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SYNTHESIS

Evidence for Long-term Impacts of COVID-19 on Immune Cells and Autoimmune Conditions in Adults – What We Know So Far

Published: August 2023

Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19. This synthesis summarizes evidence related to the long-term impacts of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on immune cells and autoimmune conditions.

Key Findings

- Patients with post-acute COVID-19 syndrome (PASC) or patients in the post-acute stage of disease (≥3 months post-symptom onset) have elevated cluster of differentiation 8 ($CD8^+$) T-cell levels, compared to patients with non-PASC, healthy controls and those with acute disease. Elevated expression of $CD8^+$ T-cell pro-inflammatory cytokines during the post-acute period indicate a persistence of activated $CD8^+$ T cells. Among the included studies, changes in B-cell and $CD4^+$ T-cell levels in the post-acute stage of disease were inconsistent.
- Levels of intermediate and non-classical monocytes were elevated in those with PASC, compared to patients with non-PASC, healthy controls and those with acute disease. The persistence of non-classical monocytes in PASC indicates continued inflammation.
- Changes in immune cells and inflammation following infection are not unique to SARS-CoV-2. Persistence of elevated CD8+ T cells and non-classical monocytes occur in chronic inflammatory diseases and with other respiratory pathogens.
- Autoantibody and autoreactivity levels could not distinguish among those with PASC and non-PASC. Changes in risk of autoimmune conditions, autoantibody levels and autoreactivity levels in patients with PASC or during convalescence, compared to health controls, were inconsistent.

Background

As the world approaches year four of the COVID-19 pandemic, questions continue to emerge about potential long-term impacts on immune cells following a SARS-CoV-2 infection. The terms PASC or "long COVID" describe prolonged health changes after recovery from acute COVID-19. The World Health Organization (WHO) defines PASC as a condition in which a set of new, fluctuating or persistent symptoms occur three months after COVID-19 infection and last for at least two months.[1]

One approach to understanding PASC is to examine long-term impacts on immune cells in patients following SARS-CoV-2 infection. Immune cell changes may affect long-term health outcomes at the individual and population level. Understanding immune cell alterations and PASC may help develop improved treatments and public health policy. **This synthesis concentrates on answering the research question: are immune cells impacted following SARS-CoV-2 and, if so, are they associated with PASC?**

Methods

PHO Library Services conducted searches of the indexed literature in MEDLINE, Embase and National Institutes of Health COVID-19 iSearch Portfolio (preprints) from January 1, 2020 up to November 29, 2022. We conducted an updated search on April 14, 2023 (MEDLINE, Embase) and May 4, 2023 (National Institutes of Health COVID-19 iSearch Portfolio) that included studies published since initial search. These databases also captured multiple preprint studies. We excluded preprints uploaded before January 1, 2022, which have yet to be peer-reviewed and published. Preprints are research papers that have not undergone peer-review but made publicly available to provide the latest data; these provide important evidence in the context of the evolving COVID-19 pandemic. However, lack of peer-review is a limitation to keep in mind when interpreting results. We conducted additional targeted searching in the preprint server medRxiv and PubMed on June 6, 2023 for relevant articles appearing since our last formal literature search. Formal critical appraisal of published and preprint COVID-19 literature was out of scope for this rapid review.

We included English language full text systematic reviews or primary studies published after January 1, 2020, that investigated post-COVID-19 impact on immune cell levels and excluded studies that did not meet the sample size cut off, n≥99. We reviewed references of included studies for additional articles of interest. We included studies: 1) describing long-term changes to the adult immune system after a SARS-CoV-2 infection; 2) describing immune cell/subtype levels from PASC patients and non-PASC patients, healthy controls or non-COVID-19 patients; and 3) investigating autoimmune conditions (or other non-SARS-CoV-2 infections) following SARS-CoV-2 infection. We excluded studies: 1) describing immunology of acute disease only; 2) describing SARS-CoV-2-specific immune cells post-infection or post-COVID vaccination; 3) describing immunity in relationship to COVID-19 vaccine effectiveness; 4) using animal models; 5) focused on treatment outcomes; 6) focused on specific populations (studies on children <18 years old; a single age group; pregnant people; people with serious comorbidities [e.g. undergoing dialysis], people with immune conditions pre-SARS-CoV-2 infection).

We performed single-author screening, with checks from a second author for any records where eligibility was uncertain. For data extraction, we conducted single-author extraction with a double check by a second author. Meta-analysis was outside the scope of this rapid review, and we synthesized results narratively.

Results

The total number of screened articles was 1,246, of these 489 were preprints and 757 records were from Embase and/or MEDLINE. Of these references, 15 were included in this synthesis. Seven additional articles were included after a final search of PubMed. We did not identify any randomized controlled trials (RCTs) or systematic reviews with meta-analyses. We included 13 cohort (matched and unmatched) studies, four reviews, two case control studies, two cross-sectional studies and one meta-analysis. No studies investigating non-SARS-CoV-2 infections following COVID-19 or studies investigating SARS-CoV-2-induced immune suppression met our eligibility criteria.

Lymphoid Cells

Key findings: We included nine studies that investigated the immune profiles of T cells and B cells in patients following SARS-CoV-2 infection.[1,4,6,9-14] Patients with PASC or patients in the post-acute stage of disease showed elevated $CD8^+$ T-cell levels, compared to controls (uninfected, healthy, non-COVID-19), while changes to $CD4^+$ T-cells were inconsistent among studies. $CD8^+$ T cells showed elevated expression of cytotoxic and cytolytic immune markers such as programmed cell death protein 1 (PD-1), interleukin 8 (IL-8), interferon beta (IFN-β), IFN-γ and IFN-λ2/3; elevated levels of immune cells and immune modulators indicate activated, rather than exhausted, $CD8^+$ T cells.

While not fully understood, and out-of-scope for this review, multiple mechanisms potentially contribute to the development of PASC. Several authors have suggested PASC is the result of continued activation of CD8+ T cells, which are indicative of viral antigen persistence, or even viral replication, in the post-acute stage of disease.[4,12,14] Alternative proposed mechanisms of PASC are 1) reactivation of latent infections (e.g. Epstein-Barr virus); 2) immune-mediated tissue injury; 3) persistent elevation of cytokines; and 4) persistent inflammation; 5) elevated autoantibodies and autoimmune processes; and 6) changes in monocyte levels.

REVIEWS

Three reviews reported on T- and B-cell levels, along with cytokine levels, following SARS-CoV-2 infection.[1,12,14] In a review of three studies investigating the proportion of T_{regs} among $CD4^+$ T cells in patients following SARS-CoV-2 infection, Haunhorst et al. (2023) reported that two studies showed an increased proportion of T_{regs} among patients with PASC, compared to non-PASC or seronegative controls (sampling 3–12 months post-symptom onset).[1] As the authors note, the low number of studies does not allow for conclusions regarding T_{reg} proportions and PASC. In a review of 35 studies, Islam et al. (2023) reported elevated activated $CD8^+$ T cells in those with PASC, compared to controls (uninfected, healthy, non-COVID-19), with evidence for elevated cytokines such as IL-8. Human interferon-inducible protein 10 (IP-10) was elevated in those with PASC, compared to those with non-PASC (n=2 studies, sampling 3–8 months post-symptom onset). Changes in the levels of $CD4^+$ T cells and B cells were inconsistent.[12]

PASC VS. NON-PASC

In a single-center prospective cohort study in Portugal, Santa Cruz et al. (2023) evaluated the immune response in patients with PASC at 6 months post-COVID-19 diagnosis (PASC, n=62), compared to convalescent-asymptomatic individuals (non-PASC, n=65) and controls (uninfected, healthy) controls (n=37).[4] There was no significant difference in the levels of $CD8^+$ and $CD4^+$ T cells in those with PASC or non-PASC.

Three of four studies reported elevated levels of pro-inflammatory cytokines and interferons (e.g., IL-6, IL-8, IFN-β, IFN-γ, IFN-λ2/3) in those with PASC, compared to those with non-PASC.[4,8,9,13] For instance, when peripheral blood mononuclear cells (PBMCs) were challenged with SARS-CoV-2 antigens (nucleocapsid protein and spike protein [S]), lymphocytes produced less IFN-γ and $CD8^+CD69^+$ (only following stimulation with S) compared to patients with non-PASC (Santa-Cruz et al. 2023).[4] From the same study, elevated levels of IL-6 and IL-8 during acute disease were associated with increased risk of developing PASC ($p<0.05$). In an age- and sex-matched case-control study (n=133) in Australia, Phetsouphanh et al. (2022) focused on four groups at 8 months post-symptom onset: PASC, matched non-PASC (asymptomatic convalescent), healthy unexposed controls and those infected with other coronaviruses but not SARS-CoV-2 (HCoVs).[9] Pro-inflammatory cytokine levels were not significantly different between PASC and non-PASC groups, including IFN-β, IFN-λ1 and IL-8 ($p>0.05$). Levels of post-acute IFN-β, pentraxin 3PTX3, IFN-λ2/3 and IL-6 were associated with PASC. Queiroz et al. (2022) examined cytokine levels following COVID-19 in patients during the acute stage of disease (n=92), PASC (n=135) and non-PASC (n=90) (sampling unclear, at least ≥1 month post-symptom onset).[13] Patients with PASC had elevated levels of IL-2, IL-4, IL-10 and IL-17, compared to the non-PASC group; there was no change in the levels of IL-6, IFN-γ and TNF-α.

Klein et al. (2022) (preprint) examined immune cell changes in a cross-sectional study of 217 patients sampled at least ≥3 months post-symptom onset (PASC, n=101; non-PASC, n=41; healthy controls, n=41) in the United States (USA).[7] Immune profiling revealed that levels of naïve B-cells and other B-cells did not differ between patients with PASC and the non-PASC group.

PASC VS. CONTROLS (UNINFECTED, HEALTHY, NON-COVID-19)

Four studies reported elevated $CD8^+$ T-cell levels in patients with PASC, compared to controls (uninfected, healthy, non-COVID-19); changes in $CD4^+$ T-cell levels were inconsistent among the studies.[4,6,9,10] For example, Santa Cruz et al. (2023) reported that patients with PASC had elevated $CD8^+$ T-cell levels compared to healthy controls ($p=0.0004$), no change in CD4+ T cells, and increased expression of PD-1 ($p<0.0001$), perforin ($p=0.014$) and granzyme B ($p=0.004$).[4] Elevated levels of IL-6, IL-8 and IP-10 during acute disease were associated with an increased risk of developing PASC ($p<0.0001$). There were decreased levels of $CD8^+\beta7Integrin^+$ in patients with PASC compared to healthy controls ($p=0.034$). The authors concluded that the decreased levels of $CD8^+\beta7Integrin^+$, along with increased expression of cytolytic proteins, indicated viral persistence and mucosal immune cell changes in patients with PASC and non-PASC. Similarly, in a case-control study (acute and hospitalized, n=57; convalescent [4–6 months post-discharge], n=39; healthy controls, n=43) performed in Italy, Loretelli et al. (2021) reported elevated levels of $CD4^+$ T-cells expressing $PD\text{-}1^+$ in patients with PASC, compared to healthy controls ($p<0.001$) and patients during acute disease ($p<0.05$).[5]

Seven studies reported elevated levels of pro-inflammatory cytokines and interferons (e.g., IL-6, IL-8, IFN-β, IFN-γ, IFN-λ2/3) in those with PASC, compared to controls (uninfected, healthy, non-COVID-19).[4,5,6,7,9-11] For example, Phetsouphanh et al. (2022) reported that the pro-inflammatory cytokines IFN-β ($p<0.0001$) and IFN-λ1 ($p<0.001$) were elevated in patients with PASC at 8-months post-symptom onset, compared to healthy controls. In the case-control study of Loretelli et al. (2021), IL-1β, IL-1RA, IL-7, IL-8, IL-10 and IFN-γ were significantly elevated ($p<0.05$) in patients with PASC and IL-9, macrophage inflammatory protein-1 beta (MIP-1β) and Eotaxin, significantly lower ($p<0.05$), compared to healthy controls; there was no change in several cytokine levels (e.g., IL-4, IL-6, IL-13, IL-17) in patients with PASC compared to healthy controls.[5] Santa-Cruz et al. (2023) reported that patients with PASC, compared to healthy controls, had elevated levels of IFN-β ($p=0.037$) and IFN-λ2/3 ($p=0.02$), with decreased levels of IFN-α2 ($p=0.004$).

Three studies examined levels of B cells in those with PASC, compared to controls (uninfected, healthy, non-COVID-19).[5-7] For instance, Shuwa et al. (2021) examined the functional and phenotypic characteristics of B cells in sera of 58 hospitalized patients with COVID-19 (sampled within 7 days and at discharge) and again at 3–6 months post-symptom onset in another unpaired cohort of 83 convalescent patients (United Kingdom [UK]).[6] There were no differences between acute and convalescent levels of unswitched memory B cells, switched memory B cells and naïve B cells. Any alterations in B cell subsets in acute stage returned to normal in convalescent stage.

Myeloid Cells

Key findings: Six studies described the changes in myeloid cell levels or myeloid cell marker levels following SARS-CoV-2 infection.[7,9,12-15] Studies demonstrated that there were elevated levels of intermediate and non-classical monocyte in those with PASC, compared to compared to controls (uninfected, healthy, non-COVID-19), along with their associated markers. The persistence of non-classical monocytes in PASC indicates continued inflammation, similar to that seen in chronic inflammatory diseases and other respiratory diseases.

REVIEWS

Three reviews reported increases in intermediate and non-classical monocytes following SARS-CoV-2 infection.[12,14,15] For example, in a review of 35 studies, Islam et al. (2023) reported that inflammatory markers like intermediate monocytes ($CD14^{+}CD16^{+}$), non-classical monocytes ($CD14^{lo}CD16^{+}$), cytokine markers (e.g., tumor necrosis factor [TNF], IL-10, IL-1β) and/or receptor markers (e.g., human leukocyte antigen DR [HLA-DR], CD14, C-X-C motif chemokine receptor 6) were higher in patients during the-post acute period (PASC, convalescent), compared to controls (non-PASC, healthy, acute disease).[12] One study demonstrated an increase in intermediate monocytes among those with PASC, compared to those with non-PASC at 8 months post-symptom onset. At ≥3 months post-symptom onset, 2/2 studies showed no change or a decrease in neutrophils during convalescence, compared to those with acute disease or healthy controls. Review authors propose there is long-term activation of non-classical monocytes following COVID-19.

PASC VS. NON-PASC

Two studies showed increased levels of non-classical monocytes in those with PASC, compared to those with non-PASC.[9,13] Queiroz et al. (2023) reported significantly elevated levels of the monocyte receptor marker TNF in patients with PASC, compared to patients with non-PASC.[13] Phetsouphanh et al. (2022) reported that patients with PASC, compared to patients with non-PASC, had elevated activated monocytes ($CD38^{+}HLA\text{-}DR^{+}$) and plasmacytoid dendritic cells (pDCs) ($p<0.01$).[9]

PASC VS. CONTROLS (UNINFECTED, HEALTHY, NON-COVID-19)

Klein et al. (2022) (preprint) reported that mean levels of non-classical monocytes ($CD14^{lo}CD16^{hi}$, $p=0.015$) were higher in patients with PASC (at 12 months since symptom-onset), compared to controls (uninfected, healthy, non-COVID-19).[7] Specifically, patients with PASC, compared to healthy controls, displayed elevated levels of maturing ($CD15^{+}$), HLA-DR-expressing non-classical monocytes ($p<0.01$). There was no statistical difference in mean levels of additional granulocyte cells in patients with PASC compared to healthy controls; e.g., neutrophils, eosinophils, classical and intermediate monocytes and pDC populations.

Autoimmune Conditions Following COVID-19: Incidence and Risk

Key findings: Nine studies examined incidence or risk of autoimmune conditions, autoantibody levels or autoreactivity levels following SARS-CoV-2 infection.[7,11,18-24] Two studies determined autoantibody or autoreactivity levels could not distinguish among those with PASC and non-PASC. The remaining studies found inconsistent changes in the risk of autoimmune conditions, autoantibody levels and autoreactivity levels in those with PASC or in controls (uninfected, healthy, non-COVID-19).

REVIEWS AND META-ANALYSES

A systematic review and a meta-analysis found no change in the risk of new-onset systemic lupus erythematosus (SLE) and arthritis following a SARS-CoV-2 infection.[18,21] In a meta-analysis of European cases and matched controls, Xu et al. (2023) reported that there were no increased risks of developing SLE for those that had any SARS-CoV-2 infection (odds ratio [OR]: 1.0; 95% CI: 0.70, 1.43; cases, n=38,984; controls, n=1,644,784), had severe COVID-19 (OR: 1.0; 95% CI: 0.86, 1.27; cases, n=5,101; controls, n=1,644,784) or were hospitalized for COVID-19 (OR: 0.9; 95% CI: 0.74, 1.03; cases, n=9,986; controls, n=1,877,672).[21] In a systematic review, Gracia-Ramos et al. (2021) reported on 99 patients with new-onset systemic and rheumatic autoimmune diseases following COVID-19.[18] Thirty-two patients developed arthritis, most diagnosed as isolated reactive arthritis (n=17), followed by peripheral spondyloarthritis (n=9) and rheumatoid arthritis (n=6). For the remainder of autoimmune findings, nine had idiopathic inflammatory myopathies, six had other rheumatic autoimmune diseases and four had SLE. The authors reported that rheumatic autoimmune diseases following SARS-CoV-2 infection were rare; however, due to the small sample size, an estimate of the population-wide prevalence of rheumatic diseases following SARS-CoV-2 infection was not possible.

PASC VS. NON-PASC

Two studies determined that autoantibody and autoreactivity levels could not distinguish among those with PASC and non-PASC.[7,24] In a matched cohort study (PASC, n=121; non-PASC, n=64; median age: 48 years) in the USA sampled at 2–8 months post-symptom onset, Bodansky et al. (2023) (preprint) reported on autoantibodies and their potential role in patients with PASC.[24] Autoreactivity signatures (peptide enrichment) could not distinguish between patients with PASC and non-PASC. In addition, Klein et al. (2022) (preprint) reported no statistical difference in autoantibody levels against the extracellular proteome among those with PASC and non-PASC.[7]

PASC VS. CONTROLS (UNINFECTED, HEALTHY, NON-COVID-19)

Three studies demonstrated increased risk of autoimmune conditions, autoantibody levels and autoreactivity levels in patients with PASC, compared to controls (uninfected, healthy, non-COVID-19).[19,22,24] For example, in a cohort study matched on sex and age (infected and immune mediated inflammatory diseases [IMID]-naive, n=458,147; non-COVID-19 controls, n=1,818,929; adults >18 years old) in the UK, Syed et al. (2022) (preprint) examined the incidence of IMIDs at a median 0.3 person-years (interquartile range [IQR]: 0.24, 0.42) following COVID-19 diagnosis.[19] The incidence of any IMID increased in those with previous COVID-19 (3.5 per 1,000 person years), compared to controls (2.8 per 1,000 person years), for an increased risk of developing IMID (adjusted hazard ratio [aHR]: 1.2; 95% : 1.10, 1.34). Patients with previous SARS-CoV-2 infection had an increased risk, compared to controls, of developing type 1 diabetes (aHR: 1.6; 95% CI: 1.09, 2.23), inflammatory bowel disease (aHR: 1.5; 95% CI: 1.23, 1.88) and psoriasis (aHR: 1.2; 95% CI: 1.05, 1.42). In addition, Lavi et al. (2023), in a cross-sectional study (n=246) in the USA, reported on neuronal and CNS autoantibody levels post-symptom onset (mean range: 54–60 days) in 169 patients with PASC and 77 healthy controls.[22] Patients with SARS-CoV-2 exposure, compared to healthy controls and independent of disease severity, showed changes in IgA and IgG

autoantibodies against numerous epitopes (e.g., N-methyl D-aspartate receptor, dopamine 1 receptors, α-synucleins, amyloid β peptide). The authors suggest that changes in the levels of these autoantibodies are responsible for the clinical manifestations seen in PASC (e.g., cognition, memory and emotional disturbances).

COVID-19 CONVALESCENCE VS. CONTROLS (UNINFECTED, HEALTHY, NON-COVID-19)

In three studies, the risk of new-onset autoimmune conditions was not significantly different among convalescent patients <3 months following COVID-19 and controls (uninfected, healthy, non-COVID-19.[11,20,23] For instance, in a retrospective observational cohort of children and adults in Region Skåne, Sweden (population: 1.4 million in 2021), Lexnar et al. (2023) examined celiac disease incidence in 2016 (non-COVID-19 controls) and 2021 (patients with COVID-19).[23] The incidence of verified celiac disease with and without previous COVID-19 was 21.1 and 22.4 per 100,000 person-years, respectively, with no change in risk (incidence rate difference: -1.3; 95% CI: -8.5, 5.9). Researchers diagnosed 50% (284/568) of patients with celiac disease within 6 months of SARS-CoV-2 infection, the remainder diagnosed in following the 6 months. In addition, Zareini et al. (2023) performed a nested case-control study following young adults <30 years old from 2015 through 2021 in Denmark.[20] Each COVID-19 case (n=338,670) was matched to three healthy controls (n=1,004,688) based on age, sex and vaccination status, with observations at a median of 42 days (IQR: 11, 225) since diagnosis of COVID-19. Prior SARS-CoV-2 infection was not associated with an increased risk of developing type 1 diabetes, compared to patients without SARS-CoV-2 infection (HR: 0.90; 95% CI: 0.60, 1.35).

Discussion

In this review, we explored the long-term impacts of COVID-19 on the immune response. In patients with PASC, CD8+ T-cell and non-classical monocyte levels were higher at least 3 months after symptom onset compared to control groups. $CD8^+$ T-cells in PASC cases also had elevated expression of cytotoxic immune modulators such as IL-6, PD-1 and IL-8 compared to non-PASC patients and/or healthy controls. We found conflicting evidence on $CD4^+$ T cell and B cell changes between disease states. The majority of studies found no evidence for the increased incidence and risk of new-onset autoimmune diseases (e.g., arthritis, celiac disease, SLE, type 1 diabetes).

We should highlight that changes in immune cells following infection is not unique to SARS-CoV-2. Persistence of elevated CD8+ T cells and non-classical monocytes occurs in chronic inflammatory diseases (atopic dermatitis, arthrosclerosis, cardiovascular disease, rheumatoid arthritis) and with other respiratory pathogens (e.g., influenza A virus, respiratory syncytial virus).[25-28] While not fully understood, persistence of elevated CD8+ T cells are potentially involved in immunopathology following respiratory infections.[29]

Limitations

This synthesis provides a summary of a limited number of studies with sample sizes ≥99, which we drew from a much larger body of evidence comprised mostly of smaller, uncontrolled, retrospective, observational studies. The relatively small sample sizes of the included studies limit their generalizability and power to draw meaningful conclusions. While including smaller studies may have increased the body of evidence, we feel this would not have resulted in increased certainty of the results.

Heterogeneity between and within studies is a major limitation in this review. Study-specific limitations to consider in when interpreting results of this synthesis include the following themes:

- **PASC definition and methodology:** How authors diagnosed or defined PASC varied among the included studies, leading to different case classifications.[7,9] While some studies may consider viral persistence in mucosa or specific tissues as pivotal disease markers of PASC, others looked at perforin expression in $CD8^+$ T cells. The types of cell changes and markers considered in each study, how those changes were measured and post COVID-19 follow-up times varied between studies.[10] Identification and isolation of T_{regs} is challenging because markers expressed by these cells are not exclusive and, while recommendations exist to help with the detection and phenotyping of T_{regs}, not all the included studies followed the same guidelines.[1] Since there is no established standard for a clinically-significant impact on immune cells, findings in this review are not always comparable among studies. Immune system response and PASC incidence and duration may vary depending on circulating SARS-CoV-2 variants of concern (VOCs), but not explored in the included studies.[1,12] Additionally, the time period measuring onset of PASC also varied between studies.
- **Disease severity:** Severity was characterized by self-reported symptoms, clinical diagnoses and the proportion of patients hospitalized, leading to heterogeneity among studies increased bias, making it difficult to appropriately match study arms.[6]
- **Observational studies:** Given the novelty of COVID-19 and our poor understanding of resulting immune response, most studies were retrospective, exploratory and not necessarily designed to demonstrate changes in immune cells over time or the factors contributing to immune cell changes.[1,4,6]
- **Confounding:** Confounding was not accounted for in all studies, meaning differences between study groups may have been due to other factors aside from SARS-CoV-2.[10]
- **Small sample size:** The small sample sizes and lack of consistent longitudinal follow-up of patients make it difficult to generalize the results. Small sample sizes also meant that the racial and social makeup of participants was not uniform among studies, with some studies having primarily white participants.
- **Comparator:** The comparison groups amongst studies were diverse with some studies considering healthy controls who were not infected with COVID-19 as their comparator arm and others including COVID-19 recovered individuals without any long-term symptoms as their control group. Moreover, the available literature did not compare PASC individuals to those infected with other respiratory viruses or other infections that generate sequelae.

Conclusions and Public Health Implications

SARS-CoV-2 infection is associated with changes in some immune cell levels 3 months post-symptom onset; however, the clinical significance between these observations and PASC requires further research. Long-term impacts on immune cells following COVID-19 highlights the continued importance of promoting COVID-19 vaccination and other infection prevention measures that facilitate reductions in transmission and incidence of SARS-CoV-2 (e.g., paid sick time, masking, layering of measures). Minimizing SARS-CoV-2 infections remains an important public health goal to limit acute and long-term health impacts at the population level, and the associated burdens on both primary care and public health resources, especially for populations more susceptible to severe COVID-19 disease.

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Citation

Ontario Agency for Health Protection and Promotion (Public health Ontario). Evidence for long-term impacts of COVID-19 on immune cells and autoimmune conditions in adults – what we know so far. Toronto, ON: King's Printer for Ontario; 2023.

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