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Systematic Review/Meta-analysis

Impact of Long COVID-19 on Health Outcomes Among Adults With Preexisting Cardiovascular Disease and Hypertension: A Systematic Review

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ABSTRACT

Background: This review summarizes the impact of long COVID (LC) on the health of adults with preexisting cardiovascular disease (CVD) and hypertension.

Methods: We searched Medline, Web of Science (Core Collection), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), without language restrictions, for articles published from December 1, 2019 through October 10, 2023, to ensure all relevant studies were captured. We included studies that enrolled adults (aged ≥18 years) diagnosed with CVD prior to COVID-19 infection whose infection was subsequently determined to be LC per the World Health Organization definition. We excluded studies with adults diagnosed with CVD concurrent with or subsequent to COVID-19 or with those who solely self-reported LC. We used a custom-built data extraction form to collect a range of study characteristics. Study quality was assessed using modified versions of the National Heart, Lung, and Blood Institute quality-assessment tools.

Results: A total of 13,779 studies were identified; 53 were included in the final analysis. Of these, 27 were of good quality and 26 were of fair

RÉSUMÉ

Contexte : Cette analyse résume les effets de la COVID longue sur la santé des adultes présentant une maladie cardiovasculaire et une hypertension préexistantes.

Méthodologie : Nous avons interrogé les bases de données Medline, Web of Science (Core Collection) et Cumulative Index to Nursing and Allied Health Literature (CINAHL), sans restriction quant à la langue, pour répertorier les articles publiés entre le 1er décembre 2019 et le 10 octobre 2023 et nous assurer que toutes les études pertinentes étaient prises en compte. Nous avons inclus les études portant sur des adultes (≥ 18 ans) qui ont reçu un diagnostic de maladie cardiovasculaire avant un diagnostic de COVID-19 et chez qui l'infection s'est ensuite transformée en COVID longue selon la définition de l'Organisation mondiale de la Santé. Nous avons exclu les études portant sur les adultes ayant reçu un diagnostic de maladie cardiovasculaire au même moment qu'un diagnostic de COVID-19 ou après l'infection, ou sur ceux qui ont signalé eux-mêmes souffrir de COVID longue. Nous avons utilisé un formulaire personnalisé d'extraction des données pour recueillir un ensemble de caractéristiques

COVID-19 is a highly contagious respiratory illness.[1] In December 2019, the World Health Organization (WHO) declared the disease a Public Health Emergency of International Concern, before moving to formally proclaim it a pandemic on January 30, 2020.[2] Initially, the cause was described as simply a "novel coronavirus," which was later identified as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1]

COVID-19 presents with a wide spectrum of symptoms, including cough, sore throat, fever, diarrhea, headache, muscle and joint pain, fatigue, and loss or disturbance of taste and/or smell.[3-5] The symptoms of COVID-19 can also extend beyond those that occur in the initial period, to include respiratory (eg, dyspnea, diminished exercise capacity), cardiovascular (eg, heart palpitations, chest pain), and neurologic symptoms (eg, confusion, disorientation).[5] Several names have been used to describe these prolonged symptoms, including post-COVID-19 syndrome, post-COVID-19 sequelae of SARS-CoV-2 infection, and, perhaps most commonly, "long COVID." (LC)[5,6]

A clinical definition of LC that includes 12 domains and is suitable for use in all settings was developed by the WHO in 2021, using the Delphi methodology.[6] Under this definition, LC is defined as the presence of persisting symptoms occurring at least 3 months after the initial onset of the disease, lasting for at least 2 months, that cannot be explained by any alternative diagnosis.[6] The condition generally affects daily functioning, with symptoms such as fatigue, shortness of breath, and cognitive impairment.[6] Symptoms may be new after recovery from an acute COVID-19 episode or persist from the time of the initial infection. Symptoms also can fluctuate or relapse over time.[6]

Among individuals with SARS-CoV-2 infection, cardiovascular disease (CVD) is a common comorbidity.[7-10] In addition, evidence indicates that CVD, which is the leading

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quality. Health outcomes consisted of the presence of prolonged symptoms of LC (n = 29), physiological health outcomes (n = 20), lifestyle behaviours (n = 19), psycho-social outcomes (n = 13), CVD complications (n = 5), and death and hospital readmission (n = 5). Thirty-four studies incorporated 2 or more outcomes, and 19 integrated only 1.

Conclusions: Given the significant impact of LC among individuals with preexisting CVD, specially tailored clinical management is needed for members of this population. Additional studies on the impact of LC among those with CVD and other underlying conditions also would be beneficial.

des études. La qualité des études a par ailleurs été évaluée à l'aide de versions modifiées des outils d'évaluation de la qualité du National Heart, Lung, and Blood Institute.

Résultats : Au total, 13 779 études ont été relevées; 53 ont été incluses dans l'analyse finale. Parmi celles-ci, 27 étaient de bonne qualité et 26 étaient de qualité acceptable. Les issues comprenaient la présence de symptômes persistants de COVID longue (n = 29), des problèmes de santé physiologiques (n = 20), des changements d'habitudes de vie (n = 19), des problèmes psychosociaux (n = 13), des complications découlant de la maladie cardiovasculaire (n = 5) et des décès ou des réadmissions à l'hôpital (n = 5). En tout, 34 études portaient sur au moins 2 issues, et 19 n'en intégraient qu'une seule.

Conclusions : Étant donné l'effet notable de la COVID longue chez les personnes présentant une maladie cardiovasculaire préexistante, une prise en charge clinique adaptée est nécessaire dans cette population. Il y aurait également lieu de mener d'autres études sur les effets de la COVID longue chez les personnes atteintes de maladies cardiovasculaires et d'autres maladies sous-jacentes.

cause of death worldwide,[11] has been associated with greater severity of COVID-19.[12,13] A study of comorbid diseases among 202,005 patients with COVID-19 found that those with CVD had a relatively higher mortality rate, compared to that for other comorbid conditions.[14]

Despite this identified impact of CVD on the clinical course of COVID-19, studies examining the health effects of LC among adults with preexisting CVD have been scarce. Given the high prevalence of CVD, a review examining this population is necessary. Therefore, we conducted a systematic review of the published literature, to identify the impact of LC on health outcomes among adults with preexisting CVD, broadly defined in alignment with the WHO's clinical definition,[15] including hypertension as the risk factor with the strongest causal association with development of CVD.[16]

Methods

We undertook a comprehensive search using a systematic approach following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[17] The review was pre-registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42022331549) on May 9, 2022, with updates made on: July 5, 2022; August 10, 2022; December 12, 2022; and December 21, 2023. Relevant articles were identified by conducting a literature search using the MEDLINE, Web of Science (Core Collection), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. The initial search included articles indexed from December 1, 2019 through May 16, 2022. Given the rapidly changing evidence base in this area, an updated search was conducted on October 10, 2023, to include articles indexed between May 17, 2022 and that date. Search terms for the identification of relevant studies were developed by all 3 members of the research team, in consultation with a research librarian, and no language restrictions were placed on included studies.

Using both Medical Subheadings (MeSH) and keywords (see Supplemental Appendix S1), we searched for articles using the following inclusion criteria:

1. Studies that included adults (aged $\geq$ 18 years) diagnosed with CVD prior to SARS-CoV-2 infection, and whose infection was subsequently determined to qualify as LC, were eligible for inclusion. Studies that included only adults diagnosed with CVD concurrent with or subsequent to a COVID-19 diagnosis were excluded. Key criteria used to guide our selection of studies with a LC diagnosis were the timing (at least 3 months following initial diagnosis or symptoms), duration (for at least 2 months), and effects (a detrimental impact on "everyday functioning"), recognizing its role as a potential source of bias.
2. LC must have been diagnosed formally by a qualified medical provider during the course of medical treatment or as part of a research program. Studies that relied solely on self-reported diagnoses were excluded. For studies in which the definition of LC was unspecified, and those published before the concept of LC was clarified, we applied the WHO's clinical case definition, as published on October 6, 2021, as follows: "Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and persist for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time."[6]
3. Study types other than full-length research articles or publications with original epidemiologic data were excluded (including protocols, clinical trials registries, laboratory-based studies, and commentaries); in addition, publications based on a single case (ie, case studies), reviews (including systematic reviews, narrative reviews, and meta-analyses), and qualitative analyses, correspondences, letters, preprints, and the grey literature were excluded. Due to the large number of studies identified through the standard searches, we did not carry out any backward citation-tracking.

4. No restrictions were placed on the language of a publication during the title and abstract review process, but only reports in English were eligible for full-text review.

After each search, duplicates were removed using Zotero (Roy Rosenzweig Center for History and New Media, George Mason University, Fairfax, VA) (Fig. 1). Title and abstract screening were conducted independently by 2 authors (T.B.D. and E.J.R.), and any questions regarding a study's inclusion were discussed with the other team member (S.A.L.). The full text of each study selected for inclusion was screened and assessed by all 3 review team members (T.B.D., E.J.R., and S.A.L.), with any resulting disagreements about the inclusion of a study being determined through consensus.

Data were extracted using a custom-built extraction form adapted from earlier reviews[18] and pilot-tested by T.B.D. and E.J.R. on a set of 3 studies each. Resulting changes to the form were noted as a revision to the protocol available through

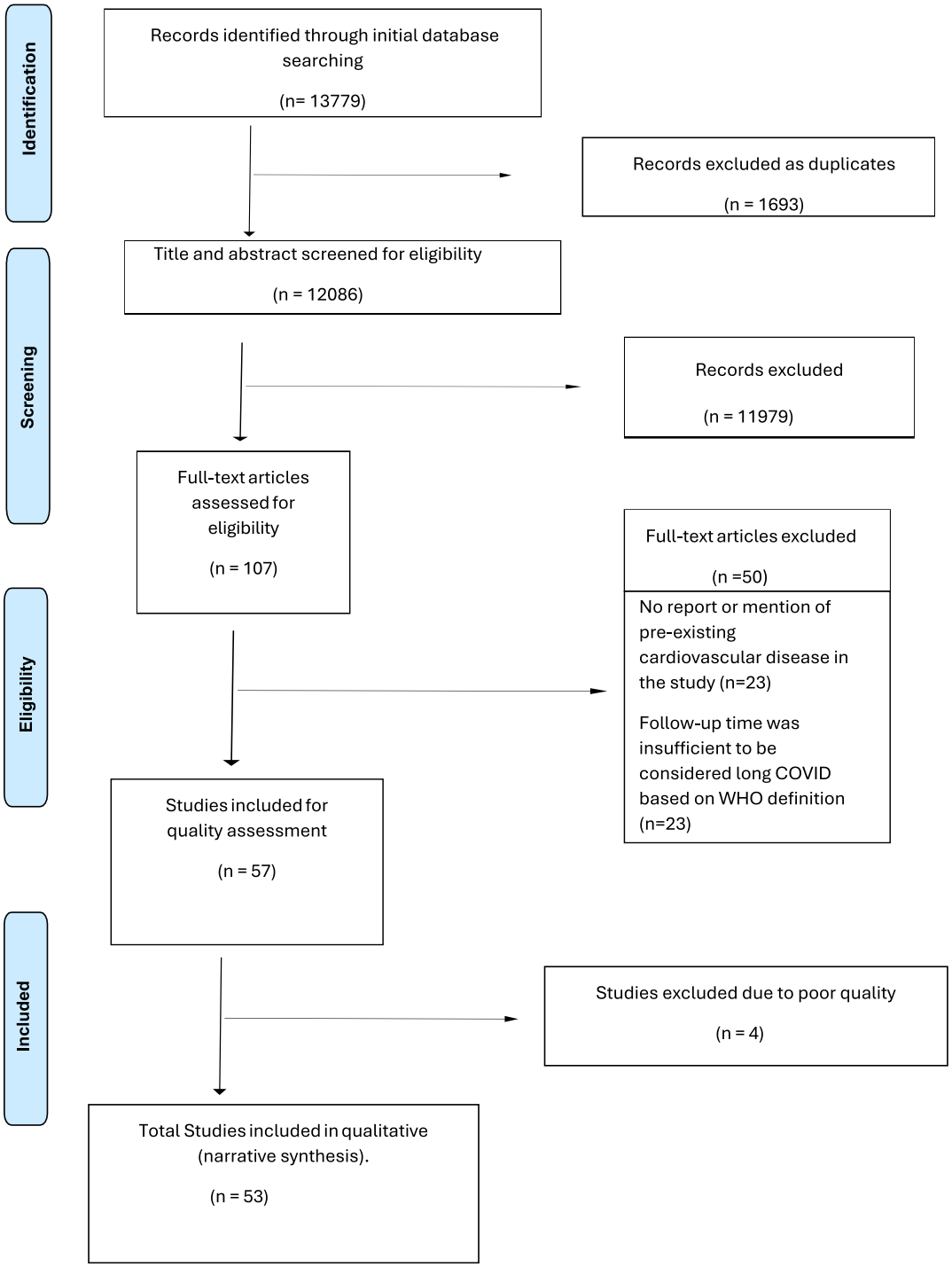

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. WHO, World Health Organization.

PROSPERO on August 10, 2022. The data-extraction step was carried out independently by a single member of the study team. The final version of the data-extraction form collected information on the following: author(s), study design, population, study characteristics, study bias, health outcomes, and results. A template version of this form may be found in Supplemental Appendix S2. Quality assessment was performed by 2 independent reviewers, with any conflicts being resolved through a discussion with the third review team member, using a modified version of The National Heart, Lung, and Blood Institute (NHLBI) quality-appraisal tool appropriate for the study's design (cohort and/or cross-sectional, case-control, or pre-post). This tool grades observational studies on several important criteria, including a clearly stated research objective, sample-size justification, validity of exposure and outcome measures, and the inclusion of potential confounding variables in statistical analyses. After pilot-testing the NHLBI tools on a small sample of studies representing the full range of study designs, the templates were modified to exclude the following 3 items for which the answers were previously determined as part of the study selection process: (i) "for the analyses in this paper, were the exposure(s) of interest measured prior to the outcomes(s) being measured?"; (ii) "was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?"; and (iii) "for exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome?". These changes reflect the following facts: (i) the exposure of interest (SARS-CoV-2 infection that subsequently developed into LC) always predated the outcome (sequelae of LC); (ii) the WHO definition we relied upon delineates the sufficient timeframe ("3 months from the onset of COVID-19"); and (iii) although an individual's case of COVID-19 can vary in severity, being diagnosed with or without a SARS-CoV-2 infection at a particular point in time is binary in nature. Tables 1-3 detail the complete list of checklist items for the 3 tools relevant to our included studies—cohort and/or cross-sectional, case-control, and pre-post, respectively.

Each of the included studies was given an overall rating of either good quality, fair quality, or poor quality. The **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses (PRISMA) flow diagram (Fig. 1) details the number of studies excluded at each stage of the review process, as well as the reasons behind the exclusion. We further excluded studies we defined as being of poor quality from the narrative synthesis, in line with prior research that has demonstrated that this step increases the robustness of such synthesis, without reducing richness.[19]

The final set of 53 included studies was categorized based on included health outcomes, with the identification of outcomes and their grouping into categories carried out by the full study team (Supplemental Table S1).

Because we were interested in the full spectrum of LC sequelae, no restrictions were placed on the outcomes included within individual studies. Due to the heterogeneity of these identified outcomes, no meta-analysis was conducted; in addition, the number of studies within any individual outcome group was insufficient to carry out any analysis of subgroups or subsets. Instead, the results below present a narrative analysis of findings across studies by outcome.

Table 1. Modified National Heart, Lung, and Blood Institute quality-assessment tool for observational cohort and cross-sectional studies

Criteria
1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Were a sample-size justification, power description, or variance and effect estimates provided?
6. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
7. Was the exposure(s) assessed more than once over time?
8. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
9. Were the outcome assessors blinded to the exposure status of participants?
10. Was loss to follow-up after baseline 20% or less?
11. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Results

Study characteristics and risk of bias

The 53 studies were conducted in 21 countries—7 in Spain; 7 in the US; 6 in Italy; 4 each in China and Poland; 3 each in Saudi Arabia and the United Kingdom; 2 each in India, Brazil, Greece, Turkey, and France; and 1 each in Austria, Bangladesh, Denmark, Egypt, Germany, Hong Kong, The Netherlands, Philippines, and Switzerland. The most-common study designs were prospective cohort (43%) and cross-sectional (23%); 19% used case-control approaches, 11% used a retrospective cohort design, 1 study was longitudinal (2%), and 1 was a pre-post study (2%). The sample size of included studies ranged from 28 to 1,833,788 participants, with a median of 388,457.

After assessing the quality of our included studies via the appropriate adapted version of the NHLBI tools, 27 studies were found to be of good quality, 26 were of fair quality, and 4 were of poor quality. Within this final set, Pretorius et al. failed to include a clear objective and lacked critical details on a number of important aspects of study methodology, including recruitment and analyses.[20] Araz et al. was unclear with respect to case definitions and the selection of controls, as well as integration of an unadjusted analytic approach.[21] Rinaldi et al. lacked sufficient details on recruitment methodology, failed to specify how 1 of the 2 primary outcomes (all-cause mortality) was assessed, and lacked details on both what confounders were included and how they were measured.[22] Wang et al. suffered from a number of serious methodologic flaws, including unclear reporting (particularly with respect to their recruitment methodology, assessment of comorbidities, and statistical analyses), a simplistic analytic approach, and inconsistent outcome data assessment.[23] See Figure 2 for the complete quality-assessment results for cohort and cross-sectional studies; see Figure 3 for case-control studies; and see Figure 4 for the single pre-post study.

Assessment of preexisting CVD

Pre-existing CVD was assessed within the included studies in a multitude of ways. In studies that included a participant

Table 2. Modified National Heart, Lung, and Blood Institute quality-assessment tool for case-control studies

Criteria
1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Did the authors include a sample-size justification?
4. Were controls selected or recruited from the same population or one similar to the one that gave rise to the cases (including the same timeframe)?
5. Were the definitions, inclusion and exclusion criteria, algorithms, or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?
6. Were the cases clearly defined and differentiated from controls?
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?
8. Were concurrent controls used?
9. Were the investigators able to confirm that the exposure and/or risk occurred prior to the development of the condition or event that defined a participant as a case?
10. Were the measures of exposure and/or risk clearly defined, valid, reliable, and implemented consistently (including in the same time period) across all study participants?
11. Were the assessors of exposure and/or risk blinded to the case or control status of participants?
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?

Table 3. Modified National Heart, Lung, and Blood Institute quality-assessment tool for pre-post studies

Criteria
1. Was the study question or objective clearly stated?
2. Were eligibility and/or selection criteria for the study population prespecified and clearly described?
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?
4. Were all eligible participants that met the prespecified entry criteria enrolled?
5. Was the sample size sufficiently large to provide confidence in the findings?
6. Was the test/service/intervention clearly described and delivered consistently across the study population?
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
8. Were the people assessing the outcomes blinded to the participants' exposures and/or interventions?
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided *P* values for the pre-to-post changes?
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (ie, did they use an interrupted time-series design)?
12. If the intervention was conducted at a group level (eg, a whole hospital, a community, etc.), did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

population with other comorbidities, preexisting CVD was defined as having one or more of the following conditions: hypertension, chronic heart failure, coronary heart disease, atrial fibrillation, peripheral vascular disease, or other CVD prior to COVID-19 infection within the participant population, as seen in 15 studies.[24-38] Preexisting CVD was also identified and assessed based on a medical evaluation conducted by healthcare professionals in 5 studies[39-43] and from medical records at the location where study participants were recruited in another 14 studies.[27,44-56] Prehospitalization hypertension diagnoses were also integrated in 2 studies, based on records collected prospectively.[57,58] Seventeen studies did not adequately report the assessment of CVD in detail, but preexisting CVD was listed in the studies' demographic details.[56,59-74]

SARS-COV-2 diagnoses

In 33 studies, COVID-19 was diagnosed either by polymerase chain reaction (PCR) or reverse transcription-polymerase chain reaction test (RT-PCR),[25,26,29-31,33-37,39,41-43,46-50,54,55,57,60-66,68-70,72] whereas a smaller set of 13 studies relied on PCR-based diagnoses captured in medical records.[27,32,38,44,45,51-53,56,71,73-75] The precise nature of the diagnosis was unclear or not reported in 7 studies.[24,28,40,58,59,67,76]

Follow-up time

In the majority of studies, 25 in all, the follow-up time used to assess the outcome measure was between 3 and 6 months.[26-28,30,31,37,39,40,42,43,45,46,49,50,53-55,58,59,65,67,68,72,73,76] Twenty-four studies reported a follow-up time longer than 6 months[24,25,29,32-36,38,44,47,48,51,52,56,57,60-62,64,70,71,74,75] and 4 studies reported a follow-up time of less than 3 months.[41,63,66,69]

Health outcomes

Health outcomes consisted of the presence of prolonged symptoms of LC (n = 29), physiologic health outcomes (n = 20), lifestyle behaviours (n = 19), psycho-social outcomes (n = 13), CVD complications (n = 5), and death and hospital readmission (n = 5). A total of 34 studies incorporated 2 or more outcomes, and 19 integrated only 1.

Prolonged symptoms of LC. A range of prolonged symptoms were reported in the 29 studies. These symptoms included loss of smell (anosmia), loss of taste (ageusia), sore throat, smell disorder, headaches, low-grade fever, chest and joint pain, weight and muscle loss, breathlessness, cold limbs, and gastrointestinal symptoms, including diarrhea, arthralgia, nausea, decreased appetite, vomiting, and abdominal pain. Fatigue was the most-reported persistent symptom, noted in 17 separate studies.[27,28,30,39,41-43,45,46,53,57,62,66,68,69,72,74] Prolonged symptoms generally were reported to persist more often among individuals who were hospitalized initially,[24,28,30,34,36,38,39,41,43,50,52-54,57,62,66,70-72] particularly those with preexisting hypertension.[28,66] The persistent nature of these symptoms adversely impacted patients' quality of life, and resulted in an increase in pulmonary, cardiac, and vascular complications.[28,36,41,51,53,62,66,69,72] Some of the complications reported included dyspnea, heart palpitations, cardiac injury, and symptomatic myocarditis.[26,29,46,53,57,69]

Physiological health outcomes. Biomarker levels, including inflammation parameters (such as C-reactive protein [CRP], interleukin (IL)-6, and ferritin) and D-dimer, were reported in 4 studies to have slight, persistent alterations in individuals

Authors	Checklist items											Score
	1	2	3	4	5	6	7	8	9	10	11	
Shuakla et al.[24] (2023)	Y	Y	Y	Y	Y	CD	N	N	CD	NA	NA	Fair
Fortini et al.[39] (2021)	Y	Y	Y	Y	N	Y	N	Y	N	Y	CD	Fair
Aparisi et al.[59](2021)	Y	Y	NR	Y	N	Y	Y	Y	N	N	NA	Good
Izquierdo et al.[25](2021)	Y	Y	Y	Y	N	Y	N	Y	N	Y	NR	Good
Cecchetto et al.[44](2023)	Y	Y	NR	Y	Y	Y	Y	Y	N	N	NA	Fair
Chathoth et al.[45](2023)	Y	Y	NR	Y	N	Y	N	CD	N	N	N	Good
van Bakel et al.[61] (2022)	Y	Y	NR	Y	N	Y	N	Y	N	N	NA	Good
Di pentima et al. [46](2023)	Y	Y	NR	Y	N	Y	N	Y	N	NR	NA	Fair
Lemhöfer et al.[40] (2023)	Y	Y	NR	Y	N	Y	N	Y	N	N	NA	Fair
Almutair et al.[47] (2022)	Y	Y	Y	Y	Y	Y	Y	Y	N	NR	Y	Good
de Miranda et al.[62] (2022)	Y	N	NR	Y	N	Y	N	Y	N	NR	N	Fair
Righi et al.[63](2021)	Y	Y	Y	Y	N	Y	N	Y	N	Y	NR	Good
Monzon & Li [26](2023)	Y	Y	NR	Y	Y	Y	N	N	NR	NR	N	Fair
Pretorius et al.[20](2022)	N	N	NR	NR	N	N	N	N	N	NR	NA	Poor
Beghi et al.[75] (2022)	Y	Y	NR	Y	Y	Y	N	Y	N	N	Y	Good
Kalamara et al.[27](2022)	Y	Y	NR	Y	N	Y	N	Y	N	NR	Y	Fair
Dorelli et al.[58] (2021)	Y	N	CD	Y	N	N	N	Y	N	CD	N	Fair
Tleyjeh et al.[28] (2021)	Y	Y	Y	Y	N	Y	N	Y	N	N	Y	Good
Tleyjeh et al.[65](2022)	Y	Y	CD	Y	N	Y	N	Y	N	N	Y	Good
Akova & Gedikli[66](2022)	Y	Y	NR	Y	Y	Y	N	Y	N	N	Y	Fair
Galal et al.[41] (2021)	Y	Y	NR	Y	Y	Y	N	Y	N	Y	N	Fair
Szoltysek-Boldys et	Y	Y	Y	Y	Y	Y	N	Y	NR	Y	Y	Good
Lapa et al.[50] (2023)	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Good
Zhang et al.[30](2022)	Y	Y	NR	Y	Y	Y	Y	Y	NR	NR	Y	Good
Bamps et al.[51](2023)	Y	Y	N	Y	Y	Y	N	Y	CD	NA	NA	Good
Schouborg et al.[32] (2022)	Y	Y	Y	Y	N	Y	N	Y	N	Y	Y	Good
Pływaczewska-Jakubowska et al.[68] (2022)	Y	N	NR	NR	N	Y	N	N	CD	NR	NA	Fair
Wieteska-Miłek et al.[42] (2023)	Y	Y	Y	Y	N	Y	N	Y	N	Y	NA	Fair
Imamura et al.[34] (2023)	Y	Y	NR	Y	Y	Y	N	Y	NR	NA	NA	Good
Chudzik et al.[52] (2022)	Y	Y	NR	Y	Y	Y	N	N	CD	NR	Y	Fair
Horberg et al.[35] (2022)	Y	Y	Y	Y	Y	Y	Y	Y	N	NR	Y	Good
Maestre-Muñiz et al.[69](2021)	Y	Y	Y	Y	N	Y	N	Y	N	N	N	Fair
Belkacemi et al.[36](2022)	Y	Y	Y	Y	Y	Y	N	N	N	N	CD	Fair
Nguyen et al.[70](2022)	Y	Y	Y	Y	Y	CD	N	Y	NR	NA	NA	Fair
Ogungbe et al.[71](2022)	Y	Y	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Sibila et al.[72] (2022)	Y	Y	Y	Y	N	Y	N	Y	N	Y	N	Fair
Xiong et al.[53] (2021)	Y	Y	Y	Y	N	Y	N	Y	N	N	N	Fair
Rinaldi et al.[22](2022)	Y	Y	NR	Y	Y	Y	N	N	CD	NR	NR	Poor
Salihi et al.[37](2021)	Y	Y	Y	Y	N	Y	N	Y	N	CD	N	Fair
Zisis et al.[38] (2022)	Y	Y	Y	Y	NR	Y	Y	Y	NR	N	N	Good
Wang et al.[23] (2022)	N	Y	NR	Y	N	N	N	N	N	NA	NA	Poor
Chowdhury et al.[43] (2021)	Y	Y	Y	Y	N	Y	N	N	N	Y	N	Fair
Bai et al.[73] (2022)	Y	N	Y	Y	N	N	N	Y	N	Y	N	Fair
Chen et al.[74](2022)	Y	Y	Y	Y	N	Y	N	Y	N	N	N	Good
Akhtar et al.[56] (2022)	Y	Y	Y	Y	Y	N	N	CD	NR	Y	NA	Fair

Figure 2. Quality assessment of included cohort and cross-sectional studies. CD, cannot determine; N, no; NA, not applicable; NR, not reported; Y, yes.

Study Authors	Checklist items												Score
	1	2	3	4	5	6	7	8	9	10	11	12	
Zheng et al.[60] (2023)	Y	Y	N	Y	Y	Y	NR	Y	Y	Y	N	Y	Good
Fernández-de-Las-Peñas et al.[57] (2022)	Y	Y	N	Y	Y	Y	Y	NR	N	Y	N	Y	Fair
Guardino et al.[48] (2023)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Good
Joy et al.[64] (2021)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	NA	Good
Lam et al.[29] (2023)	Y	Y	CD	Y	Y	Y	Y	Y	Y	Y	CD	Y	Good
Aranyó et al.[67] (2022)	Y	Y	N	Y	N	N	NR	Y	Y	CD	N	N	Fair
Vonbank et al.[31] (2021)	Y	Y	N	Y	Y	Y	Y	Y	N	Y	N	N	Fair
Araz et al.[21] (2022)	Y	Y	N	N	Y	Y	Y	N	N	Y	N	N	Poor
Sedgley et al.[54] (2023)	Y Y	Y	N	Y	Y	Y	CD	Y	Y	Y	N	Y	Good
Venkatakrishnan et al.[55] (2021)	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	N	NR	Good
Al-Aly et al.[76] (2021)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Good

Figure 3. Quality assessment of included case-control studies. CD, cannot determine; N, no; NA, not applicable; NR, not reported; Y, yes.

with preexisting CVD.[34,39,59,67] Other studies reported changes in blood pressure and cardiac biomarkers, as well as impaired pulmonary and cardiac function.[25,31,32,34,37,39,44,49,58,59,62,64,65,72,73,76] Pulmonary function was determined by forced expiratory volume (FEV1) and forced vital capacity (FVC) in 2 studies,[58,72] which reported that patients with preexisting CVD had one or more abnormal lung-function values, compared to those of patients without preexisting CVD. Eight studies also reported a lower value in vital capacity and FVC, FEV1 and/or FVC, total lung capacity, residual volume, and diffusing capacity for carbon monoxide among adults with preexisting CVD, compared to the values for those without it, as well as the persistence of varying degrees of exertional dyspnea.[31,32,39,58,59,65,72,73] Five studies that integrated echocardiography[25,56,67] and echocardiograms at 6-month follow-up revealed that study participants with myocardial injury had significantly thicker walls of the heart, higher levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and elevated high-sensitivity cardiac troponin (hs-cTn) levels,[25,44,76] which indicate the presence of impaired cardiac function, and in severe cases, these factors can lead to heart failure.

Lifestyle behaviours/outcomes. Cardiopulmonary peak oxygen consumption (VO2) according to cardiopulmonary exercise testing,[59] metabolic equivalent of task (MET) score,[31,65] and 6-minute walking distance[24,44,58,67] were used to assess exercise tolerance in 6 studies. Exercise tolerance was observed to be below average or poor among individuals with preexisting CVD, compared to the level among participants without CVD.[31,65] Cardiopulmonary peak VO_2 also was found to be lower than the population average, especially among those who experienced persistent dyspnea post-COVID, as compared to individuals in the broader population (ie, patients without SARS-CoV-2 infection who did not require hospital admission).[24,60] Patients with LC who had symptomatic preexisting CVD also recorded a shorter distance in the 6-minute walking distance assessment in 4 studies,[44,58,59,67] presenting a positive correlation with the peak VO_2. In a study carried out by Dorelli et al.,[58] aerobic capacity at 6 months following COVID-19 infection (as captured via an exercise stress test carried out using a cycle ergometer) was reported to be lower among participants who had more severe cases, compared to the capacity among those with mild COVID-19 cases. One study also found reduced

Study Authors	Checklist items												Score
	1	2	3	4	5	6	7	8	9	10	11	12	
Gounaridi et al.[33] (2023)	Y	Y	Y	NR	N	Y	Y	N	NR	Y	N	NA	Good

Figure 4. Quality assessment of included pre-post studies. CD, cannot determine; N, no; NA, not applicable; NR, not reported; Y, yes.

maximal exercise capacity and impaired submaximal exercise performance at both 3 and 6 months following initial diagnosis among individuals with preexisting CVD, compared to that among controls.[31]

Six studies assessed physical-activity levels[32,58,61,63,65,71] using the Barthel Index for Activities of Daily Living,[63] accelerometer with an inclinometer,[44] the International Physical Activity Questionnaire (IPAQ),[58] the MET score,[61] Chronic Fatigue Syndrome Questionnaire,[65] and the Functional Assessment of Chronic Illness Therapy Fatigue Scale.[71] Based on accelerometry, physical activity levels were found to be substantially lower among posthospitalized patients with COVID-19, which included those with preexisting CVD, at 3 to 6 months following hospital discharge.[61] Sedentary behaviour, which was defined as awake time spent at a MET score of < 1.5, was also reported to be lower among these posthospitalized individuals.[61] The Barthel Index for Activities of Daily Living score was lower compared with values documented pre-COVID-19 in a study conducted by Righi et al. at a university hospital among individuals with symptomatic SARS-CoV-2 infection, indicating a poor perception of general health.[63] In a study done by Aranyó et al., the Barthel score also was found to be lower in a cohort of patients with preexisting CVD.[67] Based on the self-reported Chronic Chronic Fatigue Symptom Questionnaire used by Tleyjeh et al., extreme mental and physical fatigue was higher among women than it was among men with CVD.[65]

Hypertensive patients reported poorer sleep quality than normotensive patients in 5 studies,[24,34,39,51,53] characterized by difficulty falling asleep or having short, interrupted sleep, based on the Pittsburgh Sleep Quality Index (PSQI). Fernández-de-Las-Peñas et al. also reported poor sleep quality among a post-COVID cohort population that included those with preexisting CVD or hypertension,[57] and sleep diaries attested to the presence of sleep disorders in van Bakel et al.[61] Sleep disturbance also was seen to persist in studies done by Chathoth et al.[45] and Kalamara et al., the latter of which reported a significant percentage of patients with preexisting CVD suffering from sleep disturbance and deterioration following a COVID infection.[27] Both the Patient-Reported Outcomes Measurement Information System (PROMIS) Scale Global Health V.1.2, a 10-item scale and the general mental and physical health score were used to assess physical and mental health outcomes in a cohort study that included those with preexisting CVD or hypertension by Ogungbe et al., which reported lower scores among these individuals.[71]

Psycho-social outcomes. The EuroQol 5-Dimension Health-Related Quality of Life Instrument (EQ-5D-5L) was used in 4 studies to examine quality of life related to LC among individuals with preexisting CVD.[32,59,66,67] These studies reported a negative correlation between the number of symptoms and quality of life. Neuropsychiatric outcomes—including anxiety,[24,36,39,45,57] depression,[25,42,47,72] post-traumatic stress disorder,[29,36] memory lapses,[57] cognitive impairment,[75] and chemosensory dysfunction[47]—were evaluated in 11 of the included studies. Anxiety and depression were measured using the Hospital Anxiety and Depression Scale, and a higher proportion of hypertensive individuals were found to have a greater number of anxiety and depression symptoms,[57] compared to the number among normotensive individuals. Also, in a study done by Bamps et al., anxiety was assessed with the State-Trait Anxiety Inventory, with higher scores found among patients with comorbidities, including those with preexisting CVD.[51] Chemosensory dysfunction characteristics, recovery patterns, and treatments were collected using a simple questionnaire in one study, which found both complete and incomplete chemosensory dysfunction in adults with preexisting CVD.[47]

CVD complications. Four studies integrated a clinical evaluation of deep venous thrombosis (DVT) at follow-up visits, as well as associated complications, such as pulmonary embolism, using computed tomography angiography and venous duplex ultrasonography.[29,37,51,69] In a study done by Maestre-Muñiz et al., venous thromboembolism events were seen after a 90-day follow-up, despite participants being under standard thromboprophylaxis, especially among hypertensive individuals.[69] Venkatakrishnan et al. reported that individuals with baseline hypertension had a higher risk of life-threatening complications of CVD, including DVT, when COVID-associated complications were analyzed via collection of registry data from the Society of Critical Care Medicine.[55]

Hospital readmissions and death. Izquierdo et al. reported hospital readmissions over a follow-up period of 1 year following initial hospitalization among individuals with preexisting CVD, noting that most of these rehospitalizations occurred as a result of CVD complications, including arrhythmias, cardiac ischemic events, and heart failure.[25] According to Tleyjeh et al., the incidence of hospital readmission was significantly higher among patients with myocardial injury in a long-hauler population (ie, among those who suffered from symptoms of COVID-19 for an unusually long time).[28] Five studies examined death, either as an individual outcome or as part of a composite outcome along with hospital readmissions.[25,28,48,56,76] Health resources, such as participant medical charts, also were used to report death in a study conducted by Al-Aly et al., in which individuals with LC were reported to have an increased risk of death at 6 months postinfection.[76]

Discussion

In this systematic review, we evaluated and synthesized existing evidence regarding the impact of LC on multiple health outcomes among adults with preexisting CVD and hypertension. The results of this review indicate that LC has a significant effect on a range of health outcomes among members of this population, including prolonged symptoms of LC, physiological health outcomes, lifestyle behaviours, psychological outcomes, CVD complications, and death and hospital readmission.

According to our findings, patients with preexisting CVD or hypertension affected by LC are more likely to experience lasting symptoms than are LC patients without CVD or hypertension. This finding also was reported in the Polish Long-COVID Cardiovascular (PoLoCOV-CVD) study,

which looked at the independent predictors of LC in individuals without comorbidities,[77] reporting that these individuals experienced fewer symptoms, such as dyspnea, fatigue, chest pain, leg muscle pain, headache, arthralgia, and chill, than did individuals with cardiovascular comorbidities.[77] That study recommended early treatment to reduce the risk of developing prolonged symptoms, which our included studies indicated adversely impact quality of life.[25,39,57,59]

SARS-CoV-2 infections can affect the heart and blood vessels of previously healthy individuals, posing a risk to cardiopulmonary functioning.[78-81] These effects can be identified via a thorough evaluation of individuals diagnosed with COVID-19, and methods of addressing their impact can be integrated into the ongoing clinical management of individuals with preexisting CVD or hypertension, to mitigate the potential cardiopulmonary harms.[81] Multiple measures of cardiopulmonary function—including vital capacity, FVC, FEV1 and/or FVC, total lung capacity, residual volume, and diffusing capacity for carbon monoxide —were reported to have been impacted significantly and negatively following LC. Integrating effective monitoring of these parameters therefore is critically important among individuals with CVD or hypertension, particularly during the postdischarge management phase for those hospitalized with COVID-19. Studies that have looked at examining such biomarkers among individuals with CVD reported a positive impact on quality of life.[82,83] Our review also found that most studies that reported on quality of life found a significantly lower quality of life among LC patients who had preexisting risk factors (such as CVD), as well as more greatly impaired functional status following severe acute COVID-19 infections.[32,59,66] With this impact in mind, both monitoring and appropriate treatment over the long-term should be used to optimize quality of life among individuals with CVD or hypertension following an LC diagnosis.

Exercise has been shown to reduce the rate of clinical degradation among individuals with CVD or hypertension,[84-86] with adequate daily exercise slowing disease progression.[84] Our included studies reported that exercise capacity was generally low following LC among individuals with preexisting CVD or hypertension, compared to that among matched control groups of heathy individuals.[31,58,59,65] Considering the known effectiveness of exercise in this patient population, these findings demonstrate the need for exercise-based management of post-COVID patients, which would likely reduce rehospitalization and mortality rates.

Our review also identified chemosensory dysfunction as an important outcome of LC among individuals with CVD or hypertension.[47,59] Chemosensory dysfunction was identified as a unique COVID-19 symptom early in the pandemic, and was used as one of the best predictors of infection.[59,87,88] More recent studies have shown this symptom to be present even after the initial COVID-19 infection, but before progression into LC.[89] As reported by Almutairi et al., this symptom might be more severe among individuals with CVD or hypertension,[47] as a similar effect is seen with other conditions, such as allergic rhinitis and diabetes mellitus.[6,11,47]

Among our included studies, anxiety and depression symptoms as part of LC were not related directly to the presence of preexisting CVD or hypertension; however, anxiety and depression symptoms often worsened following LC, especially among individuals who were hospitalized due to their initial infections.[65] As a result, all individuals diagnosed with LC should be provided with appropriate identification and long-term management of anxiety and depression symptoms, as is now being done within the post-COVID-19 recovery phase program for COVID-19 patients being conducted by the Psychiatric Research Institute at Montefiore-Einstein, Albert Einstein College of Medicine, Bronx, NY.[90,91]

The CVD complications that our review found following LC, such as DVT, are perhaps the most significant and life-threatening outcomes. Therefore, diagnosing these complications at the earliest stages, and identifying potential risk factors for developing such complications, is critically important, both during hospitalization for COVID-19, as well as during postdischarge follow-up. Recognizing that individuals with preexisting CVD or hypertension are at increased risk of developing blood clots in the early stages of COVID-19 can help mitigate this specific complication.

Strengths and Limitations

One of the major limitations of this review is the nature of the underlying included studies. Most individuals with CVD were included as part of a broader study population; few studies specifically examined the long-terms impacts of SARS-CoV-2 infection on individuals with preexisting CVD or hypertension. In addition, not all studies directly compared patients with CVD to those without CVD, precluding a more detailed comparison in our analyses. Also, a great deal of heterogeneity was present in definitions of LC, as well as in the timeframes used to conduct follow-up on individuals with the condition, which ranged from 5 weeks to 14 months. We attempted to overcome the first limitation by adhering to the WHO's definition of LC, but fully integrating this definition was challenging because many studies lacked sufficient detail on the timing of an LC diagnosis, relying instead on the time elapsed since initial infection with SARS-CoV-2, or on the date of hospital discharge for inpatient populations. Fully addressing the second limitation would result in omitting much of the early published work in this area, but we believe these concerns are offset by the fact that nearly half of our included studies integrated at least 6 months of follow-up.

Because additional research in this area is currently underway, we cannot confirm that this review provides a global overview of the impact of LC. The lasting effects of LC, including the potential impact of the evolution of COVID variants, can be understood only with the passage of time. Our search also was restricted to studies in the English language, which may limit the generalizability of our findings. Finally, as part of a prespecified approach that considered the potential for heterogeneity of outcomes, we relied on a narrative analysis, so an additional meta-analysis examining the relationship between LC and distinct outcomes among individuals with preexisting CVD or hypertension remains to be done.

Conclusions

Individuals with CVD or hypertension who are infected with SARS-CoV-2 should be monitored closely for continuing symptoms, and managed with an eye specifically to their increased risk of developing a range of adverse health

outcomes. Given the negative impacts of LC, adequate monitoring and evaluation should be included as a part of posthospitalization management for all members of this patient population. Because individuals with preexisting CVD may be asymptomatic during their initial infections, integrating regular screening for LC symptoms during routine clinical care would also be beneficial. In addition to reshaping patient care in this manner, a range of improvements should be made to future research studies in this area. These improvements include integrating more-robust assessments of comorbidities, incorporating longer follow-up periods, and including individuals with both CVD and other underlying conditions. Finally, closer attention should be given to the precise definition of LC and its ever-evolving terminology, to support comparability across studies.

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Ethics Statement

This article was reported in accordance with the relevant ethical standards and guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article because it is a systematic review that integrates solely previously published data.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2024.03.003.