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Definition and measurement of post-COVID-19 conditions in real-world practice: a global systematic literature review

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ABSTRACT

BACKGROUND

Post-COVID-19 conditions (PCC) is an umbrella term that encompasses a range of signs, symptoms and conditions present weeks after the acute phase of a SARS-CoV-2 infection. This systematic literature review summarises the heterogeneous methodology used to measure PCC across real-world studies and highlights trends by region, age group, PCC follow-up period and data source.

Methods Medline, EMBASE and the Cochrane Library were searched and supplemented with conference and grey literature searches. Eligible studies included individuals with (1) PCC or (2) a positive SARS-CoV-2 test or COVID-19 diagnosis who were followed over time. Included studies were published in English between 1 January 2020 and 14 November 2022.

Findings Of 291 publications included, 175 (60%) followed individuals with confirmed COVID-19 over time for PCC and 116 (40%) used a prespecified PCC definition. There was substantial heterogeneity in study design, geography, age group, PCC conditions/symptoms assessed and their classification and duration of follow-up. Among studies using a prespecified PCC definition, author-defined criteria (51%) were more common than criteria recommended by major public health organisations (19%). Measurement periods for PCC outcomes from date of acute COVID-19 test were primarily 3 to <6 months (39.2%), followed by 6 to <12 months (27.5%) and <3 months (22.9%). When classified by organ/system, constitutional-related PCC were the most frequently assessed in adult (86%) and paediatric (87%) populations. Within constitutional symptoms, fatigue was most frequently assessed in adult (91.6%) and paediatric (95.0%) populations, followed by fever/chills (37.9% and 55%, respectively).

Conclusions PCC definitions are heterogenous across real-world studies, which limits reliable comparisons between studies. However, some similarities were observed in terms of the most frequently measured PCC-associated symptoms/conditions, which may aid clinical management of patients with PCC.

PROSPERO REGISTRATION NUMBER

CRD42022376111.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review provides a succinct summary of the methodological characteristics of studies on post COVID-condition (PCC).
⇒ PCC outcomes were extracted verbatim and summarized individually and then grouped according to organ and system class to facilitate analysis.
⇒ Studies including participants with a specific comorbidity or focusing on a specific residual outcome of PCC were excluded, which might introduce selection bias or under-estimate the extent to which certain PCC-associated symptoms/conditions are measured in those subpopulations.
⇒ Heterogeneity of study design posed difficulties in the comparison of the results from the included studies
⇒ New or persisting symptoms/signs/conditions following a SARS-CoV-2 infection, now widely referred to as 'post COVID-conditions (PCC)' in scientific literature, have posed a significant burden to societies and healthcare systems.
⇒ Due to the complex and evolving nature of PCC, clinical and real-world studies vary in how PCC is defined and investigated. This has resulted in a broad range of PCC-associated symptoms and conditions, making it difficult to compare findings across studies.
⇒ Rather than using definitions published by major public health organizations such as the WHO or CDC, most publications derived their own definition or referenced definitions used by other published studies.
⇒ This study identified substantial heterogeneity with respect to how PCC were defined and measured, including study design, geography, length of follow-up, data sources, and the PCC symptoms/conditions assessed. Even so, constitutional symptoms/conditions were the most frequently assessed PCC-associated symptoms/conditions in both adult and pediatric populations, followed by neurologic and respiratory symptoms

STRENGTH AND LIMITATIONS OF THIS STUDY

⇒ Until there is a standardized definition for PCC, it will remain difficult to measure changes in the burden of PCC over time and differences across populations. Additional studies are needed to facilitate translation of real-world evidence into the clinical management of patients with PCC.

INTRODUCTION

Some patients with COVID-19 exhibit mild or no symptoms and fully recover within the acute infection phase (ie, initial 28 days).[1 2] However, other patients have persistent symptoms or develop new sequelae after the acute phase of an infection with SARS-CoV-2. Post-COVID-19 conditions (PCC) is an umbrella term used by the US Centers for Disease Control and Prevention (CDC) that encompasses a range of signs, symptoms and conditions that are present for at least 4weeks after infection. PCC can include conditions that first appear during the acute infection phase and persist beyond the expected recovery period and those that first appear after the acute phase, some of which may relapse and remit while others worsen or improve over time. Other public health organisations (eg, WHO, National Institute for Health and Care Excellence (NICE)) in the UK have adopted slightly different terms and definitions.[3 4] For example, the CDC definition considers signs, symptoms and conditions present at 4 or more weeks after infection, whereas WHO uses a cut-point of 3 or more months post-COVID-19 onset.[4 5] Moreover, NICE defines post-COVID-19 syndrome as new or persistent symptoms that continue >12 weeks after diagnosis.[6] Another commonly used term is postacute sequelae of SARS-CoV-2 (PASC), which is separately defined by the CDC, as the direct and indirect effects of SARS-CoV-2.[7] The varying definitions used makes it challenging to measure the overall burden and to compare findings across different regions and populations.[8 9]

PCC presents a significant burden to global public health.[10 11] At least 65 million individuals globally are estimated to have long COVID and the true number is likely much higher due to under-reported cases.[12] The prevalence is estimated at 10%–30% of non-hospitalised cases and 50%–80% of hospitalised cases.[10 13] However, estimates vary depending on study design (ie, study population, PCC definition, data source, follow-up duration, time period and predominant variant). For example, PCC prevalence is estimated to be higher for certain patients such as older adults, unvaccinated individuals and those who were hospitalised (higher still in those who required critical care or mechanical ventilation) during the acute phase.[10 11] Furthermore, recent findings from the UK Office for National Statistics show that PCC-associated symptoms have adversely affected the day-to-day activities of 1.5 million people in the UK (77% of those with self-reported PCC).[14]

While there have been several literature reviews assessing the mechanism, prevalence and risk factors of PCC, to the best of our knowledge, no studies have systematically reviewed the definitions of PCC in real-world practice.[12 15 16] Given that it is widely acknowledged that the new or persisting signs, symptoms and conditions comprising PCC and the time intervals over which PCC are assessed vary across public health agencies and researchers, it is crucial to systematically summarise how PCC is defined and measured in real-world studies.

The purpose of this systematic literature review (SLR) was to (1) summarise the approaches used to define and collect data on PCC in real-world studies, (2) identify PCC-associated symptoms and conditions assessed in real-world studies and (3) qualitatively summarise similarities and differences across regions, age groups, data collection approaches and follow-up periods.

METHODS

This review was conducted according to the updated 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the review protocol is registered in the international registry of systematic reviews (PROSPERO registration number: CRD42022376111).[17]

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Search strategy

Searches were carried out in Medline and EMBASE (via the OVID platform) and the Cochrane Library, using the search strategies presented in online supplemental tables 1–3. Each search strategy was designed to capture publications from 1 January 2020 to 14 November 2022 (date range was identified to capture the emergence of potential PCC outcomes) reporting on real-world studies exploring PCC in adult and/or paediatric populations. This SLR included studies using any of the following terminology, to ensure all relevant data were captured: PCC, long COVID, chronic COVID, PASC or long-hauler COVID-related outcomes. Clinical trials were excluded from this review.

To capture a comprehensive evidence base, conference proceedings including abstracts and posters from European Society of Clinical Microbiology and Infectious Diseases, American Thoracic Society International Conference, Conference on Retroviruses and Opportunistic Infections and American Academy of Pediatrics published between 2020 and 2022 were included in the search. Grey literature reports, including epidemiology data and real-world studies published by WHO, European Centre for Disease Prevention and Control and the US CDC were also reviewed for eligibility.

Study selection and data extraction

Abstracts of retrieved citations were screened according to the study PICO criteria (online supplemental table 4). Studies including adult and/or paediatric patients with self-reported or clinically diagnosed PCC or those with a confirmed SARS-CoV-2 infection or COVID-19 diagnosis that were followed over time for the development of PCC were included in this review. Studies restricted to patient populations defined by comorbid conditions were excluded, due to potentially limited generalisability. Screening was conducted by two independent reviewers, with a third reviewer resolving any discrepancies in decisions. For abstracts that met the inclusion criteria, full-text publications were reviewed for eligibility and progressed to data extraction. Where full texts were unavailable, abstracts were extracted. Extraction was conducted by a single reviewer and each data point verified by a second reviewer.

For each eligible study, information was extracted on study sample, PCC definition (ie, author-defined, CDC, NICE, WHO), specific PCC assessed and measures used, data collection approach (ie, patient-reported, clinical diagnosis, laboratory measurements), length of follow-up. A risk-of-bias assessment was performed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists.[18]

Due to substantial heterogeneity in terminology used to assess symptoms/conditions, both via clinical diagnoses and patient-reported methods, outcomes in this SLR were extracted verbatim before grouping by organ and system class to facilitate analyses. Existing approaches in the literature and medical specialists were consulted.[19–22] Individual symptoms and conditions were grouped by domains, as described in online supplemental table 5.

RESULTS

Summary of included studies

A total of 2033 articles were identified via electronic database searches, and a further 33 articles were sourced using supplementary search methods. Following deduplication and abstract screening against the PICOS criteria, 452 full-text articles (including those sourced through supplementary methods) were assessed for inclusion in the review. A total of 291 articles were deemed eligible for inclusion and were extracted. The majority of included studies were journal articles (n=262), followed by conference abstracts (n=28). Studies were most frequently excluded for not meeting the eligibility criteria set for PCC (n=73), followed by population (n=24; primarily studies focusing on populations defined by their comorbid conditions). The screening and inclusion process is summarised in the PRISMA flow diagram (figure 1).

Summary of study characteristics

A tabular summary of included study characteristics is presented in online supplemental table 6. Across included studies (n=291), the median sample size was 323 (IQR 134, 1106). Most studies included adults (76%; n=222), while 8% (n=23) included only children, and 14% (n=40) included both adults and

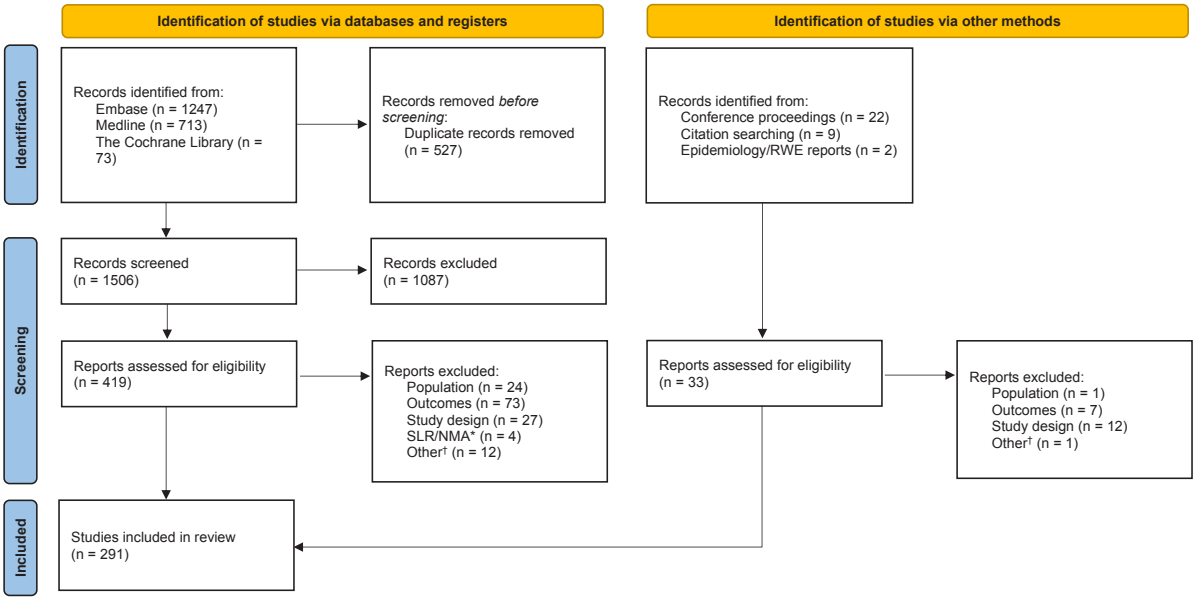

Figure 1 PRISMA flow chart of publications included in the SLR. *SLR/NMA were excluded but bibliographies were reviewed to ensure all relevant publications were included. †Duplicate and non-English publications were excluded as 'other'. NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RWE, real-world evidence; SLR, systematic literature review.

Table 1 Distribution of prespecified PCC definition sources used in included studies by age group, n=291 studies

Definition source	Total (n=291) N (%)	Paediatric (n=23) N (%)	Adult (n=221) N (%)	Mixed (n=41) N (%)	Not reported (n=6) N (%)
Author definition	150 (51.5)	10 (43.5)	119 (53.1)	18 (43.9)	3 (50.0)
Based on another referenced study	37 (12.6)	4 (17.4)	24 (10.7)	9 (22.5)	0 (0)
CDC	7 (2.4)	0 (0)	6 (2.7)	1 (2.5)	0 (0)
ICD-10 U09.9*	5 (1.7)	1 (4.3)	3 (1.3)	2 (4.9)	0 (0)
ICD-10 codes†	1 (0.3)	1 (4.3)	0 (0)	0 (0)	0 (0)
National guidelines‡	1 (0.7)	0 (0)	1 (0.4)	0 (0.0)	0 (0)
NICE	18 (6.2)	4 (17.4)	14 (6.3)	0 (0)	0 (0)
Not prespecified by author§	53 (18.1)	0 (0)	38 (17.2)	8 (17.5)	3 (50.0)
WHO	22 (7.5)	3 (13.0)	16 (7.1)	3 (7.5)	0 (0)

*Includes studies explicitly reporting ICD-10 U09.9 diagnoses, and a mixed adult and paediatric study that used a Danish equivalent of ICD-10 U09.9 diagnostic code (DB948A implemented 1 April 2020 by the Danish Board of Health.[64]
†A literature review[65] which analysed ICD-10 codes by clustering 121 syndromic, and systemic symptoms and conditions, and medication uses (therapeutic classes) reported for postacute sequelae of COVID-19, to predict clinically relevant symptoms.[65]
‡Adult study used definition from National Comprehensive Guidelines for Management of Post-COVID Sequelae for India.[66]
§Refers to included studies that prospectively followed patients with confirmed acute SARS-CoV-2 to investigate and characterise persistent symptoms.
CDC, Centers for Disease Control and Prevention; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; NA, not applicable; NICE, National Institute for Health and Care Excellence.;

children. Of note, age was not reported in 2% (n=6) of studies.

Most studies were conducted in the USA (25%, n=73), followed by the UK (8%, n=24).

Summary of PCC definitions in real-world practice

A summary of the distribution of pre-specified PCC definition sources used in included studies by age group is presented in table 1. The majority of studies used author-created definitions (52%, n=150), followed by definitions that had been used in prior studies (13%, n=37) (table 1). There was no clear trend across countries as to which definition researchers used. For example, the NICE definition was used in 18 (6.2%) studies across 12 countries, of which only 1 was conducted in the UK.[23] In addition, the CDC definition was used by 7 (2%) studies, of which 6 were conducted in the USA and 1 in Saudi Arabia, while the WHO definition was used by 22 (7.5%) studies, conducted in 15 different countries. Of note, all 53 studies without a prespecified PCC definition prospectively followed patients with a confirmed SARS-CoV-2 infection over time to investigate and characterise persistent symptoms.

The SLR captured evidence from all six WHO regions. The global distribution of PCC definitions used is presented in online supplemental table 7.

Comparison of study designs

The majority of studies included participants with a recent documented COVID-19 diagnosis that were followed-up for a specified period of time (n=175). The remaining 116 studies included participants with PCC.

Retrospective cohort studies (n=102) were the most commonly used study design, followed by prospective cohort (n=91), cross-sectional (n=77) and case-control (n=11). Of the prospective cohort studies, 48 (64%) followed participants after a positive COVID-19 diagnosis. See online supplemental figure 1 for a breakdown of included studies by study design. Overall, 44% (n=128) of studies were conducted in a single-centre setting and 47% (n=137) were conducted in a multicentre setting. The remaining 9% (n=26) of studies were community (n=2), online (n=2), remote (n=2) or studies that did not report the setting (n=20).

With respect to data collection methods/sources, 229 studies assessed PCC using patient/self-reported questionnaires or surveys, 61 analysed data from administrative claims and/or electronic health record (EHR) databases, and 20 used a combination of patient-reported PCC with at least one other measurement type (eg, ICD-10 codes, laboratory results).

Length of follow-up varied across included studies, both by measure (eg, mean, median, range) and duration. We grouped follow-up periods used in included studies as <3, 3 to <6, 6–12 and >12 months post-SARS-CoV-2 infection or COVID-19 diagnosis (see table 2). The most common follow-up period was ≥3 months to <6 months (n=97).

Summary of PCC assessed

Across studies, PCC outcomes were assessed as symptoms/conditions (93%), health state and quality of life (QoL) measures (43%), clinical and laboratory assessments (15%), healthcare resource utilisation (8%) and new or worsened comorbidities (18%). Of symptoms/conditions

Table 2 Distribution of measurement periods for PCC outcomes relative to most recent SARS-CoV-2 test results or diagnosis, n=291

Follow-up range	Number of studies (%)*
<3 months	66 (22.9)
3 months to <6 months	114 (39.2)
6 months to <12 months	80 (27.5)
≥12 months	38 (13.1)
Overlapping range†: <3 months to 6 months	2 (0.9)
Overlapping range†: <3 months to ≥12 months	1 (0.5)
Not reported	26 (8.9)

*Studies reporting multiple follow-up points have been included in each respective category therefore, total number of studies is ≥100%.
†Studies capturing data at a single timepoint over a range of time.
.PCC, post-COVID-19 condition.

reported across all studies, 74% (4842/6578) were self-reported (ie, no clinical diagnosis; includes reported via parent proxy).

Symptoms/Conditions by symptom/condition domains

Symptoms/Conditions were measured in 271 of 291 (93%) included studies. Due to the heterogeneity in terminology used, individual symptoms/conditions were categorised based on organ system to facilitate analysis. The number of studies measuring each symptom/condition (ie, the frequency), stratified by adult versus paediatric population, data source, study design and follow-up duration across studies is presented in figure 2.

As depicted in figure 2A, constitutional symptoms/conditions were most frequently assessed in both adult and paediatric populations (86% and 87%, respectively). Neurological and respiratory symptoms were the next most frequently assessed conditions (84% and 82% among adults, respectively; 83% for each among children). When stratified by data source (figure 2B), studies using databases (n=61; eg, EHR, medical/insurance databases), questionnaires (n=229) and studies conducting laboratory-based testing or clinical assessment (n=20) most frequently assessed constitutional PCC (82.0%, 84.7% and 90.0%, respectively). Laboratory results were more likely to be used to measure symptom severity and PCC in the genitourinary symptom/condition domain (figure 2B). In all symptom/condition domains bar symptom severity, there was a lower proportion of database studies than questionnaire-based studies (figure 2B).

Constitutional PCC were most commonly measured in retrospective cohort (79%), cross-sectional (90%) and ambidirectional cohort (100%, n=10) studies. Neurological PCC were most frequently assessed in case-control studies (91%; n=11), followed by prospective cohort studies (87%) (figure 2C). Of the five study designs, ambidirectional cohort studies were more likely than other study designs to measure musculoskeletal, cardiovascular, genitourinary, immune, gastrointestinal and dermatological symptom/condition domains (figure 2C).

The symptom/condition domains measured did not differ substantially by follow-up duration (figure 2D).

Frequency of symptom/condition domains

The three most frequently assessed symptom/condition domains by age group are reported in figure 3. A summary of the distribution of number of symptoms/

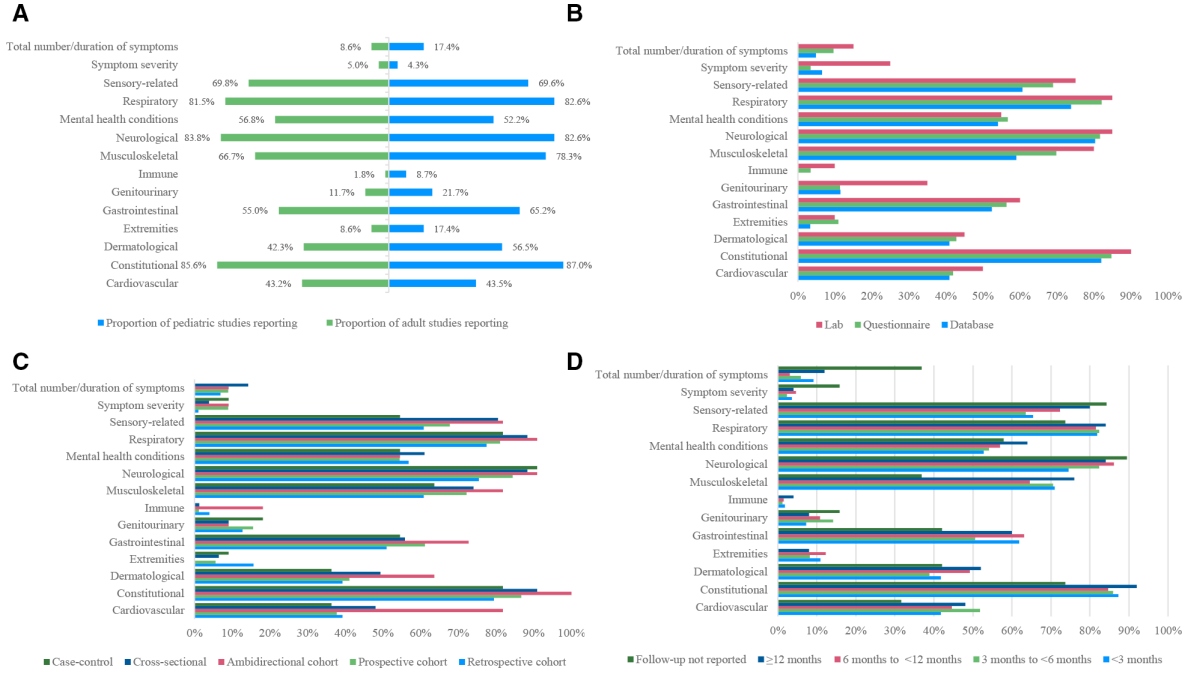

Figure 2 Distribution of the most frequently assessed symptom/condition domains stratified by (A) age group, (B) data source, (C) study design and (D) follow-up length.

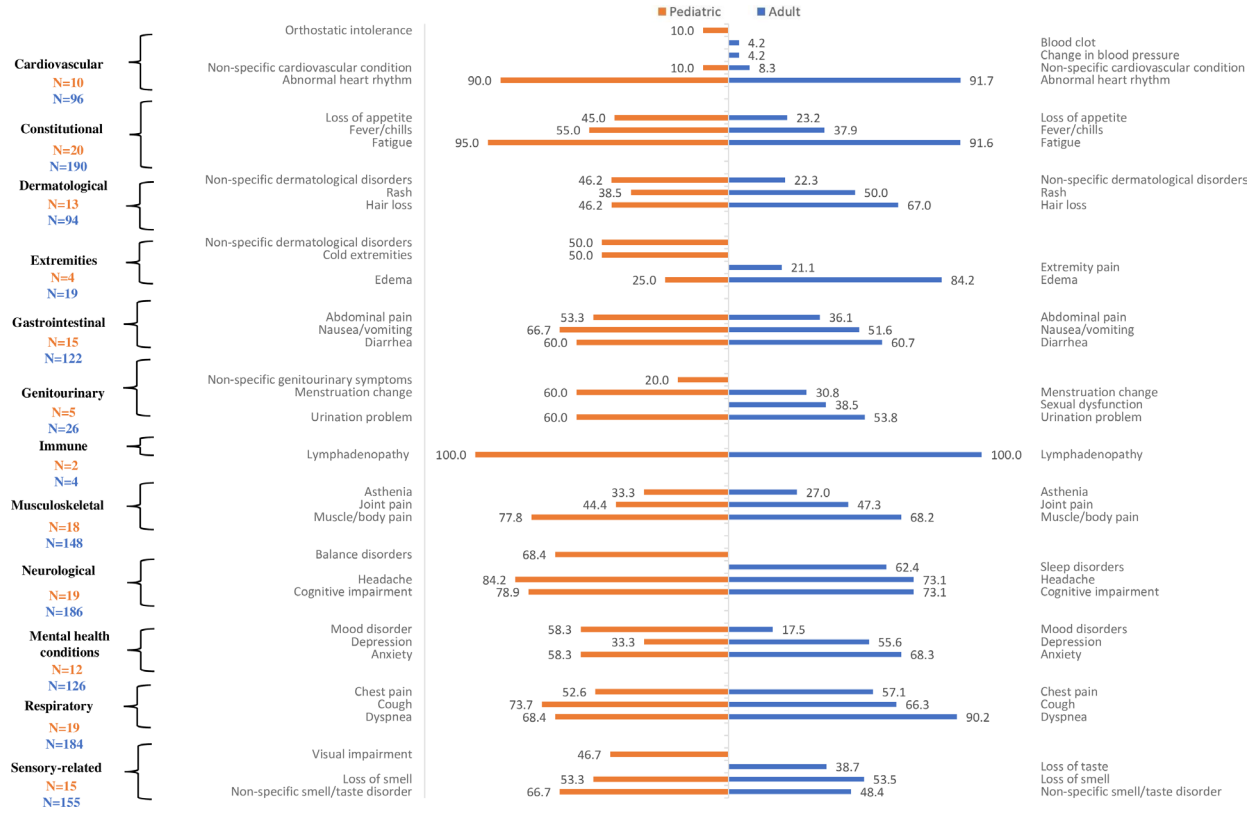

Figure 3 Distribution of the most frequently assessed symptoms/conditions by symptom/condition domain in adult and pediatric population.

conditions assessed in each PCC domain is presented in online supplemental table 8.

Similarities across symptom/condition domains were observed however, some individual symptoms/conditions were unique to adult or paediatric populations, making it difficult to compare the grouped domains directly.

Abnormal heart rhythm (eg, included palpitations, dysrhythmia, arrhythmia, tachycardia and bradycardia) was the most frequently assessed symptom/condition in adults (91.7%, 88/96), and 90% (9/10) of paediatric studies. Fatigue was the most frequently assessed constitutional PCC among adult (91.6% (174/190)) and paediatric populations (95.0% (19/20)).

Age-related differences were observed. For example, change in blood pressure, sexual dysfunction, extremity pain, oedema and sleep disorders were more frequently assessed in adults. Conversely, in paediatric populations, a notable difference was the proportion of studies assessing mood and balance disorders (58.3% vs 17.5%; 68.4% vs 0%, respectively).

Other PCC outcomes

Health state measures and quality of life

Health state and QoL outcomes were assessed in 124 studies. The most frequently assessed health state measure was general QoL (n=50), which was primarily measured using the EQ-5D (n=20), followed by limitations in daily activities (n=30) (online supplemental figure 2).

Clinical and laboratory assessment

Clinical and laboratory testing was conducted in 45 studies. These assessments were used to identify biomarkers or diagnostic criteria for PCC and were reported by 40 studies. The laboratory measures most frequently used to assess PCC were inflammatory markers (37.8%), followed by lymphocyte testing (15.6%) (online supplemental figure 3).

Healthcare resource use

Twenty-two studies assessed PCC-associated healthcare resource use (HCRU) outcomes, broadly categorised as hospitalisation, intensive care unit admission, pharmaceutical treatment and outpatient clinical visit or rehabilitation (online supplemental table 9). HCRU outcomes were more likely to be assessed in outpatient clinical visits/rehab (86/150 studies overall; 70/97 studies among adults; 13/14 studies among paediatrics).

New or worsened comorbidities

A range of new or worsening comorbidities were assessed in 52 of the included studies, and were measured as distinct outcomes from PCC-associated symptoms/conditions. These outcomes refer to reported disease manifestations either during the acute COVID-19 illness or post-COVID-19—as opposed to diagnosed symptoms/conditions. Due to uncertainty in reporting, these conditions have been grouped separately and were excluded from analysis of PCC-associated symptoms/conditions as

they are not necessarily COVID-19-related. Diabetes and cardiac events/disease (including heart failure and myocarditis) (n=16) were the most commonly assessed new or worsening comorbidities, followed by stroke (n=12).

Summary of validated methods for PCC outcome assessment

Several studies reported use of validated measures for PCC outcomes, with terminology varying between COVID-19/long COVID/post-COVID. These studies refer to measures/tools designed, tested and validated specifically for assessment of PCC outcomes. The key characteristics of these validated methods and measures are presented in the online supplemental table 10.

Quality appraisal of included studies

A risk-of-bias assessment was performed using the JBI Critical Appraisal Checklist (online supplemental table 11–14).[18] Studies were assessed using a series of study design-specific questions, and the meeting of each criteria rated as 'yes', 'no', 'unclear' or 'not applicable'. A qualitative conclusion of low, high or unclear risk of bias was assigned to each study.

An assessment of high risk of bias or unclear in cohort studies was assigned for 25 studies, primarily due to limited description of study sample characteristics, confounding factors and study follow-up presented within conference abstracts (n=10). However, within published full texts, a high risk of bias was also assigned for differences between comparative study samples, lack of control group and selective inclusion of most severe acute cases (eg, study sample only comprising hospitalised patients with PCC). Similarly, among cross-sectional studies, limited description of study sample characteristics, unclear inclusion criteria and follow-up led to assessment of high risk of bias or unclear (n=12). One case-control study was deemed 'unclear', as it was a journal letter and did not provide comprehensive study details.

DISCUSSION

This SLR sought to summarise how PCC are defined and measured in real-world evidence studies. Of the 291 studies included, substantial heterogeneities across study design, geography, age group, data sources, PCC-associated conditions/symptoms assessed and duration of follow-up were identified. The adoption of PCC definitions that matched guidance from NICE, WHO and the CDC was low, with variations of author-generated definitions being most common in the literature. This is consistent with the findings published in a recent review study on PCC definitions, which found that 66.8% of 193 studies reviewed used their own definitions for PCC, while 33.2% studies did not define PCC.[24] The use of multiple and varied definitions further impaired our qualitative synthesis of PCC definitions across studies. A standardised universally accepted definition and nomenclature is the first step to appropriately diagnose and manage a disease, to measure the disease burden and changes in the burden over time and across different populations. WHO and other related organisations might consider an integrative classification and unified terms or PCC measurement tools to homogenise the literature. However, irrespective of age group, data collection method and study design, the most frequently assessed PCC-associated symptoms/conditions were constitutional, and included fatigue, fever/chills and loss of appetite, which may shed light on targeted intervention strategies for patients with PCC.

The time reference points for measuring PCC or follow-up periods are also critical to establish in order to define PCC.[25] Across studies, PCC were measured over different follow-up periods (sometimes across multiple time periods and other times only at one time point). Furthermore, the way studies described the follow-up period differed. For example, 140 studies reported the mean, median or range of follow-up time, 104 reported time intervals (eg, <3 months to ≥12 months), and the remaining 47 studies did not specify a follow-up duration. Furthermore, some studies assessed PCC at consistent time intervals while others collected data at any time-point within a range (eg, one completed questionnaire >6 months postacute COVID-19 infection). Prior reviews suggested that studies assessing PCC over shorter periods (eg, 1 month after an infection) may not capture the full range of PCC-associated symptoms/conditions.[16 26] Davis *et al*[12] noted that the onset and time course of symptoms differ across patients and by type of symptom. For instance, neurological symptoms often have a delayed onset, and some worsen over time and will likely persist longer, whereas respiratory and gastrointestinal symptoms are more likely to resolve within weeks.[27–29] Other symptoms like body and joint pain, and swelling of the legs and feet, are more commonly seen at 1 year.[30] An analysis of ICD-10 codes with potential links to long COVID was conducted by Mizrahi *et al*, to compare symptoms and diagnoses recorded in an early post-COVID-19 period (30–180 days postinfection) versus a later period (180–360 days postinfection).[31] HRs for a variety of symptoms and diagnoses differed across the two follow-up periods, for example, dyspnoea and weakness remained high throughout 1 year while palpitations and chest pain and cough returned to baseline within 8 and 4 months of a COVID-19 diagnosis, respectively.[31] Thus, a sufficient follow-up length defining people 'at risk for long COVID' is extremely important to minimise misclassification or misdiagnosis of PCC.[32]

We observed substantial heterogeneity in the frequency in which different PCC-associated symptom/condition domains were assessed, which was consistent with previous studies.[12 16 33 34] However, constitutional-related PCC were the most frequently assessed in both adults and children (n=190, n=20). Prior PCC studies presenting the prevalence of persistent symptoms following SARS-CoV-2 infection reported that constitutional symptoms are very common, which supported the high frequency of measurements. For example, the prevalence of fatigue was estimated to be 35%–45% at 4 weeks, 30%–77% at 8 weeks and 16%–55% at 12 weeks after infection and 21%

more likely ≥6 months after infection.[34–41] Neurological-related PCC were the next most frequently assessed PCC (measured in 83% of studies among both children and adults). This finding likely reflects ongoing concerns regarding the impact of PCC-associated neurological symptoms/conditions in adults and children.[42–44] Brain fog, loss of smell and taste (anosmia and ageusia) and headache are among the most prevalent neurological symptoms.[45–47] According to two single-centre cohort studies conducted in the USA and France, respectively, 60% of hospitalised cases reported persistent neurocognitive symptoms at 6 months and 33% had a dysexecutive syndrome including inattention, disorientation or poorly organised movements in response to command at hospital discharge.[48 49] Additionally, findings from the RECOVER cohort study highlighted that brain fog, dizziness and abnormal movements were among the most common PCC symptoms reported at 6 months postinfection, with frequencies of 64%, 62% and 15%, respectively.[50] The underlying mechanism of long-term neurological manifestations is unknown, and could involve viral neuroinvasion, persistent viral shedding and serotonin reduction.[51 52] Future studies are needed to better understand the long-term impact on neurocognitive impairment and QoL in adults, as well as neurodevelopment in children.[42 53]

Moreover, PCC-associated respiratory symptoms/conditions including cough and dyspnoea were also frequently measured, in alignment with previous assessments in the literature.[26 54] According to an SLR and MA conducted up to 15 March 2021, that included 29 peer-reviewed publications and 4 preprints, dyspnoea were among the most prevalent post-COVID-19 symptoms in both hospitalised and non-hospitalised COVID-19 cases.[55] An earlier SLR and MA conducted in 2020 also noted that 26% of the individuals experienced dyspnoea.[56] Notably, a recent retrospective study conducted in Saudi Arabia has shown a high reported frequency of residual cough within 12 months in children post-COVID-19 infection, as a cough was reported in 69.8% of patients.[54] Moreover, a longitudinal study conducted in Spain explored the recovery curve of dyspnoea in previously hospitalised COVID-19 cases aged around 60 years and found that patients with dyspnoea tend to slowly recover during the 3 years post-SARS-CoV-2 infection, which might also explain why those symptoms were likely well captured regardless of the study design and follow-up length.[57]

Well-designed studies, including sufficient longitudinal follow-up and a well-matched control group (eg, the same amount of time in the study following an initial infection), are also needed to correctly identify PCC.[58] In the present study, only 8% of the studies were longitudinal and only 4% included a control group.

This SLR also identified substantial heterogeneity in terminology used to measure symptoms/conditions, both via clinical diagnoses and patient-reported methods. A lack of standardised symptom/condition nomenclature and recording methods has been similarly reported in landscaping and systematic literature reviews investigating persistent symptoms associated with PCC.[59–61] These studies identified loss of granularity due to grouping of similar symptoms under umbrella terms, poor EHR characterisation and general ambiguity in measurement of acute SARS-CoV-2 infections.[59–61] A chart review of the ICD U09.9 code across three US healthcare databases found that the definition varied by provider and that bias was introduced by inclusion of long COVID clinic attendance data.[32 62] Furthermore, among patients with the U09.9 code (n=300), only 40% and 65% met the WHO and CDC definitions of PCC, respectively.[32 62]

There are distinct limitations associated with self-reported and database methods of collection. Less severe PCC-associated symptoms may not be accurately captured by diagnostic codes, due to bias towards more severe diagnoses that require medical attention or where patients feel a medical intervention will resolve the complaint. Furthermore, there may be inconsistencies across doctors regarding which conditions are discussed and documented as relevant to PCC, highlighting the lack of certainty surrounding the definition of PCC. Conversely, patients may be more likely to report minor symptoms using a self-completed survey such as headache or cough. A study exploring self-reported long COVID prevalence raised uncertainty regarding their prevalence estimates, due to higher frequency of self-reported outcomes versus clinical diagnosis reported in other disease areas.[63]

Another key consideration for clinician diagnosed/EHR database PCC is that some symptoms/conditions are reported as incident outcomes (ie, not present prior to or during the acute phase of infection), while others distinguish between chronic, acute and persistent symptoms.[31] Thus, comparisons of findings between different studies on this topic should be approached with caution. Our study assessed the frequency that different PCC-associated symptoms/conditions (and PCC-related symptoms/conditions, when grouped by organ system) were measured. However, further research that quantifies the prevalence of specific PCC symptoms/conditions as well as common phenotypes are needed to guide clinicians on the diagnosis, treatment and management of PCC. Also, additional studies are needed to identify appropriate physical, mental and biological tests to diagnose PCC symptoms/conditions, aiding clinical decision-making.

Due to heterogeneity in terminology used for to assess symptoms/conditions, both via clinical diagnosis and patient-reported methods, outcomes in this SLR were extracted verbatim before consolidation to allow for interpretation and presentation in tables and figures. For example, shortness of breath, breathlessness and dyspnoea were consolidated and analysed as one symptom. This consolidation approach to group by symptom/condition domain, although informed by existing approaches in the literature and included consultation with medical specialists, may have limited the reproducibility of our findings. Furthermore, as detailed in PICOS table, the exclusion of studies that focused on a specific PCC-associated symptom

or condition may have led to the exclusion of studies with relevant data. If a specific PCC-associated symptom/condition or patients with a specific underlying condition is of interest, future studies restricted to those conditions might be needed.

The format of questionnaires used in included studies that investigated patient-reported outcomes may also have impacted participant response. For example, open-ended questions or availability of free-text entries may have fewer responses than closed-ended questions. Even for close-ended questions, different questionnaires may have different wording and therefore may result in different recall periods, limiting the comparability across studies. In addition, individual clinical relevance or symptom intensity could not be accessed or differentiated across different terminologies used.

Moreover, heterogeneity by study sample, follow-up duration, method of data collection and whether outcomes were patient-reported or based on diagnostic/claims codes limited our ability to summarise differences and similarities across studies. Lastly, given the rapidly emerging literature on PCC, a timely updated review is needed in near future to better understand the evolving dynamics in PCC-related fields.

CONCLUSION

Overall, a considerable global body of evidence was identified and summarised in this SLR for adult and paediatric populations which demonstrates the wealth of evidence being generated in real-world settings for PCC. The SLR found high heterogeneity in PCC definition, study design, follow-up period, PCC symptom/condition domains assessed and data sources. It has been acknowledged that COVID-19 has a very broad clinical spectrum and thus it can have long-term impacts on various organ systems. Ongoing real-world studies assessing PCC (across multiple organs/systems) are critical as there is lack of certainty in the medical and scientific community regarding a standardised PCC definition that is appropriate in both the clinical and research settings. Care must be taken to balance the sensitivity and specificity of a diagnosis before a standard definition of PCC can be applied.

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