: 30, 60 90, 120 days (PACS overall)	Yes	No
De-la-Rosa-Martinez[13] (preprint)	Jan 31	Mixed	29 (5,586)	56 (95% CI: 45-66)	Range: 27-75	Range: 27-70	21	No	Yes	No
d'Ettorre[21]	Jan 31	Mixed	13 (total patients NR)	Range: 16.36–87	NR	NR	21	No	No	No
Deer[69]	Apr 29	Mixed	59 (total patients NR)	NR	NR	NR	21	No	No	No
Fernández-de-las-Peñas[35]	May 31	Mixed	35 (28,438)	NR	43	Mean: 46.6±17.5	30	Yes: 30, 60, 90 and ≥180 days	Yes	No
Groff[22]	Mar	Mixed	57 (250,351)	54 (IQR: 31–67)	44	Mean: 54.4±8.9	30	Yes: 1 month, 2-5 month, 6 month (PACS overall)	No	No
Han[70]	Nov 6	Mixed	18 (8,591)	NR	NR	NR	12 months	No	Yes	No
Hoshijima[14] (preprint)	Jan 15	Inpatient	35 (18,711)	NR	NR	NR	14	No	Yes	No

First author	Last search (2021)	Acute illness setting	Number of included studies (n patients)	PACS prevalence %	Proportion female patients %	Patient age (years)	Minimum follow-up (day)	Objective to assess at >1 follow-up time?	Meta-analysis?	Limited to studies with control groups?
Iqbal[71]	Mar 6	Mixed	43 (total patients NR)	NR	NR	NR	21	Yes: <12 weeks, >12 weeks	Yes	No
Jafar[72]	May	Mixed	44 (total patients NR)	NR	NR	NR	30	No	No	No
Jennings[23]	Apr	Mixed	39 (total patients NR)	62 (range: 18–89)	Range: 32-74	Range: 31%-72%	28	Yes: 4-12 weeks, >12 weeks	No	No
Khraisat[73]	Aug 1	Mixed	27 (9,605)	NR	NR	NR	14	No	Yes	No
Long[43]	Feb 23	Inpatient	16 (4,478)	NR	48	Median/mean range: 50-60	30	No	Yes	No
Lopez-Leon[24]	Jan 1	Mixed	15 (47,910)	80 (95% CI: 65-92)	NR	Range: 17-87	14	No	Yes	No
Malik[48]	Mar 10	Mixed	12 (4,828)	NR	NR	Mean: 58.895% CI: 44–65)	30	No	Yes	No
Michelin[51]	Mar 17	Mixed	39 (10,951)	NR	48	NR	90	No	Yes	No
Nasserie[25]	Mar 11	Mixed	45 (9,751)	72.5 (IQR: 55-80)	46	Median: <60	30	No	Yes	No
Natarajan[15] (preprint)	Jun	Mixed	36 (11,598)	NR	NR	NR	Min NR, Range: 30–240	No	Yes	No
Premraj[33]	Aug 1	Mixed	19 (11,324)	NR	57	Mean: 52 SD: 10	90	Yes: 3–6 months, >6 months	Yes	No
Ramadan[45]	Feb 17	Mixed	35 (52,609)	NR	NR	Mean range: 19-74	21		Yes	N
Rao[49]	Feb 14	Mixed	41 (9,362)	NR	?	Mean range: 32-67	12	Yes: 0-30, 31-60, 61-	Yes	No

First author	Last search (2021)	Acute illness setting	Number of included studies (n patients)	PACS prevalence %	Proportion female patients %	Patient age (years)	Minimum follow-up (day)	Objective to assess at >1 follow-up time?	Meta-analysis?	Limited to studies with control groups?
								90, 91-120, 121-150 and 151-180 days		
Reyes Domingo[12] (preprint)	Apr 14	Mixed	63	53 (95% CI: 41-65)	NR	Children and adults	28	Yes: 4-12 weeks, >12 weeks	Yes	No
Sanchez-Ramirez[26]	May 22	Mixed	24 (5,323)	59 (95% CI: 44-73)	44	Mean: 55.2±8.1	90	Yes: mean 4 months (range: 3-6)	Yes	No
So[27]	Jan 20	Mixed	15 (3,066)	55.7 (95% CI: 41.2-70.1)	46	Mean: 56.0 ± 14.3	28	Yes, average follow-up of 90 days	Yes	No
Van Kessel[28]	Feb 2	Outpatient	9 (total patients NR)	Range: 10–35	NR	Primary studies mean/median range: 38.7-59	21	No	No	No
Wallbridge-Bourmistrova[74]	Aug 29	Inpatient	33 (6,743)	NR	37	Median: 57 IQR: 49.3-60.7	30	No	No	No

Table 2. Characteristics of included primary studies (n=17)

First author	Country	Study period	Acute illness setting	Number of included patients	Non-COVID-19 comparator group?	Proportion female patients %	Patient age (years)	Minimum follow-up (days)	Outcomes assessed:
Al-Aly[39]	US	Mar 1 – Nov 30, 2020	Outpatient	COVID-19: 73,435 Control: 4,990,835	Yes	12.04	Mean: 59.9 SD: 15.92	30	Neurological, mental health, respiratory, cardiovascular, other, risk factors
Ayoubkhani[44]	UK	Jan 1 – Aug 31, 2020	Inpatient	COVID-19: 47,780 Control: 47,780	Yes	45.1	Mean: 64.5 SD: 19.2	NR, mean follow-up: 140	Respiratory, cardiovascular, other, risk factors
Bowe[47]	US	Mar 1, 2020 – Apr 30, 2021	Mixed	COVID-19: 89,216 Control: 1,637,467	Yes	8.9	Median: 68.5 IQR: 56.8–74.3	30	Other
Chevinski[29]	US	Mar 1 – June 30, 2020	Mixed	COVID-19: 74,446 Control: 74,446	Yes	Inpatient: 53 Outpatient: 61	NR	31	Prevalence of PACS, neurological, mental health, respiratory, cardiovascular, other, risk factors
Coleman[17] (preprint)	US	Jan 1, 2020 – Oct 20, 2021	Mixed	COVID-19: 638,121 Control: 87,969	Yes	56.7	Mean: 42.2 SD: 21.46	21	Mental health
Estiri[37]	US	Mar 2020 – Jun, 2021	Outpatient	COVID-19: 22,475 Control: 73,550	Yes	64	Mean: 50.7	90	Neurological, respiratory, cardiovascular, other, risk factors

First author	Country	Study period	Acute illness setting	Number of included patients	Non-COVID-19 comparator group?	Proportion female patients %	Patient age (years)	Minimum follow-up (days)	Outcomes assessed:
Jovanoski[52]	US	Feb 20 – Jul 4, 2020	Mixed	COVID-19: 57,748 Control: NA	No	53.3	Inpatient: 52.2-57.7 Outpatient: 41.0-46.8	30	Risk factors
Klaser[38]	UK	Feb 23 – Apr 12, 2021	NR	COVID-19: 35,827 Control: 386,150	Yes	68.02	Mean: 54.1 SD: 13.4	30	Mental health, risk factors
Lund[40]	Denmark	Feb 17 – May 31, 2021	Outpatient	COVID-19: 10,498 Control: 80,894	Yes	61	Median: 43 IQR: 30–56	14	Neurological, mental health, respiratory, cardiovascular, other
Magnúsdóttir[16] (preprint)	Denmark, Estonia, Iceland, Norway, Scotland, Sweden	Apr 2020 – Aug 2021	Mixed	COVID-19: 9,976 Control: 237,270	Yes	67.9	Mean: 46.6	60	Mental health
Matta[31]	France	May 2020 – Jan 2021	NR	COVID-19: 1,091 Control: 25,732	Yes	51.2	Mean: 49.4 SD: 12.9	56	Prevalence of PACS
Sørensen[19] (preprint)	Denmark	Sep 2020 – Apr 2021	Mixed	COVID-19: 61,002 Control: 91,878	Yes	61.2	Females Median: 50 IQR: 36–60 Males Median: 54 IQR: 41–64	180	Neurological, mental health, respiratory, cardiovascular, other, risk factors

First author	Country	Study period	Acute illness setting	Number of included patients	Non-COVID-19 comparator group?	Proportion female patients %	Patient age (years)	Minimum follow-up (days)	Outcomes assessed:
Taquet A[30]	US	Jan 20 – Dec 16, 2020	Mixed	COVID-19: 273,618 Control: 114,449	Yes	55.6	Mean: 46.3 SD: 19.8	1–90, 90–180	Prevalence of PACS, neurological, mental health, respiratory, other, risk factors
Taquet B[41]	US	Jan 20 – Dec 13, 2020	Mixed	COVID-19: 236,379 Control: 236,038	No	55.6	Mean: 46 SD: 19.7	1–180	Mental health
Wang[42]	US	Mar 4, 2020 – Feb 9, 2021	Mixed	COVID-19: 23,505 Control: NA	No	61.9	Mean: 51.6 SD: 18.2	50	Neurological, mental health, respiratory, cardiovascular, other
Whitaker[18] (preprint)	UK	Sep 15, 2020 – Feb 8, 2021	Mixed	Total: 508,707	No	57.3	Mean: NR Range: 18–74+	84	Prevalence of PACS, risk factors
Xie A[46]	US	Mar 1, 2020 May 1, 2021	Mixed	COVID-19: 153,760 Control: 5,637,647 (contemporary); 5,859,411 (historical)	Yes	9.53	67.13 IQR: 53.12–74.46	30	Cardiovascular
Xie B[53]	US	Mar 1, 2020 May 1, 2021	Mixed	COVID-19: 181,384 Control: 4,397,509	Yes	9.53	67.13 IQR: 53.12–74.46	30	Risk factors

Appendix B. Summaries of PACS Symptom Prevalence by Organ System

Table 3: Pooled mean/median prevalence of neurological sequelae in PACS (reviews: n=26)

First Author	Concentration impairment	Smell Dysfunction	Cognitive impairment	Memory impairment	Headache	Taste Dysfunction
Aiyegbusi[50]	NA	14	NA	NA	18	7
Alkodaymi[32]	22	12	15	NA	10	6
Anaya[68]	23	11	15	12	14	8
Badenoch[36]	NA	11	20	NA	7	7
Cabrera Martimbianco[20]	57	26	57	57	39	22
Ceban[34]	NA	NA	22	NA	NA	NA
Chen[11]	9	8	NA	13	4	8
De-la-Rosa-Martinez[13]	27	14	NA	23	20	12
Deer[69]	85	13	19	16	23	16
Fernández-de-Las-Peñas[35]	NA	NA	NA	NA	8	NA
Groff[22]	24	13	17	19	9	11
Han[70]	18	6	NA	19	7	4
Hoshijima[14]	12	19	NA	14	16	14

First Author	Concentration impairment	Smell Dysfunction	Cognitive impairment	Memory impairment	Headache	Taste Dysfunction
Iqbal[71]	24	17	NA	17	12	18
Jafar[72]	NA	27	NA	NA	NA	NA
Jennings[23]	11	10	15	35	17	8
Khraisat[73]	NA	NA	NA	NA	NA	NA
Long[43]	NA	11	NA	35	15	10
Lopez-Leon[24]	27	21	NA	16	44	23
Malik[48]	NA	20	NA	NA	21	NA
Michelin[51]	3	15	NA	18	5	14
Nasserie[25]	22	11	17	28	NA	9
Natarajan[15]	20	15	29	18	11	12
Premraj[33]	22	12	NA	27	10	11
Reyes Domingo[12]	9	13	29	11	9	7
Van Kessel[28]	NA	20	10	NA	38	20
Range (no. studies)	**3-85 (17)**	**6-27 (23)**	**15-29 (12)**	**11-57 (17)**	**4-44 (22)**	**4-23 (21)**

Table 4: Pooled mean/median prevalence of mental health sequelae in PACS (reviews: n=22)

First Author	Anxiety	Sleep disorder	Depression	Post-traumatic stress disorder
Alkodaymi[32]	23	30	23	NA
Anaya[68]	25	19	25	43
Badenoch[36]	19	27	13	16
Cabrera Martimbianco[20]	25	53	25	57
Chen[11]	10	13	10	NA
De-la-Rosa-Martinez[13]	33	29	19	NA
Deer[69]	22	32	21	14
Groff[22]	30	27	20	13
Han[70]	22	12	23	NA
Hoshijima[14]	11	26	12	NA
Iqbal[71]	29	44	20	NA
Jennings[23]	34	33	32	18
Khraisat[73]	22	35	21	20
Long[43]	33	27	33	NA
Lopez-Leon[24]	13	11	12	1

First Author	Anxiety	Sleep disorder	Depression	Post-traumatic stress disorder
Malik[48]	15	47	15	15
Michelin[51]	19	18	8	9
Nasserie[25]	22	NA	15	NA
Natarajan[15]	28	22	22	12
Premraj[33]	23	31	14	11
Reyes Domingo[12]	32	15	17	18
Wallbridge-Bourmistrova[74]	11	40	10	19
Range (no. studies)	**11-34 (22)**	**11-53 (21)**	**8-33 (22)**	**1-57 (14)**

Table 5. Pooled mean/median prevalence of respiratory sequelae in PACS (reviews: n=22)

First Author	Dyspnea	Cough	Sputum	Nasal congestion	Sore throat
Aiyegbusi[50]	32	18	NA	NA	NA
Alkodaymi[32]	31	6	NA	NA	NA
Anaya[68]	35	17	12	8	12
Cabrera Martimbianco[20]	61	59	59	17	11
Chen[11]	14	7	NA	NA	3
De-la-Rosa-Martinez[13]	35	19	20	16	4
Deer[69]	35	16	8	20	4
Groff[22]	30	13	NA	NA	3
Han[70]	18	5	2	NA	2
Hoshijima[14]	25	19	5	10	9
Iqbal[71]	39	11	NA	NA	NA
Jennings[23]	40	22	13	NA	12
Long[43]	33	17	7	NA	5
Lopez-Leon[24]	24	19	3	NA	3
Malik[48]	40	23	NA	NA	NA

First Author	Dyspnea	Cough	Sputum	Nasal congestion	Sore throat
Michelin[51]	25	8	6	5	5
Nasserie[25]	36	17	NA	NA	NA
Natarajan[15]	22	18	NA	NA	6
Reyes Domingo[12]	18	7	10	1	3
Sanchez-Ramirez[26]	32	13	12	NA	4
Van Kessel[28]	71	43	NA	NA	NA
Range (no. studies)	**14-71 (21)**	**5-59 (21)**	**1-59 (12)**	**5-17 (7)**	**2-12 (15)**

Table 6. Pooled mean/median prevalence of cardiovascular sequelae in PACS (reviews: n=21)

Author	Myocarditis	Chest pain	Palpitations	Pericardial effusion
Aiyegbusi[50]	NA	15	NA	NA
Alkodaymi[32]	NA	8	14	NA
Anaya[68]	10	16	12	27
Cabrera Martimbianco[20]	NA	89	62	NA
Chen[11]	NA	5	NA	NA
De-la-Rosa-Martinez[13]	1	13	NA	9
Deer[69]	20	14	13	13
Groff[22]	NA	13	9	NA
Han[70]	NA	5	5	NA
Hoshijima[14]	NA	17	11	NA
Iqbal[71]	NA	17	NA	NA
Jennings[23]	NA	10	20	NA
Long[43]	NA	7	11	NA
Lopez-Leon[24]	1	16	11	NA
Malik[48]	NA	10	NA	NA

Author	Myocarditis	Chest pain	Palpitations	Pericardial effusion
Michelin[51]	NA	6	9.7	NA
Nasserie[25]	NA	13	NA	NA
Natarajan[15]	NA	12	14	NA
Ramadan[45]	NA	25	NA	15
Reyes Domingo[12]	NA	6	5	NA
Van Kessel[28]	NA	24	NA	NA
Range (no. studies)	**1-20 (4)**	**5-89 (21)**	**5-62 (13)**	**9-27 (4)**

Table 7. Pooled mean/median prevalence of other-organ-system sequelae in PACS (reviews: n=25)

Author	Fatigue	Arthralgia	Hair loss	Myalgia	Decreased appetite or weight loss	Diarrhea or vomiting	Conjunctivitis or red eye	Fever
Aiyegbusi[50]	47	20	NA	25	NA	6	NA	NA
Alkodaymi[32]	41	15	12	22	NA	5	NA	NA
Anaya[68]	46	16	18	16	8	10	3	9
Badenoch[36]	24	NA	NA	NA	NA	NA	NA	NA
Cabrera Martimbianco[20]	64	55	29	51	NA	33	14	20
Ceban[34]	32	NA	NA	NA	NA	NA	NA	NA
Chen[11]	23	13	7	6	6	3	NA	2
De-la-Rosa-Martinez[13]	49	22	20	27	7	7	14	4
Deer[69]	45	14	19	14	31	4	9	30
Groff[22]	38	10	21	13	NA	NA	NA	1
Han[70]	28	26	7	10	NA	NA	NA	NA
Hoshijima[14]	45	13	10	11	10	6	NA	12
Iqbal[71]	48	NA	NA	NA	NA	NA	NA	7
Jennings[23]	44	13	20	34	13	8	NA	8
Long[43]	47	12	24	13	14	3	NA	2

Author	Fatigue	Arthralgia	Hair loss	Myalgia	Decreased appetite or weight loss	Diarrhea or vomiting	Conjunctivitis or red eye	Fever
Lopez-Leon[24]	58	19	25	NA	12	16	6	11
Malik[48]	64	24	NA	NA	NA	NA	NA	NA
Michelin[51]	31	9.4	14	11	18	10	2	1
Nasserie[25]	40	NA	NA	NA	NA	NA	NA	1
Natarajan[15]	29	28	20	13	5	15	NA	3
Premraj[33]	37	NA	NA	18	NA	NA	NA	NA
Rao[49]	52	NA	NA	NA	NA	NA	NA	NA
Reyes Domingo[12]	25	10	7	9	8	5	2	1
Sanchez-Ramirez[26]	38	NA	NA	NA	NA	NA	NA	NA
Van Kessel[28]	87	NA	NA	NA	NA	NA	NA	22
Range (no. studies)	**23-87 (25)**	**9-55 (17)**	**7-29 (15)**	**6-51 (16)**	**6-31 (11)**	**3-33 (14)**	**2-14 (7)**	**1-29 (16)**

Appendix C. Summary of Studies on Impacts to Daily Living

Table 8: Pooled mean/median prevalence of the impacts to daily living in PACS (reviews: n=14)

Author	Decreased quality of life	Impaired activity and function	Mobility decline	General pain and discomfort	Difficulty with self-care
Anaya[68]	NA	NA	NA	30	NA
Cabrera Martimbianco[20]	NA	50	7	66	NA
Ceban[34]	NA	63	68	NA	68
Deer[69]	NA	NA	25	30	NA
Groff[22]	NA	44	20	32	NA
Iqbal[71]	51	NA	NA	NA	NA
Jennings[23]	57	23	32	36	10
Malik[48]	59	28	36	41	8
Michelin[51]	37	NA	NA	NA	6
Natarajan[15]	NA	NA	15	13	NA
Premraj[33]	NA	NA	NA	28	NA
Reyes Domingo[12]	30	17	22	28	17
Sanchez-Ramirez[26]	52	36	NA	NA	NA

Author	Decreased quality of life	Impaired activity and function	Mobility decline	General pain and discomfort	Difficulty with self-care
Van Kessel[28]	NA	33	NA	NA	NA
Range (n studies)	**30-59 (6)**	**17-63 (8)**	**7-68 (8)**	**13-66 (9)**	**6-68 (5)**

Appendix D. Summary of Risk Factors for Developing PACS

Table 9. Risk factors contributing to PACS (reviews: n=3; primary studies: n=8)

First Author (country)	Number of patients with COVID-19 (controls)	Minimum follow-up since symptom onset or discharge (days)	Factors associated with an increased risk of developing one or more PACS symptoms
Systematic reviews and meta-analyses			
Long[43] (multiple)	4,478	30	Increased disease severity
Premraj[33] (multiple)	11,324	90	Increased disease severity
Rao[49] (multiple)	9,362	12	Female sex
Primary literature			
Chevinski[29] (US)	74,446 (74,446)	30	Increased disease severity
Estiri[37] (US)	22,475 (73,550)	90	<65 years old
Jovanoski[52] (US)	57,748 (NA)	90	Increased disease severity; female sex; increasing age (18-64 years for mental health); non-Hispanic and white (non-Hispanic only for cardiovascular sequelae); increased pre-exiting conditions or co-morbidities
Klaser[38] (UK)	35,827 (386,150)	30	Increased pre-exiting conditions or co-morbidities
Sørensen[19] (Denmark)	61,002 (91,878)	180	Increased disease severity; female sex
Taquet A[30] (US)	273,618 (114,449)	84	Increased disease severity; female sex and decreasing age for mental health sequelae; male sex and increasing age for respiratory sequelae
Whitaker[18] (preprint) (UK)	53,309 (NA)	30	Increased disease severity; female sex; increased pre-existing conditions and co-morbidities

First Author (country)	Number of patients with COVID-19 (controls)	Minimum follow-up since symptom onset or discharge (days)	Factors associated with an increased risk of developing one or more PACS symptoms
Xie B[53] (US)	181,384 (4,397,509)	30 days	Increased disease severity; female sex; increased pre-existing conditions and co-morbidities

Increased disease severity during acute phase of illness: hospital admission, ICU admission, supplementary oxygen, more symptoms during acute phase. Pre-existing conditions and co-morbidities: high/low BMI, asthma, previous mental health conditions.

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