

REVIEW ARTICLE

Late Complications of COVID-19; An Umbrella Review on Current Systematic Reviews

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Abstract: **Introduction:** Several clinical manifestations have been discovered for COVID-19 since the emergence of SARS-CoV-2, which can be classified into early, medium, and long-term complications. However, late complications can be present after recovery from acute COVID-19 illness. The present study aims to comprehensively review the available evidence of late complications related to COVID-19. **Methods:** A search was conducted, using keywords, through electronic databases, which included Scopus, Web of Science, PubMed, and Embase up to August 29, 2022. Study selection was performed according to a strict inclusion and exclusion criteria. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist was followed, and studies were appraised using the National Institute of Health (NIH) quality assessment and risk of bias tool. **Results:** In total, 50 studies were included, and nine distinct COVID-19 late complication categories were identified. A review of these studies revealed that neurologic and psychiatric (n=41), respiratory (n=27), musculoskeletal and rheumatologic (n=22), cardiovascular (n=9), and hepatic and gastrointestinal (n=6) complications were the most prevalent complications of long COVID-19. **Conclusion:** Almost all human body systems are affected by late complications of COVID-19 with different severity and prevalence. Fatigue and some other neuropsychiatric symptoms are the most common late complications among long COVID-19 patients. Respiratory symptoms including dyspnea (during exercise), cough, and chest tightness were the next most prevalent long-term complications of COVID-19. Since these complications are persistent and late, being aware of the signs and symptoms is essential for the healthcare providers and patients.

Keywords: COVID-19; SARS-CoV-2; Post-Acute COVID-19 Syndrome; Patient Outcome Assessment

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1. Introduction

In relation to the groundbreaking emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in late December 2019, several concepts were presented regarding the clinical aspects of COVID-19 caused by SARS-CoV-2 (1, 2). SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) receptors to invade the host cells (3). Due to the widespread expression of ACE2 in human organs, COVID-19 can present with different clinical manifestations, including pneumonia, myocarditis, cardiac infarction, kidney injuries, neurologic manifestations, gastrointestinal disorders, etc. (4). SARS-CoV-2 is still spreading worldwide, and growing evidence reports the de novo manifestations of COVID-19. The duration of symptoms of COVID-19 is not fully understood and the complications of COVID-19 present in different timelines and can be categorized into early (5), medium (6), and late (7) manifestations after COVID-19 infection. Manifestations and clinical and para-clinical indicators remaining different from healthy baseline level days to months after COVID-19 infection are considered post-COVID-19 complications (8). According to National Institute for Health and Care Excellence (NICE), post-COVID-19 infection is characterized by manifestations that are sustained for more than 12 weeks after COVID-19 infection, and other diagnoses cannot be made for such complications (9).

Although the majority of complications arise from the onset of COVID-19, a body of evidence reported the late complications related to COVID-19, which are present in the survivors of COVID-19 several weeks to months after the elimination of SARS-CoV-2, which can be attributed to the indirect damage of organs. Some pathways, including immune dysregulation, coagulopathy, and endothelial damage are introduced for late complications of COVID-19 (10). Consequently, it was shown that almost all human body systems are affected by COVID-19 and can show late complications. However, the percentage, severity, and duration of such late manifestations are different. Additionally, late complications are associated with an abnormal level of some laboratory parameters such as inflammatory and anti-inflammatory parameters that can indicate organ dysfunction (11, 12).

Several systematic reviews and meta-analyses documented the late complications of COVID-19, including a broad range of organ injuries. In this umbrella review, we sought to provide comprehensive evidence on the late complications of COVID-19 to improve the clinical insight of physicians and

summarize the post-COVID-19 complications and highlight the importance of follow-up in patients with COVID-19.

2. Methods

In this study we comprehensively reviewed current systematic review studies about late and long-term complications of COVID-19. To optimize validity and authenticity, we utilized items of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. Studies were appraised using the National Institute of Health (NIH) quality assessment and risk of bias tool.

2.1. Data sources

An extensive search of four online databases was performed, which included Web of Science, PubMed, Scopus, and Embase.

Articles were restricted to English language and the search was conducted up to August 29, 2022. The following is the search strategy we have used on PubMed database, whereas search strategies for other databases are provided in Supplemental material 1.

("COVID-19" [mesh] OR "SARS-CoV-2" [mesh] OR COVID-19 [tiab] OR SARS-CoV-2 [tiab] OR coronavirus disease 2019 [tiab] OR severe acute respiratory syndrome coronavirus 2 [tiab]) AND (Long-Term Outcome*[tiab] OR Long-Term complication*[tiab] OR Late complication*[tiab] OR Chronic complication*[tiab] OR Long-term effect*[tiab] OR Long-Term Impact*[tiab] OR Consequence*[tiab] OR Sequelae [tiab] OR Long COVID [tiab] OR Sequel [tiab] OR post-acute COVID syndrome [tiab] OR long-COVID [tiab] OR post-acute COVID19 syndrome [tiab]) AND (Systematic review [tiab] OR meta-analysis [tiab]). Besides searching through databases, several Journals were searched in a manual search.

2.2. Study selection

To improve the study selection process, a two-step method was employed. Two researchers screened articles with regard to titles and abstracts. The second step involved screening of full texts that were potentially eligible. Articles that met the inclusion/ exclusion criteria were advanced to the next step of data extraction. In other words, articles were included if they had a systematic review nature, were peer-reviewed, and assessed long-term complications of COVID-19. On the other hand, studies were excluded if they were non-human research studies, lacking the required data, duplications, narrative reviews, umbrella reviews, abstracts with deficient full texts, preprint articles, editorial letters, conference abstracts, case series, and case reports.

2.3. Data extraction

Four researchers were involved in extraction of data from articles that met the eligibility criteria. A preformatted spreadsheet was used to gather the extracted data. Potential complications of long COVID-19 were categorized into the following nine groups: cardiovascular, renal, hepatic and gastrointestinal, respiratory, neurologic and psychiatric, musculoskeletal and rheumatologic, stroke, ocular, thrombosis, and embolism. Information concerning late complication assessment methods, late complication onset, and time of recovery from sequelae was also extracted. Any duplicates were removed, and the accuracy of the extracted data was checked.

2.4. Quality and bias risk assessment

The quality and authenticity of the selected articles, as stated before, were evaluated by conforming to the PRISMA checklist. We also addressed bias risk by utilizing National Institute of Health (NIH) questionnaire for quality assessment. Table 1 illustrates the application of this tool to our study. Each study was assessed and rated by two independent researchers. Last two columns show their ratings of individual papers. Details of this questionnaire are available at the bottom of this table.

3. Results

The database search yielded 727 potential studies (after removing duplicates), and following the screening and quality control according to NIH quality assessment tool (Table 1), a total of 50 articles met the inclusion criteria (Figure 1).

The included studies were carried out in an extensive range of countries including USA (n=9), UK (n=8), Italy (n=4), Canada (n=3), China (n=3), Australia (n=2), Germany (n=2), Ireland (n=2), Saudi Arabia (n=2), Spain (n=2), and Switzerland (n=2). The following countries were each subject to one study: Brazil, Denmark, India, Indonesia, Iran, Iraq, Mexico, Pakistan, South Africa, and UAE.

In total 1,833 studies were included in our enrolled systematic reviews, and they had included a total of 5,425,998 COVID-19 patients. Two studies were conducted on children (103,212 children and adolescent COVID-19 patients), and the remaining 48 papers were carried out on adults. In regard to level of evidence, 19 studies were meta-analyses and had quantitative synthesis while, the remaining 31 studies were systematic reviews, two of which were conducted involving case-reports and case-series and 29 studies had included case-control, cross-sectional, and cohort studies in their qualitative synthesis.

Review of included studies demonstrated that neurologic and psychiatric (n=41), respiratory (n=27), musculoskeletal and rheumatologic (n=22), cardiovascular (n=9), and hepatic and gastrointestinal (n=6) complications were the most

prevalent complications of long COVID-19. Moreover, renal, ocular, and stroke sequelae were also reported by a few studies (n=2 for each sequela). There was one study that reported thrombosis or embolism as a complication of long COVID-19. Finally, the onset of complications ranged between 10 days up to 13 months. The thorough details of included studies are provided in Table 2.

4. Discussion

Almost all human body systems are affected by late complications of COVID-19 with different severities and prevalences. This systematic umbrella review found that late complications of long COVID-19 infection could be classified into nine groups. A discussion of each of these groups is covered below.

Neurologic and Psychiatric

It seems that late neurologic and psychiatric manifestations of the COVID-19 infection are the main and most prevalent features of this disease, and fatigue is the most prevalent symptom in long-COVID patients. Premraj L et al., (13) reviewed 18 studies and more than 10000 COVID-19 patients. They concluded that some late COVID-19 manifestations may last for more than 3 months after infection. These symptoms include psychiatric symptoms such as fatigue, cognitive impairment (memory problems, attention deficit), and sleep disorders. These symptoms and others like depression, post-traumatic stress disorder (PTSD), anxiety, anger, fear, dizziness, and mood change were reported in most studies (7, 13-46). However, COVID-19 severity in the acute phase of the infection was not correlated with increased symptoms in the post-acute phase of COVID-19 (47). There was some evidence inferring that identification of the long-term psychological consequences during the pandemic is critical to ensuring proper care provision (18, 48).

Neurologic manifestations like headache, myelitis, neuropathies, paresthesia, parkinsonism, cogwheel rigidity (49), optic neuritis, altered smell, olfactory dysfunction (anosmia, ageusia), encephalitis (50), epilepsy, Bell's palsy, and myoclonus were also reported in some studies. Guillain-Barre syndrome was the most prevalent neurological condition of long COVID-19 reported in the study by Ahmed JO et al. (50). Headache was also one of the common symptoms of long COVID-19 during the first six months after recovery in the study by Fernández-de-las-Peñas, César et al. (51).

Respiratory

The lung is the most commonly affected organ in acute severe COVID-19 infection and its involvement is not unusual in long-term COVID-19. Some patients reported shortness of breath, cough, and chest tightness during the post-COVID-19 phase for an extended period of time. Dyspnea usually worsens with increased physical exertion such as during ex-

ercise. Treatment has not been very effective in eliminating these symptoms, but the intensity of the symptoms usually reduces over time.

Some studies like the one by So et al., (52) showed that the radiographic feature was ground glass opacity (44%) and parenchymal band or fibrous stripe (33.9%). Restrictive (16%) and obstructive (8%) patterns were also reported in their systematic review. These abnormalities lasted for a long period of time (15, 53).

Musculoskeletal and Rheumatologic

As mentioned in the studies by Pinzon RT et al. (14) and Salamanna F et al. (29), manifestations like musculoskeletal, joint, and body pain have also been reported among long COVID-19 sufferers.

Gracia-Ramos et al., (54) studied 90 systematic reviews and reported that vasculitis, including small, medium and large vasculitis, have been seen among long COVID-19 patients. Inflammatory myopathies, systemic lupus erythematosus (SLE), sarcoidosis, and arthritis were also reported. Cutaneous vasculitis following COVID-19 is usually resistant to treatment and subsides over time.

Cardiovascular

The heart can also be involved in long COVID-19. Alosaimi et al. (55) concluded that the late cardiac involvements are pericardial effusion, myocarditis, pericarditis, elevated troponin levels, and myocardial edema. Ramadan et al. (56) reviewed 35 studies in relation to cardiac involvement in long COVID-19. Chest pain, dyspnea, and palpitations were usually reported by these patients. T-wave changes, ST-segment elevation/depression, and right bundle branch block were seen in the electrocardiogram (ECG) of these patients. Using echocardiography, there are reports of reduced left ventricular ejection fraction, pericardial effusion, global hypokinesis, left ventricular hypertrophy, diastolic dysfunction, and pulmonary hypertension. The researchers concluded that increased T1 intensity, late gadolinium enhancement, increased T2 intensity, pericardial effusion, decreased global longitudinal strain, decreased left ventricular ejection fraction, myocardial enhancement, pericardial enhancement, myocarditis, myopericarditis, pericarditis, and myocardial infarction may be seen in the cardiac magnetic resonance imaging (MRI) of these patients. Other reported cardiac involvements in long COVID-19 were elevated NT-pro-BNP levels, and arterial occlusion (in angiogram). Patients with long COVID-19 were more susceptible to heart failure, myocardial infarction, stroke, and arrhythmia.

Hepatic and Gastrointestinal

Choudhury et al. (57) studied 50 systematic reviews. This research reported that long COVID-19 patients were more susceptible to complaints of gastrointestinal manifestations like loss of appetite, dyspepsia, constipation, loss of taste, irritable bowel syndrome (IBS), abdominal pain, diarrhea, and

nausea/vomiting.

Renal

Urinary problems including urinary tract infections are rare but may be seen among long COVID-19 patients (40, 58).

Ocular

Ophthalmologic problems among long COVID-19 patients, including conjunctivitis, dry eye, trouble seeing/blurred vision, photophobia, sore eyes, and pain were rarely reported (54, 59).

Thrombosis or Embolism and Stroke

SeyedAlinaghi et al. (40) reviewed 65 studies. They concluded that venous/arterial thrombosis and cardiac/brain stroke may also be seen among long COVID-19 patients.

Others

Other late and less common complications of COVID-19 include sputum/nasal congestion, hyperhidrosis, rhinorrhea, cough, myalgia/arthritis, body weight changes, otalgia, sore throat, variations in heart rate, dysphonia, fever palpitations, hair loss, dysphagia, speech disturbances, hypoproteinemia and menstrual problems.

5. Conclusion

COVID-19 patients may have late and chronic manifestations. These symptoms are known as long COVID-19 and can last for more than 6 months. Additionally, long COVID-19 is usually resistant to treatment but may resolve over time. Fatigue and other neuropsychiatric symptoms are the most common late complications among patients with long COVID-19. Respiratory symptoms including dyspnea (during exercise), cough, and chest tightness were the next most prevalent long-term complications of COVID-19. Since these complications are persistent and late, being aware of the signs and symptoms is essential for the health care providers and patients.

6. Declarations

6.1. Acknowledgments

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6.2. Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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6.4. Authors' contribution

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- Final version was read and approved by all author.

6.5. Ethics approval and consent to participate

Not applicable

6.6. Consent to publication

Not applicable

6.7. Availability of data and material

The authors stated that all information provided in this article could be shared.

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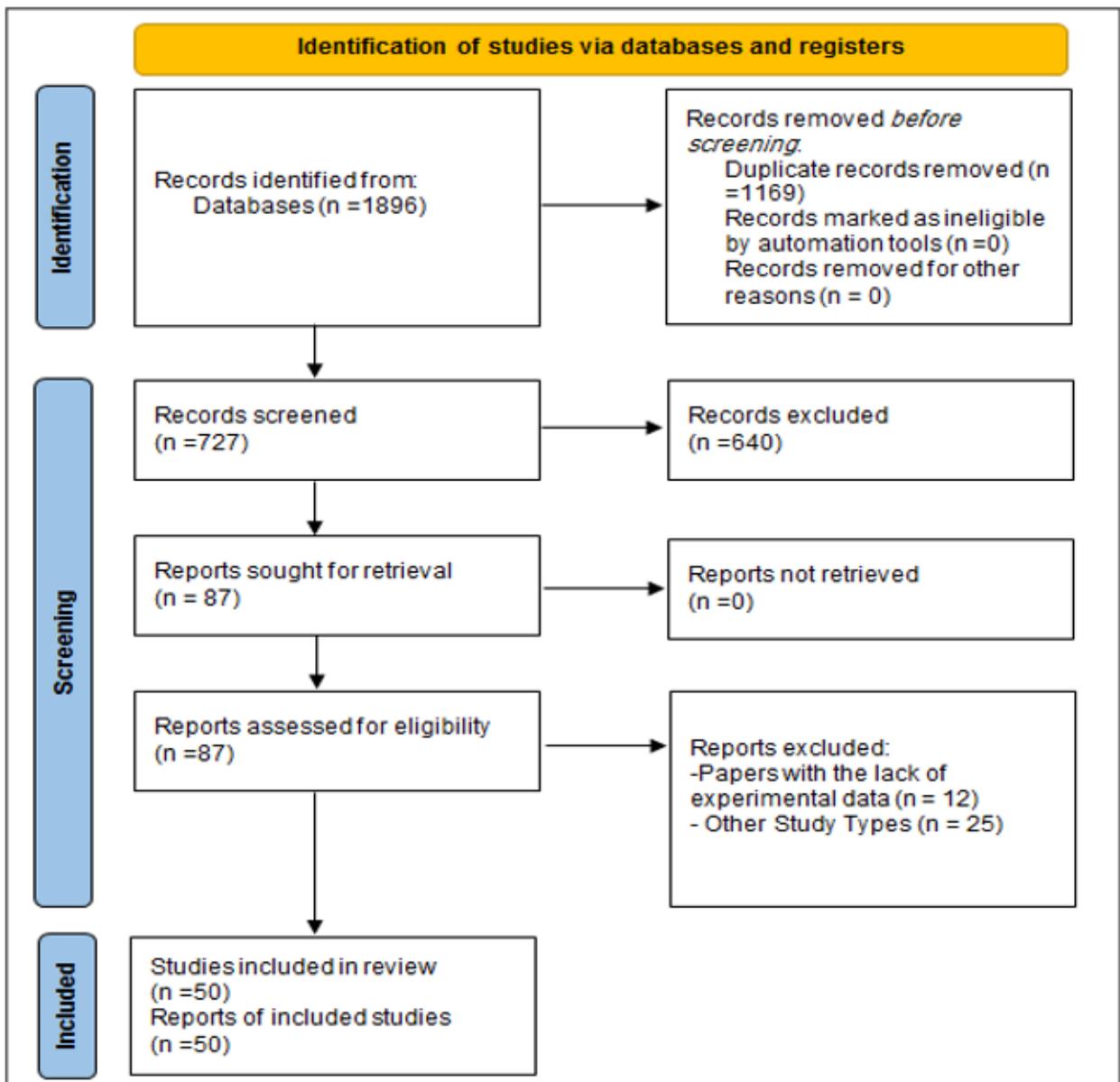


Figure 1: Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram of study retrieval process.

Table 1: Quality ratings of included studies in accordance with NIH quality assessment tool

First Autor	*Question									Rating by Reviewers	
	1	2	3	4	5	6	7	8	9	#1	#2
Fernández-de-las-Peñas C (51)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
De Luca P (60)	Yes	Yes	CD	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Ahmed JO (50)	Yes	Yes	CD	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Ali SS (61)	Yes	Yes	NA	CD	NA	Yes	CD	NA	Yes	Fair	Fair
Premraj L (13)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Pinzon RT (14)	Yes	Yes	NA	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
So M (52)	Yes	Yes	CD	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Long Q, Li J (15)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Patria YN (53)	Yes	Yes	NA	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Vanderlind WM (16)	Yes	Yes	NR	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Renaud-Charest O (47)	Yes	Yes	NA	NA	NA	Yes	CD	NA	Yes	Fair	Fair
Schou TM (17)	Yes	Yes	NA	CD	NA	Yes	CD	NA	Yes	Fair	Fair
Arora T (18)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Zürcher SJ (48)	Yes	Yes	NA	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Bourmistrova NW (20)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Badenoch JB (19)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Khraisat B (21)	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Alosaimi B (55)	Yes	Yes	NA	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Ramadan MS (56)	Yes	Yes	NA	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Choudhury A (57)	Yes	Yes	CD	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Gracia-Ramos AE (54)	Yes	Yes	CD	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Behnood SA (59)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Lopez-Leon S (58)	Yes	Yes	NA	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Ahmed H (22)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Alkodaymi MS (23)	Yes	Yes	NR	CD	NA	Yes	CD	NA	Yes	Fair	Fair
Ceban F (24)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Chen C, Hauptert SR (25)	Yes	Yes	NA	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Fernández-de-Las-Peñas C (26)	Yes	Yes	NA	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Lopez-Leon S (7)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Michelen M (27)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Nguyen NN (28)	Yes	Yes	NA	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Salamanna F (29)	Yes	Yes	NA	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Sandra Willi (62)	Yes	Yes	NR	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Yang T (30)	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Zeng N (31)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Almas T (32)	Yes	Yes	NA	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Ahmad MS (33)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Healey Q (34)	Yes	Yes	CD	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
d'Ettoire G (35)	Yes	Yes	NA	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Groff D (36)	Yes	Yes	NA	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Han Q (37)	Yes	Yes	NA	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Iwu CJ (38)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Iqbal FM (39)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
SeyedAlinaghi S (40)	Yes	Yes	CD	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Jennings G (41)	Yes	Yes	CD	NA	NA	Yes	CD	Yes	Yes	Fair	Fair
Ma Y (42)	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Malik P (43)	Yes	Yes	NA	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Cabrera Martimbianco AL (44)	Yes	Yes	NA	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Sanchez-Ramirez DC (45)	Yes	Yes	CD	CD	NA	Yes	CD	NA	Yes	Fair	Fair
Sandler CX (46)	Yes	Yes	CD	NA	NA	Yes	CD	Yes	Yes	Fair	Fair

NIH = National Institutes of Health; CD = cannot determine; NR = not reported; NA = not applicable.

*The NIH Quality Assessment Tool for Case Series Studies (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>) contains nine questions:

1 = Was the study question or objective clearly stated?, 2 = Was the study population clearly and fully described, including a case definition?, 3 = Were the cases consecutive?, 4 = Were the subjects comparable?,

5 = Was the intervention clearly described?, 6 = Were the outcome measures clearly defined, valid, reliable, and implemented

consistently across all study participants?, 7 = Was the length of follow-up adequate?, 8 = Were the statistical methods well-described?,

9 = Were the results well-described?

Table 2: Characteristics of 50 included studied in the umbrella review

First Author and Country	Included studies	Study population	Late complication										Complication Assessment methods	Time of late complication onset	Time of recovery from mentioned Sequelae	Late complications	
			Cardiovascular	Renal	Hepatic and Gastrointestinal	Respiratory	Neurologic and Psychiatric	Musculoskeletal and Rheumatologic	Stroke	Ocular	Thrombosis or Embolism						
Fernández-de-las-Peñas C (51) Spain	35	28, 438				*									47.1% at onset or hospital admission, 10.2% at 30 days, 16.5% at 60 days, 10.6% at 90 days, and 8.4% at ≥180 days after onset/hospital discharge		Post-COVID headaches seems to be stable during the first 180 days.
De Luca P (60) Italy	16	5582				*									-	-	Association between SARS-CoV-2 infection and persistent hearing or chemosensory problems in patients with COVID-19
Ahmed JO (50) Iraq	40	55				*		*							Average interval between COVID-19 infection to the onset of neurological sequelae was 33.2 days.	-	Guillain-Barre syndrome was the most commonly reported neurological condition. Transverse myelitis, critical illness neuromyopathy/neuropathy, encephalopathy, parkinsonism, optic neuritis, status epilepticus, encephalitis, bell's palsy, vestibulocochlear neuritis, opsoclonus myoclonus syndrome, and myopathy were also reported.
Ali SS (61) Pakistan	10	13				*								Magnetic resonance imaging (MRI): 6(46.2%) cases, electroencephalography (EEG): 3(23.1%) cases, fluorodeoxyglucose (FDG): 3(23.1%) cases, positron emission tomography (PET): 3(23.1%) cases.	-	-	Cogwheel rigidity was the most common symptom of Parkinsonism in patients.

Table 2: Characteristics of 50 included studied in the umbrella review

Premraj L (13) Australia	18	10,530				*					-	-	3 or more months post-infection	Fatigue, cognitive dysfunction (brain fog, memory issues, attention disorder), and Psychiatric manifestations (sleep disturbances, anxiety, and depression)
Pinzon RT (14) Indonesia	36	9944				*					Chest CT: 13 studies, pulmonary function test (PFT): 10 studies	During the first six months after the onset of illness	-	Fatigue- cognitive disorder; paresthesia; sleep disorder; musculoskeletal pain; and dizziness
So M (52) USA	15	3066				*					Lung Function Pulmonary function tests (including spirometry, lung volume, and diffusion capacities): 20% (95% CI 13–17%)	-	-	Chest CT abnormalities: glass opacity in 44.1%, parenchymal band or fibrous stripe in 33.9%. Abnormal pulmonary function test: 44.3%, impaired diffusion capacity 34.8%. Restrictive and obstructive patterns: 16.4% and 7.7%, respectively.
Long Q, Li J (15) China	16	4478				*					-	-	-	Fatigue, weakness, psychosocial symptoms, and abnormalities in lung function
Patria YN (53) Indonesia	7	378				*					Lung function test: (77.56, 95% CI: 47.83–107.29)	-	-	Abnormal lung function for at least several weeks in the recovery period.
Vanderlind WM (16) USA	33	9676				*					-	-	-	Sleep difficulties, fatigue, anxiety, acute and posttraumatic stress, depression, self-reported cognitive functioning, psychiatric sequelae
Renaud-Charest O (47) Canada	8	1058				*					The DSM-V criteria (n = 1), 13-items Beck's Depression Inventory (BDI-13) (n = 2), Zung Self-Rating Depression Scale (ZSDS) (n = 1), Depression, Anxiety and Stress Scale (DASS-21) (n = 1), Hospital Anxiety and Depression Scale (HADS) (n = 3), Patient Health Questionnaire (PHQ-9) (n = 1), and Quality of Life in Neurological Disorders (Neuro-QoL) (n = 1).	-	-	Depressive symptoms

Table 2: Characteristics of 50 included studied in the umbrella review

Schou TM (17) Denmark	6	751955				*								-	-	-	Anxiety and/or depression, post-traumatic stress disorder (PTSD), cognitive deficits, fatigue, and sleep disturbances
Arora T (18) UAE	28	97173				*								-	-	-	Anxiety, PTSD, stress/distress, depression, anger, fear, worry, sleep quality/insomnia
Zürcher SJ (48) Switzerland	59	11248				*								High ZSDS scores: (symbol coding test: Wald = 8.37, p = 0.003), DASS-21 depression scores (Mini-Mental State Examination: $\beta = -0.039$, p = 0.007), performance on tests assessing immediate recall in verbal memory (California Verbal Learning Test: $\beta = -0.432$, p = 0.016), visual reaction times (Test of Everyday Attention: $\beta = 6.298$, p = 0.007), executive abilities (Tower of London test: $\beta = -0.149$, p = 0.008) and visuospatial abilities (Rey figure copy and recall: $\beta = -0.096$, p = 0.044).	-	-	Mental health problems
Bourmistrova NW (20) UK	33	4935				*								-	-	-	Sleep disturbances (primarily insomnia), PTSD, anxiety, and depression
Badenoch JB (19) UK	51	18917				*								-	-	-	Sleep problems and fatigue appear to affect roughly one-quarter of survivors. Cognitive impairment, anxiety, post-traumatic symptoms, and depression are also common in the first 6 months.
Khraisat B (21) USA	27	9605				*								-	-	-	PTSD, anxiety, psychological distress, depression, and sleeping disorders
Alosaimi B (55) Saudi Arabia	15	6229	*											Cardiac MRI, ECG, Echocardiography, cardiac enzyme (Troponin I or T), and Holter monitoring	-	-	Pericardial effusion, myocarditis, pericarditis, elevated troponin levels, and myocardial edema
Ramadan MS (56) Italy	35	52, 609	*											Cardiac MRI, echocardiography, troponin, Questionnaires, N-terminal proB-type natriuretic peptide (NT-proBNP), endomyocardial biopsy, 24-hour ECG, clinical assessment, coronary angiography, and registry analysis.	41 to 71 days	-	Cardiovascular findings in MRI were: increased T1 intensity, late gadolinium enhancement, increased T2 intensity, pericardial effusion, decreased global longitudinal strain, decreased left ventricular ejection fraction, myocardial enhancement, pericardial enhancement, myocarditis, myopericarditis, pericarditis, and myocardial infarction as cardiac sequelae. Studies using echocardiography reported reduced left ventricular ejection fraction, pericardial effusion, global hypokinesis, left ventricular hypertrophy, diastolic dysfunction, and pulmonary hypertension.

Table 2: Characteristics of 50 included studied in the umbrella review

Lopez-Leon S (58) USA	21	80,071 children and adolescents	*	*	*	*	*	*	*	-	*	-	-	from 1 to 13 months.	-	General prevalence of long-COVID-19 in children and adolescents was 25.24%. For hospitalized patients, the prevalence of long-COVID-19 was 29.19%. Mood changes, fatigue, sleep disorders, headache, respiratory symptoms, sputum/nasal congestion, cognition difficulties, loss of appetite, exercise intolerance, altered smell, hyperhidrosis, chest pain, dizziness, rhinorrhea, cough, myalgia/arthralgia, body weight changes, altered taste, otalgia, ophthalmologic problems, abdominal pain, dermatologic problems, sore throat, chest tightness, variations in heart rate, constipation, dysphonia, fever, diarrhea, vomiting, palpitations, hair loss, neurological abnormalities, urinary symptoms, dysphagia, and speech disturbances Compared to controls, children with long-COVID-19 had a higher risk of persistent dyspnea, anosmia/ageusia, and/or fever.
Ahmed H (22) UK	28	2,854				*	*	*	*		*		SF-36 for health-related quality of life, George's Respiratory Questionnaire (SGRQ), chest CT	Up to 6 months after discharge	-	Post-traumatic stress disorder, depression, and anxiety were considerable beyond 6 months after discharge.
Alkodaymi MS (23) USA	63	257,348				*							Physical assessment, ICD-10 codes, electronic medical records	3-12 months after recovery from COVID-19	-	Fatigue.
Ceban F (24) Canada	81	29,128				*							mesoscale-discovery (MSD) multiplexed immunoassay (Immunological parameters), Self-report, TICS-M (cognitive function), EQ-5D-5L (quality of life), MoCA (cognitive function), SF-20 (quality of life)	3-6 months after testing positive for COVID-19	Median 85 days	Fatigue
Chen C, Haupt SR (25) USA	50	1,680,003				*	*						-	3-9 months after diagnosis	-	Fatigue and joint pain

Table 2: Characteristics of 50 included studied in the umbrella review

Fernández-de-Las-Peñas C (26) Spain	29	24, 255	*			*	*	*			-	Median 82 days	-	Palpitation, fatigue, depression, apnea, throat ache, joint pain
Lopez-Leon S (7) USA	15	47, 910				*	*				Chest X-ray, chest CT, D-dimer, CRP	-	-	Fatigue, depression, shortness of breath
Michelen M (27) UK	32	10, 951				*	*				Self-report, physical assessment	Median 221 days	-	Fatigue, depression, shortness of breath, lung abnormalities
Nguyen NN (28) Germany	37	N/A				*	*	*			Self-report, physical assessment	35-90 days	-	Fatigue, depression, apnea, joint pain
Salamanna F (29) Italy	145	22, 254	*			*	*				-	Abnormal lung functions up to 6 months, cardiovascular up to 8 months	-	Palpitation, cardiovascular injury, anxiety, depression, fatigue, body aches, olfactory dysfunction,
Sandra Willi (62) Switzerland	31	48, 246	*			*	*				Chest CT, radiological findings	11-90 days Respiratory up to 12 weeks after hospital admission Cardiovascular 11 weeks after onset of COVID-19 symptoms	-	Impaired pulmonary function, breathlessness, decrease in quality of life, pulmonary fibrosis, myocarditis, fatigue
Yang T (30) Germany	72	88, 769	*			*	*	*			-	Average 95 days	Average after more than 9 months	Fatigue, depression, joint pain, arthralgia, dyspnea, alopecia, anxiety
Zeng N (31) China	151	1, 285, 407				*	*				Chest CT, radiological findings	Mental sequela up to 12 months	-	Abnormal pulmonary function tests, fatigue, memory impairment, depression, PTSD
Almas T (32) Ireland	21	54730				*	*	*			-	Chest pain after 60 days of illness, ongoing palpitations after 6-months	60 days – 6 months	Fatigue, dyspnea, arthralgia, alopecia, anxiety, hyperhidrosis, insomnia
Ahmad MS (33) Saudi Arabia	20	14146				*	*	*	*		Standard questionnaires, PFTs, QoL assessment parameters, chest CT, MRI, Spirometry	From 4 weeks – 6 months	-	Fatigue, dyspnea, cough, sore throat, joint pain, chest pain, loss of smell/taste, depression, headache, diarrhea, anxiety, loss of memory
Healey Q (34) UK	19	10643				*	*	*	*		Chest CT, Biomarkers	Up to 4 weeks after acute infection	-	Fatigue, dyspnea, gustatory dysfunction, cough, olfactory dysfunction, myalgia

Table 2: Characteristics of 50 included studied in the umbrella review

d'Ettorre G (35) Italy	13	4395				*	*	*					Chest CT, MRI, 6MWT, D-dimer, PFTs	From 9 – 291 days	-	Sleep difficulties, dyspnea, chest pain, loss of smell, PTSD, anxiety, depression, headache, pulmonary fibrosis, muscle weakness, brain fog, dizziness
Groff D (36) USA	57	250351					*	*					PFTs , CT, MRI, PHQ, mMRC, 6MWT, Body plethysmography, Echo, GAD-7, SGRQ, EQ-5D-5L, HADS, MMSE, SF-12, SCIP, WAIS-III, PTSD (DTS), CFQ-11	30 days after illness and beyond	Up to 6 months	Difficulty concentrating, generalized anxiety disorder, memory deficits, fatigue, cognitive impairment, anosmia, dysgeusia
Han Q (37) UK	18	8591				*	*	*					Validated questionnaires, mMRC, HADS, Insomnia Severity Index	Up to 12 months	From 3-12 months	Fatigue, dyspnea, depression, arthromyalgia, anxiety, insomnia, memory loss, concentration difficulties
Iwu CJ (38) South Africa	11	86				*	*	*					CT, Biomarkers, laboratory tests, PFTs, validated survey instruments, Vascular changes	Up to 6 weeks after infection	12th week after discharge	Fatigue, cough, sleep disorders, shortness of breath, depression, anxiety
Iqbal FM (39) UK	43	12974				*	*	*					MRI, SF-36, WEMWBS, PET scan, CT scan, ImMRC scale, CFS, SF-36, PTSD, HADS questionnaires	Up to 12 weeks and beyond	-	Fatigue, sleep disturbance, dyspnea, anxiety
SeyedAli-naghi S (40) Iran	65	N/A	*	*	*	*	*	*	*	*	*	*	MRI	Up to 8-10 weeks and beyond	-	Lung, liver, kidney, and heart injuries, neurological injuries, cardiac/brain stroke, hypoproteinemia, encephalopathy, thromboembolism, septic shock, multiple organ dysfunction syndromes, psychological distress
Jennings G (41) Ireland	39	8293				*	*	*					Spirometry, CT, HRCT, CXR, MRI, PFTs, EQ-5D-5L	Up to 31 weeks	-	Fatigue, Sleep disorder, depression, cognitive impairments, confusion, cough, dyspnea, anxiety, arthralgia, myalgia, headache, chest pain, throat pain, fever, expectoration, weight loss, skin problems, anosmia, ageusia, hair loss
Ma Y (42) China	40	10, 945				*	*	*					CT, PFTs, mMRC, GAD-7 scores, 6MWT, EQ-5D-5L	Up to 6 months and above	at 12 months and beyond	Fatigue, mild dyspnea, anxiety, depression, sleep difficulty, difficulty concentrating, myalgia, joint pain, rhinorrhea
Malik P (43) USA	12	4828				*	*	*					EQ-5D-5L, VAS scale	-	-	Fatigue, cough, chest pain, dyspnea, anosmia, arthralgia, headache, sleep disturbances, mental health problems, poor QoL

Table 2: Characteristics of 50 included studied in the umbrella review

Cabrera Martim-bianco AL (44) Brazil	25	5440				*	*	*						-	From 3 to 24 weeks	-	Chest pain, arthralgia, dyspnea, cough, fatigue, sputum production, sleep disorders, cognitive and memory impairment, myalgia, functional impairment
Sanchez-Ramirez DC (45) Canada	24	5323				*	*							CT, PFTs, mMRC, WPAI, performance-based tests, SPPB, 1-MSTST, 2MWT, 6MWT, EQ-5D-5L, SF-36	up to 6 months after infection	-	Fatigue, chest pain, cough, dyspnea, poor QoL
Sandler CX (46) Australia	21	7639					*							Blood count, CXR, CT, PFTs, ECG, Echo, validated multi-item fatigue questionnaire	Up to 16–20 weeks	From 8 weeks and beyond	Fatigue

Abbreviations: chest X-ray (CXR), chronic fatigue syndrome (CFS), computed tomography (CT), George's Respiratory Questionnaire (SGRQ), High-resolution computed tomography (HRCT), Hospital Anxiety and Depression (HADS), Magnetic resonance imaging (MRI), Mini-Mental State Examination (MMSE), Modified Medical Research Council (mMRC), positron emission tomography (PET), posttraumatic stress disorder (PTSD), Pulmonary function tests (PFTs), Quality of Life (QoL), The 36-Item Short Form Survey (SF-36), The Short Physical Performance Battery (SPPB), The Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS), Work Productivity and Activity Impairment (WPAI)

Supplementary 1: The study search strategy in different databases

PubMed Search Query; Time of search: 29 August 2022; Results: 453
("COVID-19"[mesh] OR "SARS-CoV-2"[mesh] OR COVID-19[tiab] OR SARS-CoV-2[tiab] OR coronavirus disease 2019[tiab] OR severe acute respiratory syndrome coronavirus 2[tiab]) AND (Long-Term Outcome*[tiab] OR Long-Term complication*[tiab] OR Late complication*[tiab] OR Chronic complication*[tiab] OR Long-term effect*[tiab] OR Long-Term Impact*[tiab] OR Consequence*[tiab] OR Sequelae[tiab] OR Long Covid[tiab] OR Sequel[tiab] OR post-acute COVID syndrome[tiab] OR long-COVID[tiab] OR post-acute COVID19 syndrome[tiab]) AND (Systematic review[tiab] OR meta-analysis[tiab])
Embase Search Query; Time of search: 29 August 2022; Results: 496
('coronavirus disease 2019'/exp OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'COVID-19':ab,ti OR 'SARS-CoV-2':ab,ti OR 'coronavirus disease 2019':ab,ti OR 'severe acute respiratory syndrome coronavirus 2':ab,ti) AND ('long COVID'/exp OR 'Long-Term Outcome*':ab,ti OR 'Long-Term complication*':ab,ti OR 'Late complication*':ab,ti OR 'Chronic complication*':ab,ti OR 'Long-term effect*':ab,ti OR 'Long-Term Impact*':ab,ti OR 'Consequence*':ab,ti OR 'Sequelae':ab,ti OR 'Long Covid':ab,ti OR 'Sequel':ab,ti OR 'post-acute COVID syndrome':ab,ti OR 'long-COVID':ab,ti OR 'post-acute COVID19 syndrome':ab,ti) AND ('Systematic review':ab,ti OR 'meta-analysis':ab,ti)
Scopus Search Query; Time of search: 29 August 2022; Results: 495
(TITLE-ABS ("COVID-19" OR "SARS-CoV-2" OR "coronavirus disease 2019" OR "severe acute respiratory syndrome coronavirus 2")) AND (TITLE-ABS ("Long-Term Outcome*" OR "Long-Term complication*" OR "Late complication*" OR "Chronic complication*" OR "Long-term effect*" OR "Long-Term Impact*" OR "Consequence*" OR "Sequelae" OR "Long Covid" OR "Sequel" OR "post-acute COVID syndrome" OR "long-COVID" OR "post-acute COVID19 syndrome")) AND (TITLE-ABS ("Systematic review" OR "meta-analysis"))
Web of Science Search Query; Time of search: 29 August 2022; Results: 452
(TS= ("COVID-19" OR "SARS-CoV-2" OR "coronavirus disease 2019" OR "severe acute respiratory syndrome coronavirus 2")) AND (TS= ("Long-Term Outcome*" OR "Long-Term complication*" OR "Late complication*" OR "Chronic complication*" OR "Long-term effect*" OR "Long-Term Impact*" OR "Consequence*" OR "Sequelae" OR "Long Covid" OR "Sequel" OR "post-acute COVID syndrome" OR "long-COVID" OR "post-acute COVID19 syndrome")) AND (TS= ("Systematic review" OR "meta-analysis"))