Received: 23 August 2021 | Revised: 2 November 2021 | Accepted: 3 November 2021

DOI: 10.1002/rmv.2315

REVIEW

WILEY

Proposed subtypes of post-COVID-19 syndrome (or long-COVID) and their respective potential therapies

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Summary

The effects of coronavirus disease 2019 (COVID-19), a highly transmissible infectious respiratory disease that has initiated an ongoing pandemic since early 2020, do not always end in the acute phase. Depending on the study referred, about 10%–30% (or more) of COVID-19 survivors may develop long-COVID or post-COVID-19 syndrome (PCS), characterised by persistent symptoms (most commonly fatigue, dyspnoea, and cognitive impairments) lasting for 3 months or more after acute COVID-19. While the pathophysiological mechanisms of PCS have been extensively described elsewhere, the subtypes of PCS have not. Owing to its highly multifaceted nature, this review proposes and characterises six subtypes of PCS based on the existing literature. The subtypes are non-severe COVID-19 multi-organ sequelae (NSC-MOS), pulmonary fibrosis sequelae (PFS), myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS), post-intensive care syndrome (PICS) and medical or clinical sequelae (MCS). Original studies supporting each of these subtypes are documented in this review, as well as their respective symptoms and potential interventions. Ultimately, the subtyping proposed herein aims to provide better clarity on the current understanding of PCS.

KEYWORDS
intervention, long-COVID, post-COVID-19 syndrome, SARS-CoV-2, sequelae, subtype

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; BPM, beats per minute; CBT, cognitive behavioural therapy; CCC, Canadian Consensus Criteria; CDC, Centres for Disease Control and Prevention; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CT, computed tomography; CVD, cardiovascular disease; DLCO, diffusing capacity of the lung for carbon monoxide; DVT, deep vein thrombosis; FVC, forced vital capacity; GET, graded exercise therapy; GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; HRCT, high-resolution computed tomography; ICU, intensive care unit; IOM, Institute of Medicine; IT, impact tool; LRT, lower respiratory tract; MCS, medical or clinical sequelae; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; MRI, magnetic resonance imaging; MV, mechanical ventilation; NCS-MOS, non-severe COVID-19 multi-organ sequelae; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NIH, National Institute of Health; NIHR, National Institute for Health Research; O_2, oxygen; OR, odds ratio; ONS, Office for National Statistics; PASC, post-acute sequelae of SARS-CoV-2; PE, pulmonary embolism; PEM, post-exertional malaise; PCR, polymerase chain reaction; PCS, post-COVID-19 syndrome; PFS, pulmonary fibrosis sequelae; PICS, post-intensive care syndrome; POTS, postural orthostatic tachycardia syndrome; PTSD, post-traumatic stress disorder; RAAS, renin-angiotensin-aldosterone system; RR, rate ratio; RCT, randomized clinical trial; RCGP, Royal College of General Practitioners; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGLT2, sodium-glucose co-transporter-2; SIGN, Scottish Intercollegiate Guidelines Network; ST, symptom tool; TLC, total lung capacity; URTI, upper respiratory tract infection; UTI, urinary tract infection; WHO, World Health Organization.

1 | INTRODUCTION

The advent of the highly infectious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the coronavirus disease 2019 (COVID-19) pandemic, announced by the World Health Organization (WHO) in 2 March 2020.[1] COVID-19 is a respiratory infectious disease that is generally mild in younger but severe in older individuals. Current pharmaceutical interventions against COVID-19 include antivirals, immunomodulators, monoclonal antibodies, and vaccines.[2] Globally, as of November 2021, COVID-19 has surpassed 245 million cases and 4.9 million deaths, and over 6.8 million doses of COVID-19 vaccines have been administered (https://covid19.who.int/). The pandemic health toll does not end there, however, as survivors of COVID-19 may continue to develop post-COVID-19 syndrome (PCS; also called long-COVID-19). The National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), and Royal College of General Practitioners (RCGP) characterised PCS by symptoms lasting for over 3 months after the first COVID-19 symptom onset.[3,4] An overview of the disease course from acute COVID-19 to PCS is described in Figure 1.

Fatigue, dyspnoea, and cognitive impairments are the most typical PCS symptoms[3,10,11]; other symptoms such as mood changes, anxiety, insomnia, headache, sore throat, smell and taste dysfunctions, cough, chest pain, palpitations, tachycardia, diarrhoea, nausea, myalgia, joint pain, hair loss and skin rashes may also be present[11–13] (Figure 2). These symptoms can differ in prevalence, relapse pattern, duration and severity level. According to published reports, about 10%–30% (or even higher in certain studies) of COVID-19 survivors develop PCS (Table 1). The WHO and UK Office for National Statistics (ONS) have estimated that 10% of COVID-19 cases, regardless of hospitalisation history, will lead to PCS.[14,15]

A syndrome refers to a collection of symptoms with aetiology that may not be clear. In contrast, a disease has a defined set of symptoms and aetiology.[16] Thus, PCS, being a syndrome, likely comprises multiple pathophysiology and subtypes. Although many systematic and narrative reviews on PCS have been published,[8,10,17–19] PCS subtyping has not received much attention thus far. To this end, this review aimed to characterise PCS into five putative subtypes, as well as their respective manifestations, pathophysiology and therapeutic interventions of each subtype.

2 | METHODS

We performed a narrative review semi-systematically. We did not conduct a systematic review per the standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[20] as this review aims to propose and characterise several subtypes of PCS. Therefore, the review topic is broad, involving multiple PCS subtypes and their respective putative symptoms, pathophysiology and therapeutic interventions, making it more suitable as a narrative review.

2.1 | Eligibility criteria

Primary studies (i.e., original research) that reported persistent symptoms or sequelae lasting for ≥3 months after symptom onset, hospital discharge, hospital admission, or diagnosis in the context of COVID-19 are recognised as PCS.[3] To narrow the scope to specific subtypes, the PCS-related studies were considered eligible if they contained relevant information about non-severe COVID-19 multiorgan sequelae (NSC-MOS), pulmonary fibrosis sequelae (PFS), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS), post-intensive care syndrome (PICS) or medical or clinical sequelae (MCS). These

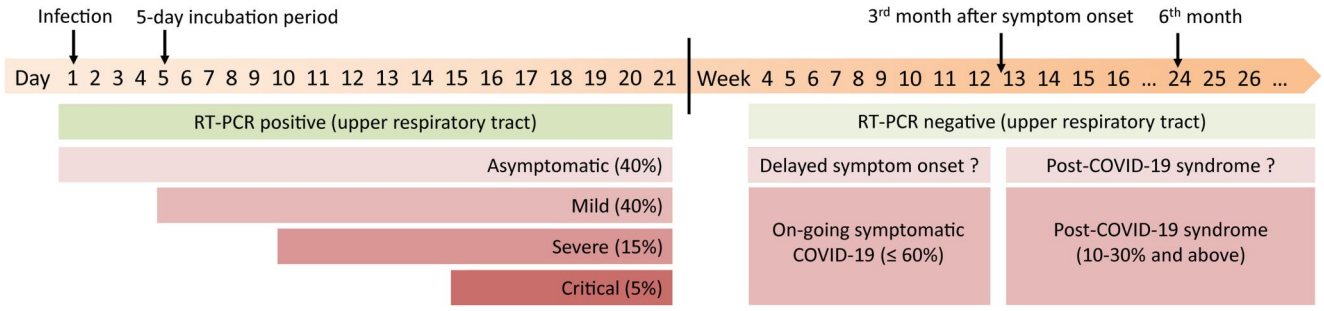

FIGURE 1 An overview of the disease course of COVID-19. Following an incubation period of about 5 days, people infected with SARS-CoV-2 may remain asymptomatic or develop symptomatic COVID-19. In the latter case, individuals usually develop mild disease first, which may progress to severe or critical disease at about day 5–10 after symptom onset, respectively.[1,5] The prevalence of asymptomatic, mild, severe and critical COVID-19 is estimated at 40%, 40%, 15% and 5% of cases, respectively.[1,6,7] Following acute COVID-19 lasting about 3–4 weeks, individuals are usually no longer positive for SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR) test of the upper respiratory tract, but ongoing symptoms may still be present.[8,9] When such ongoing symptoms persist for more than 3 months since symptom onset, post-COVID-19 syndrome (PCS) is characterised, per the National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN) and Royal College of General Practitioners (RCGP) guidelines.[3] Notably, several studies have reported that PCS could last for beyond 3–6 months (Table 1)

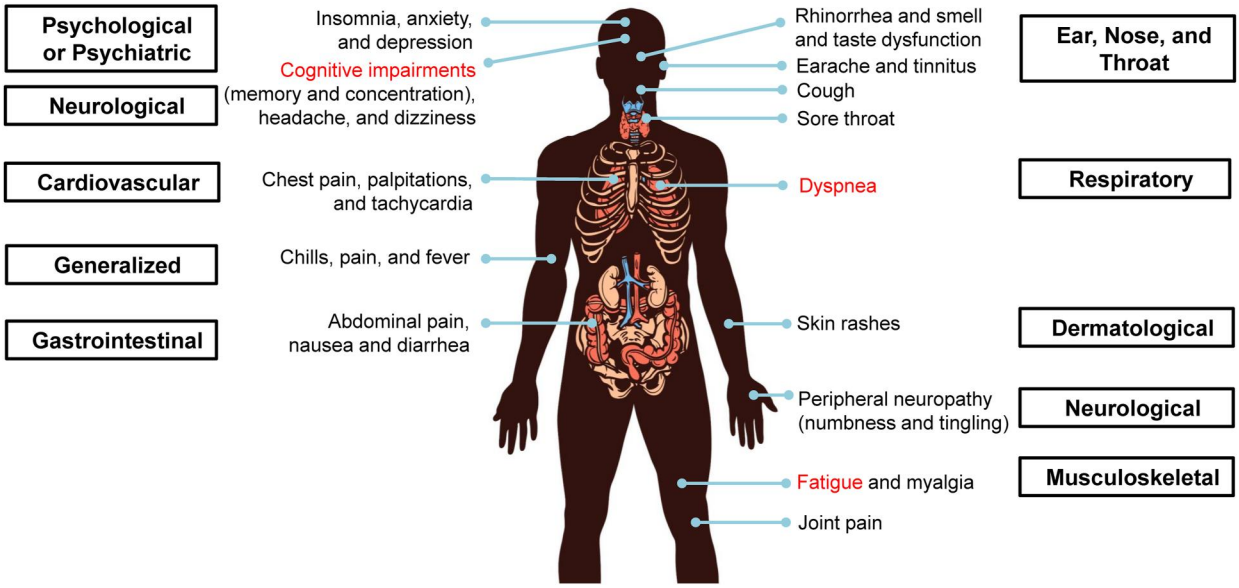

FIGURE 2 Symptoms of the post-COVID-19 syndrome (PCS). Multiple organ systems are affected, such as psychological or psychiatric (insomnia, anxiety and depression), neurological (cognitive impairments involving memory and concentration, headache, dizziness and peripheral neuropathy), ear, nose, and throat (rhinorrhoea, smell and taste alterations, earache, tinnitus, cough, and sore throat), respiratory (dyspnoea and cough), cardiovascular (chest pain, palpitations and tachycardia), gastrointestinal (abdominal pain, nausea and diarrhoea), generalised (chills, pain and fever) and musculoskeletal (fatigue, myalgia and joint pain). Dyspnoea, fatigue, and cognitive impairments are among the topmost common PCS symptoms (references in Table 1), as reviewed in Shah et al.,[3] Nasserie et al.,[10] Michelen et al.[11] and Lopez-Leon et al[19]. (The human body vector was licenced from Freepik.com.)

subtypes were determined based on initial narrative search and understanding of the PCS literature.

Studies were excluded if they were not in English, not an original study (i.e., reviews, editorials, etc.), or not involving COVID-19 or SARS-CoV-2 survivors. Articles with inaccessible full texts, incompatible or irrelevant outcomes, insufficient information were also excluded. Case studies were excluded as well. If more than 10 original studies were identified for a particular PCS subtype, those with relatively less information (e.g., low sample size or less extensive clinical evaluations) were excluded.

2.2 | Search strategy

The following keywords were searched in all fields in articles indexed in PubMed, SCOPUS and Web of Science from 1 January 2020 until 14 August 2021: ('post-COVID-19 syndrome' OR 'long COVID' OR 'post-COVID' OR 'post-SARS-CoV-2' OR 'post-acute SARS-CoV-2' OR 'post-acute COVID') AND ('multi-organ' OR 'pulmonary fibrosis' OR ME/CFS OR 'chronic fatigue syndrome' OR 'postural orthostatic tachycardia syndrome' OR POTS OR 'post-intensive care syndrome' OR PICS OR disease OR disorder OR sequelae). The titles and abstracts were screened to identify relevant papers that contribute to the current review's aim of characterising PCS subtypes. Reference lists of pertinent articles were also screened for any additional relevant articles that might have been omitted.

3 | RESULTS

A total of 1439 articles were identified, of which 43 met the eligibility criteria and presented qualitatively in Table 1. The excluded studies based on full texts were mainly due to a follow-up duration of <3 months and incompatible/irrelevant outcomes with PCS subtypes. Most of the included studies are retrospective or prospective cohort studies, with only a few cross-sectional studies and one case series (Figure 3). Specifically, 10, 10, 7, 5, 4 and 8 original studies were identified for the NCS-MOS, PFS, ME/CFS, POTS, PICS, and MCS subtypes, respectively. Each of these subtypes is further discussed narratively, focussing on their respective putative or potential manifestations, pathophysiology, and therapeutic interventions.

3.1 | Non-severe COVID-19 multi-organ sequelae (NSC-MOS)

Despite being a respiratory disease, COVID-19 can affect extrapulmonary organ systems, such as the nervous, gastrointestinal, renal, and cardiovascular systems, through various mechanisms.[64] Considering that tissues or organs may endure sub-clinical dysfunction from acute COVID-19, the resulting multi-organ sequelae (MOS) may lead to PCS. The specifics of these multi-organ pathological mechanisms leading to PCS are beyond the scope of this review and have been extensively reviewed elsewhere.[8,65,66]

TABLE 1 Description of pertinent studies supporting the individual proposed subtypes of the post-COVID-19 syndrome (PCS)

Study	Sample characteristics (COVID-19 survivors)	Persistent symptoms	Persistent sequelae	Other notable points
(A) Non-severe COVID-19 multi-organ sequelae (NSC-MOS) subtype				
Davis et al.[21,22]; retrospective	*N = 3762%; 85% were 30–60 years; 79% females; 6- to 7-month post-symptom onset; US, UK and other countries	• 70%–80% had fatigue and PEM • 50%–60% had cognitive impairments and sensorimotor symptoms • 30%–50% had insomnia, myalgia, palpitations, dyspnoea, dizziness, joint pain and tachycardia	• 45% required reduced work schedule compared to pre-COVID-19	• 92% were not hospitalised • Persistent symptoms were not associated with age or sex • Association between persistent symptoms and initial disease severity were not reported (presumably none)
Petersen et al.[23]; retrospective	N = 180; mean age of 40 years; 54% females; 4-month post-symptom onset; Faroe Islands, Denmark	• 55% had ≥1 persistent symptom • ~30% had fatigue and anosmia • <15% had ageusia, joint pain, rhinorrhoea, dyspnoea, headache, myalgia, nausea, chest tightness, chills, cough and diarrhoea	• N/A	• 96% were not hospitalised • Persistent symptoms were associated with older age but not sex, comorbidities or prior hospitalisation
Augustin et al.[24]; prospective	N = 958; median age of 43%; 53.5% females; 4-month (N = 442) and 7-month (N = 353) post-diagnosis or post-symptom onset; Cologne, Germany	• 28% and 35% had ≥1 persistent symptom at 4- and 7-month, respectively • 12% and 15% had anosmia at 4- and 7-month, respectively • 11% had ageusia at 4- and 7-month • 10% and 15% had fatigue at 4- and 7-month, respectively • 9% and 14% had dyspnoea at 4- and 7-month, respectively • <3% had headache, alopecia and diarrhoea at 7-month	• N/A	• 97.1% were not hospitalised • Persistent symptoms were associated with female sex, low IgG levels at baseline and ≥5 symptoms during acute COVID-19 • Persistent symptoms were not associated with age, comorbidities or initial disease severity
Dennis et al.[25]; prospective	*N = 201; mean age of 45 years; 71% females; median of 140-day post-symptom onset; Oxford and London, UK	• 99% had ≥4 and 42% had ≥10 persistent symptoms • 98% had fatigue • 80%–90% had myalgia, dyspnoea and headache • 50%–80% had joint pain, cough, chest pain, sore throat, diarrhoea and pain • <50% had wheezing, inability to walk and rhinorrhoea	• MRI abnormalities were present in single organ (70%) and multi-organ (29%); i.e., the lungs (33%), heart (32%), pancreas (17%), kidneys (12%), liver (10%), and spleen (6%)	• 81% were not hospitalised • Persistent symptoms were not associated with age, sex, BMI or prior hospitalisation • MRI abnormalities were associated with prior hospitalisation but not age, sex or BMI
Blomberg et al.[26]; prospective	N = 312; median age of 46 years; 51% females; 6-month post-acute COVID-19; Bergen, Norway	• 61% had ≥1 persistent symptom • 37% had fatigue • 20%–30% had concentration impairment, disturbed taste or smell, memory problems and dyspnoea	• N/A	• 79% were home-isolated (mild-to-moderate COVID-19) • 21% were hospitalised • 13% of children (0–15 years; all home-isolated) and 52% of young adults (16–30 years; all home-isolated) developed PCS • Overall persistent symptoms were associated with female sex, ↑ antibody titres and pre-existing lung diseases, but not initial disease severity, age or BMI

TABLE 1 (Continued)

Study	Sample characteristics (COVID-19 survivors)	Persistent symptoms	Persistent sequelae	Other notable points
Lombardo et al.[27]; cross-sectional	*N* = 303; median age of 53 years; 54% females; 12-month post-acute COVID-19; Milan, Italy	• 81% had ≥1 persistent symptom • 52% had fatigue • 48% had muscle or joint pain • 47% had sleep disorders • 36% had respiratory, cognitive or neurological disorders • 28% had sensory alterations • 18% had movement impairments • 12% had GI symptoms.	• N/A	• 38% were not hospitalised, of which 10% were asymptomatic • 62% were hospitalised, of which 35% needed supplemental O_2, 38% needed MV and 4% were in ICU • Persistent symptoms were associated with older age and female sex, but not initial disease severity
Seessle et al.[28]; prospective	*N* = 96; median age of 57 years; 55% females; 12-month post-symptom onset; Heidelberg, Germany	• 77% had ≥1 persistent symptom • 50%–56% had fatigue and reduced exercise capacity • 30%–40% had dyspnoea and cognitive impairments • 20%–30% had sleep problems, body aches, vertigo, headache, anxiety • 10%–20% had anosmia, cough, cold, hair loss and palpitations • <10% had fever, sore throat, vomiting, nausea, diarrhoea and shivering	• N/A	• 32% were hospitalised • 71% had mild-to-moderate disease • 29% had severe-to-critical disease • Persistent symptoms were associated with higher antinuclear antibodies titres and female sex, but not initial disease severity
Buonsenso et al.[29]; cross-sectional; preprint	**N* = 510; mean age of 10 years; 56% females; mean of 8-month post-symptom onset; UK, US and other countries	• 87% had tiredness and weakness • 70%–80% had fatigue, headache and abdominal pain • 50%–60% had PEM, myalgia, joint pain, rashes, irritability and cognitive impairment • 40%–50% had palpitations, nausea, diarrhoea, vomiting, sore throat and dizziness • <40% had other symptoms such as cough and flu-like symptoms	• All children had ≥1 and 64% had ≥4 health changes since infection in energy levels (83%), mood (59%), sleep (56%), and appetite (50%).	• 96% were not hospitalised • 12% had asymptomatic infection • Association between persistent symptoms and initial disease severity were not reported (presumably none)
Buonsenso et al.[30]; cross-sectional	*N* = 129; mean age of 11 years; 62% females; 162-day post-diagnosis; Rome, Italy	• 53% had ≥1 persistent symptom • 19% had insomnia • 10%–15% had respiratory symptoms, fatigue, myalgia, headache and concentration impairment • <10% had other symptoms, such as joint pain, abdominal pain, skin rashes, palpitations, chest pain, and altered smell and taste	• N/A	• 95% were not hospitalised. • 26% had asymptomatic infection, of which 27% developed persistent symptoms • Association between persistent symptoms and initial disease severity were not reported (presumably none)

(Continues)

TABLE 1 (Continued)

Study	Sample characteristics (COVID-19 survivors)	Persistent symptoms	Persistent sequelae	Other notable points
Osmanov et al.[31]; prospective	*N* = 518; median age of 10 years; 52% females; 8-month post-discharge; Moscow, Russia	• 24% had ≥1 persistent symptom • 11% had fatigue • 7% had sleep disturbance • 6% had sensory problems • <5% had other symptoms: dyspnoea, altered sense of taste and smell, headache, cough, rash, diarrhoea, hair loss, joint and muscle pain, palpitation and dizziness	• N/A	• 37% had moderate disease • 2.7% had severe disease • Persistent symptoms were associated with older age and history of allergic diseases • Persistent symptoms were not associated with sex, BMI or initial disease severity
(B) pulmonary fibrosis sequelae (PFS) subtype				
Raman et al.[32]; prospective	*N* = 58; mean age of 55 years; 41% females; 2- to 3-month post-discharge; Oxford, UK	• 64% had dyspnoea • 55% had fatigue • 40% had cognitive impairments • 10%–20% had depression and anxiety	• MRI abnormalities were present in the lungs (60% of participants), kidneys (29%), heart (26%) and liver (10%)	• All were hospitalised • 36% were in ICU • MRI abnormalities were associated with more severe acute COVID-19
Morin et al.[33]; prospective	*N* = 478; mean age of 60 years; 58% females; 4-month post-discharge; le Kremlin-Bicêtre, France	• 51% had ≥1 persistent symptom • 31% had fatigue • 10%–20% had memory impairments, dyspnoea, and paraesthesia	In those who attended ambulatory visits (*N* = 177; mean age of 57 years): • 63% had lung CT scan abnormalities • 22% had impaired DLCO • 19% had pulmonary fibrosis • 10% had echocardiography abnormalities	• All were hospitalised • 30% were in ICU • Pulmonary fibrosis and echocardiography abnormalities occurred exclusively in ICU patients
Frija-Masson et al.[34]; retrospective	*N* = 137; median age of 59 years; 49% females; 3-month post-disease onset; Paris, France	• N/A	• 75% had chest CT abnormalities • 55% had impaired DLCO • 13% had pulmonary fibrosis via CT	• All were hospitalised • 90% needed supplemental O_2 • 32% needed MV. • Impaired DLCO was associated with more severe acute COVID-19
Froidure et al.[35]; retrospective	*N* = 134; median age of 60 years; 41% females; 3-month post-discharge; Brussels, Belgium	• 35% had dyspnoea • 25% had fatigue • 10% had dry cough	• 47% had impaired DLCO • 20% had pulmonary fibrosis via HRCT • 19% had impaired FVC • 19% participated in rehabilitation post-discharge	• All were hospitalised for severe-to-critical COVID-19 • 22% were in ICU • 11% required intubation • Pulmonary fibrosis was associated with ICU admission and intubation
Mumoli et al.[36]; retrospective	*N* = 88; mean age of 63 years; 26% females; 3-month post-discharge; Varese, Italy	• 49% had dyspnoea • <10% had arthralgia and fatigue • 40% had hypocapnia	• 55% had chest HRCT abnormalities. • 17% had pulmonary fibrosis via HRCT.	• All were hospitalised • 13% needed intubation or MV • Chest HRCT abnormalities were associated with dyspnoea and C-reactive protein levels on admission

TABLE 1 (Continued)

Study	Sample characteristics (COVID-19 survivors)	Persistent symptoms	Persistent sequelae	Other notable points
Robey et al.[37]; retrospective	*N* = 221; mean age of 58 years; 39% females; 4-month post-discharge; Manchester, UK	• 30% had ≥1 persistent symptom: dyspnoea, exercise intolerance, fatigue or cough	• 24% had impaired lung function, most commonly DLCO and FVC • 14% had chest CT abnormalities • 7% had pulmonary fibrosis via CT	• All were hospitalised • 76% require supplemental O_2 • 20% were in ICU • Persistent symptoms were associated with pre-existing comorbidities • Chest CT abnormalities and fibrosis were associated with ICU admission
Han et al.[38]; prospective	*N* = 114; mean age of 54 years; 30% females; 6-month post-symptom onset; Wuhan, China	• N/A	• 35% had pulmonary fibrosis via CT • 26% had impaired DLCO	• All were hospitalised • 21% had severe disease • Pulmonary fibrosis was associated with DLCO and more severe acute COVID-19
Li et al.[39]; prospective	*N* = 289; mean age of 44 years; 51% females; 3- to 5-month post-disease onset; Shenzhen, China	• 10%–20% had cough and fatigue • <10% had dyspnoea, exercise limitation and chest tightness	• 60% had pulmonary fibrosis via CT • 33% had impaired lung function	• Pulmonary fibrosis was associated with older age, higher BMI, comorbidities, initial disease severity, and elevated inflammatory biomarkers, but not persistent symptoms or lung function
Liu et al.[40]; prospective	*N* = 41; mean age of 50 years; 46% females; 7-month post-discharge; Chongqing, China	• N/A	• 29% had pulmonary fibrosis via CT	• All were hospitalised • 63% had moderate; 37% had severe-to-critical disease • Pulmonary fibrosis was associated with older age, impaired lung function, and more severe acute COVID-19
McGroder et al.[41]; prospective	*N* = 76; mean age of 54 years; 39% females; 4-month post-hospitalisation; New York, US	• 68% had dyspnoea • 53% had weak hand grip • 10%–20% had exhaustion, cough, weight loss and decreased activities	• 59% had chest HRCT abnormalities. • 53% had impaired DLCO. • 42% had pulmonary fibrosis via HRCT • 36% had impaired FVC	• All were hospitalised and required supplemental O_2 • 42% needed MV • Pulmonary fibrosis was associated with male sex, ↑ duration on MV, and more severe acute COVID-19
(C) Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) subtype				
Simani et al.[42]; retrospective	*N* = 120; mean age of 55 years; 33.3% females; 6-month post-discharge; Tehran, Iran	• 17.5% had fatigue	• Of those who had fatigue, 14% met the 1994 CDC criteria for ME/CFS • 6% had PTSD	• All were hospitalised • 8% were in ICU • Persistent symptoms were not associated with sex or comorbidities • Association between persistent symptoms and initial disease severity were not reported (presumably none)
Kedor et al.[43]; prospective; preprint	**N* = 42; median age of 36.5 years; 69% females; 6-month post-diagnosis; Berlin, German	• 90%–100% had fatigue, PEM, cognitive impairment, and headache	• 45% had ME/CFS following the 2003 CCC criteria	• All had non-severe (76% mild and 24% moderate) disease

(Continues)

TABLE 1 (Continued)

Study	Sample characteristics (COVID-19 survivors)	Persistent symptoms	Persistent sequelae	Other notable points
			• 74% required reduced workload or unable to work • The ME/CFS group reported more severe fatigue, stress intolerance, more frequent and longer-lasting PEM, and hypersensitivity to noise, light and temperature compared to the non-ME/CFS group	• Association between persistent symptoms and initial disease severity were not reported (presumably none)
Davis et al.[21,22]; retrospective	*N = 3762%; 85% were 30–60 years; 79% females; 6- to 7-month post-symptom onset; US, UK, and other countries	• 70%–80% had fatigue and PEM • 50%–60% had cognitive impairments and sensorimotor symptoms • 30%–50% had insomnia, myalgia, palpitations, dyspnoea, dizziness, tachycardia and joint pain	• 21% received a medical diagnosis, of which 15% were ME/CFS	• 92% were not hospitalised • Association between persistent symptoms and initial disease severity were not reported (presumably none)
Gonzalez-Hermosillo et al.[44]; prospective	*N* = 130; mean age of 51 years; 35% females; 6-month post-discharge; Mexico City, Mexico	• 88% had ≥1 persistent symptom • 53% had short-term memory loss • 40%–50% had fatigue, unrefreshing sleep, dyspnoea on effort, tingling, vision focus impairment, and joint pain • 30%–40% had concentration impairment, postural dizziness, tachycardia, headache, muscle pain, anxiety and depression • 20%–30% had chest pain, constipation, and change in urinary frequency • 10%–20% had resting dyspnoea, light sensitivity, dizziness, abdominal pain, diarrhoea, and nausea • <10% had anosmia and ageusia	• 18%, 15% and 13% had ME/CFS following the 1994 CDC, 2003 CCC, and 2015 IOM criteria, respectively	• All were hospitalised • Fatigue was associated with 40–50 years compared to >50 years • Fatigue was not associated with sex (a risk trend towards female sex was present but did not reach statistical significance), initial disease severity, comorbidities, BMI and laboratory biomarkers
Mantovani et al.[45]; retrospective	*N* = 37; mean age of 52 years; 32% females; >6-month post-SARS-CoV-2 infection; Verona, Italy	• 27% had ME/CFS-like symptoms of fatigue, sleep disturbances, pain, mood changes, and cognitive complaints, following the 2003 CCC criteria	• N/A	• ME/CFS-like symptoms were not associated with comorbidities, sex, BMI or initial disease severity • ME/CFS-like symptoms were associated with an additional symptom of dyspnoea
Estiri et al.[46]; retrospective; preprint	*N* = 11,491; age and sex information were not presented; 3- to 9-month post-infection; Massachusetts, US	• N/A	• ↑ Risks of alopecia (OR: 3.1), anosmia, dysgeusia, ME/CFS (OR: 2.6), chest pain, palpitations, dyspnoea, pneumonia, and diabetes (OR: 1.3-6) at 3- to 6-month • ↑ Risks of anosmia or dysgeusia (OR: 2.1), ME/CFS (OR: 2.0), and dyspnoea (OR: 1.5) at 6-9-month	• All were not hospitalised • Association between persistent symptoms and initial disease severity were not reported (presumably none) • ME/CFS appeared more often in females and those <65 years

TABLE 1 (Continued)

Study	Sample characteristics (COVID-19 survivors)	Persistent symptoms	Persistent sequelae	Other notable points
			• Note: Risks were compared to matched controls (N = 46,131)	
Elanwar et al.[47]; cross-sectional	*N = 46; 76% females; ≥6-month onset of post-COVID-19 fatigue; Beni Suef, Egypt	• 78% had musculoskeletal pain • 76% had orthostatic intolerance • 65% had insomnia • 26% had sore throat • 11% had tender lymph nodes	Compared to control (N = 46) of COVID-19 survivors without PCS: • ↑ Median scores of physical, mental and total fatigues • ↑ Neurophysiological abnormalities in firings of muscle fibre action-potential	• All met the diagnosis for post-infectious fatigue syndrome • Post-infectious fatigue syndrome was associated with more severe acute COVID-19 and ↑ serum ferritin levels during acute COVID-19
(D) Postural orthostatic tachycardia syndrome (POTS) subtype				
Blitshteyn and Whitelaw[48]; retrospective case series	*N = 20; median age of 40 years; 70% females; 3- to 8-month post-symptom onset; New York, US	• N/A	• 75% had POTS • 60% unable to work • 30% had abnormal cardiac or pulmonary tests	• None were hospitalised • Association between persistent symptoms and initial disease severity were not reported (presumably none)
Davis et al.[21,22]; retrospective	*N = 3762%; 85% were 30-60 years; 79% females; 6-7-month post-symptom onset; U.S., U.K., and other countries.	• 70%–80% had fatigue and PEM • 50%–60% had cognitive impairments and sensorimotor symptoms • 30%–50% had insomnia, myalgia, palpitations, dyspnoea, dizziness, tachycardia and joint pain • 45% who had tachycardia measured their heart rate, of which 31% reported ↑ BPM of >30 upon standing	• 21% a medical diagnosis, of which 19% were POTS	• 92% were not hospitalised • Association between persistent symptoms and initial disease severity were not reported (presumably none)
Shouman et al.[49]; retrospective	*N = 27; median age of 30 years; 59% females; median of 119 days post-symptom onset; Minnesota, US	• 81% had symptoms during head-up tilt, such as light-headedness (63%), headache (26%), dyspnoea (26%), chest pain (19%), and palpitations (7%) • 41% had orthostatic intolerance without orthostatic hypotension	• 22% had POTS and another 11% had borderline POTS • 63% had abnormal autonomic function testing	• All were patient referrals (COVID-19 severity information was not mentioned)
Townsend et al.[50]; retrospective	N = 40; median age of 44.5 years; 90% females; median of 167 days post-diagnosis; Dublin, Ireland	• 50% had fatigue, of which 70% had orthostatic intolerance and 50% reported dizziness, palpitations, or chest discomfort upon standing	• N/A	• 82.5% were not hospitalised. • None were in ICU. • Persistent symptoms were not associated with age, sex or initial disease severity
Taylor et al.[51]; prospective	N = 675; mean age of 56 years; 42% females; 3-month post-discharge; London, UK	• 55% had fatigue • 44% had musculoskeletal symptoms • 30%–40% had dyspnoea and impairments in sleep and cognition	• N/A	• 56% had non-severe and 25% had severe COVID-19

(Continues)

TABLE 1 (Continued)

Study	Sample characteristics (COVID-19 survivors)	Persistent symptoms	Persistent sequelae	Other notable points
		• 20%–30% had anxiety and depression • 15%–20% had taste or smell impairments, cough, and GI and PTSD symptoms • 42% (out of 53 patients) had orthostatic intolerance		• Persistent symptoms were associated with longer hospitalisation and female sex, but not age
(E) Post-intensive care syndrome (PICS) subtype				
Valent et al.[52]; retrospective	*N* = 19 (from *N* = 54; mean age of 62 years; 29% females); 3-month post-ICU discharge; Paris, France	• 89% had pain or discomfort. • 40%–50% had worsened mobility, daily functioning, depression, and anxiety	• All had impaired quality of life related to physical status and general health • 10% had worsened self-care	• All were in ICU due to ARDS
Daste et al.[53]; prospective	*N* = 45; mean age of 58 years; 18% females; 3-month post-ICU discharge; Paris, France	• 82% had joint pain • 60% had peripheral nerve injury • 43% had PTSD symptoms • 38% had anxiety • 36% had depression • 29% had pressure ulcers	• 74% did not manage to return to work • ↓ Mean scores of dyspnoea and cognitive impairments compared to expected scores for healthy adults of the same age	• All were in ICU
Rousseau et al.[54]; prospective	*N* = 32; median age of 62 years; 28% females; 3-month post-ICU discharge; Liège, Belgium	• 94% had ≥1 symptom of PICS • 84% had cognitive impairments • 75% had sleep impairments • 31% had impairments in daily activities and low grip strength • 28% had PTSD symptoms • 25% had depression and anxiety	• 25% had inflammatory biomarker abnormalities • 28% had kidney biomarker abnormalities	• All were in ICU. • ↑ Duration of ICU stays and MV were associated with inpatient rehabilitation (*N* = 17)
van Veenendaal et al.[55]; prospective	*N* = 60; median age of 63 years; 32% females; 6-month post-ICU discharge; Groningen, The Netherlands	• 90% had ≥1 symptom of PICS • 33% had fatigue • 25% had weakened condition • 10%–20% had problems with cognition, hand function and walking, dyspnoea and polyneuropathy • <10% had muscle weakness, difficulty sleeping, shoulder pain and restrictions of extremities • Presence of pain (median score of 50) at 3- and 6-month • Weight loss at median of 6.5 and 5.4 kg at 3- and 6-month	• 90% of previously employed persons (*N* = 30) did not manage to return to work • 69% had impaired DLCO • 20% had impaired FVC • Poor physical health with median scores of 33 and 50 (out of 100) at 3- and 6-month • Impaired social activities (median score of 0) at 3- and 6-month	• All were in ICU
(F) Medical or clinical sequelae (MCS) subtype				
Ayoubkhani et al.[56]; retrospective	*N* = 47,780; mean age of 64.5 years; 45% females; 140-day post-discharge;	• N/A	• ↑ Risks of death (RR: 7.7), re-hospitalisation (RR: 3.5), respiratory	• Risk of MCS was associated with older age (>70 years)

TABLE 1 (Continued)

Study	Sample characteristics (COVID-19 survivors)	Persistent symptoms	Persistent sequelae	Other notable points
	England, UK		disease (RR: 6.0; new-onset, RR: 27.3), diabetes (RR: 1.5; new-onset, RR: 3.5), major adverse cardiovascular event (RR: 3.0; new-onset, RR: 5.4), CKD (RR: 1.9, new-onset, RR: 2.0), and CLD (RR: 2.9; new-onset, RR: 4.4) compared to controls (N = 50 million)	• Respiratory disease and diabetes diagnoses were associated with ICU admission • Re-hospitalisation, death, and cardiovascular event were associated with non-ICU admission
Al-Aly et al.[57]; retrospective	N = 73,435 (non-hospitalised) and 13,654 (hospitalised); mean age of 59 years; 12% females; 4-month post-diagnosis; US	• ↑ Risks of respiratory, neurological, circulatory and genitourinary symptoms, myalgia, fatigue, chest pain, arrhythmia, abdominal pain, joint pain, headache, and dysphagia (HR: 1.2–1.9)	Compared to control (N = 4,990,835), non-hospitalised COVID-19 group had: • ↑ Risk of death (HR: 1.59) • ↑ Risks of hypertension, sleep-wake, stress-related, anxiety-related, neurological, neurocognitive, lipid metabolism, skin, muscle, oesophageal and GI disorders, obesity, diabetes, anaemia, CVD, heart failure, COPD, respiratory failure (or insufficiency or arrest), asthma, UTI, bacterial infections, pressure ulcer (HR: 1.2–2.0), LRT diseases, acute thromboembolism and acute PE (HR: 2.0–3.0) • ↑ Risks of the use of bronchodilator, cough medication, anticoagulant, muscle relaxant, analgesic, antiarrhythmic, antacid, calcium channel blocker, beta-blocker, anti-inflammatory agent, insulin, hypoglycemic agent, anti-asthmatic, loop diuretic, histamine antagonist, antilipidemic agent, antidiarrheal agent, laxatives, antiemetic, penicillin, antifungal, antidepressants, and anticonvulsants (HR: 1.2–2.2) Compared to influenza control (N = 13,997), hospitalised COVID-19 group had: • ↑ Risks of lipid, metabolic, neurological, muscle and coagulation disorders, hypotension, fluid and electrolyte disorders, fatigue, acute renal failure, bacterial infections, septicaemia,	• Risk of MCS was associated with, but not limited to, more severe acute COVID-19. • No ↑ risks in COVID-19-unrelated conditions (e.g., cancers, fitting of dental or hearing devices, and accidents) between non-hospitalised COVID-19 and matched control groups and between hospitalised COVID-19 and influenza groups.

(Continues)

TABLE 1 (Continued)

Study	Sample characteristics (COVID-19 survivors)	Persistent symptoms	Persistent sequelae	Other notable points
			pressure ulcer, dysphagia, anaemia, UTI, LRT disease (HR: 1.3–2.0), respiratory failure (or insufficiency or arrest), malnutrition, shock, and acute PE (HR: 2.0–3.0) • ↑ Risks of the use of anticoagulants, laxatives, gastric medications, local anaesthetics, anxiolytics, antipsychotics, dermatological agent, mouthwashes, insulin, phosphorous, and cephalosporins (HR: 1.3–1.8)	
Taquet et al.[58]; retrospective	$N = 236,379$; mean age of 46 years; 55.6% females; 6-month post-diagnosis; US and other countries	• N/A	• ↑ Risks intracranial haemorrhage (RR: 2.4; new-onset, HR: 2.5), ischaemic stroke (HR: 1.6; new-onset, HR: 2.0), nerve disorder (HR: 1.6), myoneural junction disease (HR: 5.3), encephalitis (HR: 1.7), dementia (HR: 2.3), mood, anxiety or psychotic disorders (RR: 1.5; new-onset, RR: 1.8), substance use disorder (HR: 1.3; new-onset, HR: 1.2), insomnia (RR: 1.5; new-onset, HR: 1.9) compared to matched influenza controls ($N = 105, 579$) • ↑ Risks intracranial haemorrhage (HR: 1.2; new-onset, HR: 1.6), ischaemic stroke (HR: 1.5; new-onset, HR: 1.6), parkinsonism (HR: 1.5), Guillain–Barré syndrome (HR: 2.1), nerve disorder (HR: 1.3), myoneural junction disease (HR: 4.5), encephalitis (HR: 1.4), dementia (HR: 1.7), mood, anxiety or psychotic disorders (HR: 1.2; new-onset, HR: 1.5), substance use disorder (HR: 1.1), insomnia (HR: 1.2; new-onset, HR: 1.4) compared to matched controls with other respiratory tract infections ($N = 236,038$)	• 80% were not hospitalised. • 20% were hospitalised. • 4% were in ICU. • 3% had encephalopathy • Risk of neurological sequelae was associated with ICU admission and encephalopathy
Daugherty et al.[59]; retrospective	$N = 266,586$; mean age of 42 years; 52% females; 21- to 141-day post-SARS-CoV-2 diagnosis; median of 95-day follow-up; US	• N/A	• 14% had ≥1 medical sequalae that require medical care (5% higher than the matched controls; $N = 266,586$) • ↑ Risks of myalgia, hypertension, migraine, seizure, anxiety, depression,	• 92% were not hospitalised • 8% were hospitalised • 1% were in ICU • Risks of certain medical sequelae were higher among those who were hospitalised,

TABLE 1 (Continued)

Study	Sample characteristics (COVID-19 survivors)	Persistent symptoms	Persistent sequelae	Other notable points
			PTSD, diabetes, CKD, liver abnormalities, urticaria, sleep apnoea (HR: 1.0–2.0), fatigue, arrhythmia, heart failure, CVD, stroke, memory impairment, peripheral neuropathy, acute kidney injury (HR: 2.0–3.0), pulmonary hypertension, cardiomyopathy, hypercoagulability, DVT, PE, dementia, acute respiratory failure (HR: 3.0–4.0), anosmia (HR: 5.4), encephalopathy (HR: 6.3), interstitial lung disease (HR: 7.7), chronic respiratory failure (HR: 12.9), and myocarditis (HR: 21.0) compared to matched controls (N = 266,586)	were over 50 years, and had pre-existing conditions when compared to their respective matched controls • Risks of fatigue and anosmia were higher in females versus males • Risks of myocarditis, hypercoagulability, DVT, kidney injury, and sleep apnoea were higher in males versus females
Chevinsky et al.[60]; retrospective	Inpatients: N = 27,589%; 49% were 50-74 years; 52% females; 4-month post-discharge; US regionsOutpatients: N = 46,857%; 76% were 18–64 years; 61% females; 4-month post-COVID-19 encounter; US regions.	• 7% of inpatients and 8% of outpatients had ≥1 persistent symptom, most commonly respiratory and neurological	Note: Risks were compared to matched controls (N = 27,589 inpatients and 46,857 outpatients). • ↑ Risks of pneumonia (OR: 4.6), neurocognitive disorders, acute PE, mouth diseases, malnutrition, nerve and coagulation disorders (OR: 2.2–3.2), neurological, respiratory, circulatory and GI symptoms, LRT diseases, respiratory failure (or insufficiency or arrest), haematuria, chest pain, URTI, UTI, fungal and bacterial infections, dysphagia, pressure ulcer, anaemia, pelvic inflammatory disease, heart failure, diabetes and anxiety (OR: 1.3–2.0) at day 31–60 in adults of >18 years • ↑ Risks of pressure ulcer, acute PE, pneumonia (OR: 2.2–2.8), LRT diseases, respiratory failure, neurocognitive disorders, anaemia, chest pain, bacterial infections, URTI, and UTI (OR: 1.4–1.8), at day 61–90 in adults >18 years • ↑ Risks of neurocognitive disorders, pressure ulcer, gout (OR: 2.2–3.0), malnutrition, bacterial infection, UTI, neurological disorders, and respiratory symptoms (OR: 1.4–2.0) at day 91–120 in adults of >18 years.	• 30%–40% of inpatients were in ICU. • Outpatients had mild disease, and none were in ICU • Persistent symptoms were associated with prior hospitalisation in inpatients (vs. Outpatients) and 31- to 60-day range (vs. 1–30- and 61- to 120-day ranges) • Persistent symptoms or new disease diagnoses were not associated in persons aged <18 years.

(Continues)

TABLE 1 (Continued)

Study	Sample characteristics (COVID-19 survivors)	Persistent symptoms	Persistent sequelae	Other notable points
Hernandez-Romieu et al.[61]; retrospective	28–180-day post-diagnosis follow-up: *N* = 3171; 63% were 18–49 years; 57% females; Atlanta, Georgia. 120-180-day post-diagnosis follow-up: *N* = 1370; median age of 46 years; Atlanta, Georgia.	• 23% had ≥1 persistent symptom at 120-180-day follow-up: chest pain, dyspnoea, headache, fatigue, cough, sleep disorders, and heartbeat abnormalities.	• 69% required additional outpatient visits during the 28–180-day, of which 65% received new diagnosis. • new diagnosis at 120–180-day follow-up (*N* = 1370): 7.1% diagnosed with back pain, 7% with joint disorder, 5.3% with muscle or soft tissue disorder; 4.4% with abdominal and pelvic pain, 3.6% with anxiety, 2.6% with diabetes, 2.3% with hyperlipidaemia, 2.2% with overweight or obesity, 2% with UTI and urinary incontinence, 2% with gastroesophageal reflux, 1.7% with hypertension, and 1.6% with disorders of refraction and accommodation	• None were hospitalised • Outpatient visits declined from 2 to 24 visits per 10,000 person-days at 28- to 59-day to 1–4 visits per 10,000 person-days at 120- to 180-day post-diagnosis • Outpatient visits were associated with older age, female sex, comorbidities, and non-Hispanic Black adults
Lund et al.[62]; retrospective	*N* = 8983; median age of 43 years; 61% females; 6-month post-SARS-CoV-2 diagnosis; Copenhagen, Denmark	• N/A	Risks were compared to SARS-CoV-2-negative controls (*N* = 80,894) • ↑ Risks of use of bronchodilators, short-acting β2-agonists, and triptans (RR: 1.2–1.6) • ↑ Risks of hospital diagnoses of dyspnoea and venous thromboembolism (RR: 1.8–2.0) • No ↑ risks of other persistent symptoms (anosmia, cough and fatigue), diseases (ischaemic stroke, CKD, CVD, diabetes, pulmonary fibrosis, neurological diseases, depression and anxiety) and drug usage (paracetamol, anti-inflammatory agents, opioid-related drugs, antidepressants, anxiolytics, antipsychotics, glucose-lowering drugs, anticoagulants and antihypertensives)	• All were not hospitalised • Compared to hospitalised post-SARS-CoV-2 patients (*N* = 1310), non-hospitalised SARS-CoV-2 patients had ↓ risks of drug use (bronchodilators, short-acting β2-agonists, cough medications, paracetamol, opioid-related drugs, antidepressants, anxiolytics, antipsychotics, anticoagulants, and antidepressants; RR: 0.2–0.64), diseases (venous thromboembolism, ischaemic stroke, pulmonary and neurological diseases, and CVD; RR: 0.1–0.5), and persistent symptoms (dyspnoea and fatigue; RR: 0.2–0.4)
Maestre-Muñiz et al.[63]; cross-sectional	*N* = 543 (from *N* = 766; mean age of 65 years; 49% females); 1-year post-		• 7.5% died, half of which may be caused by COVID-19 complications	• 57% discharged from emergency room from mild-to-moderate COVID-19

TABLE 1 (Continued)

Study	Sample characteristics (COVID-19 survivors)	Persistent symptoms	Persistent sequelae	Other notable points
	discharge; Ciudad real, Spain	• 57% had ≥1 persistent symptom, most commonly dyspnoea, fatigue, hair loss, and memory problems	• 2%–2.4% developed DVT, hypertension and arthritis • 1%–2% developed diabetes, PE, acute myocardial infarction, stroke and COPD • In patients with COPD before COVID-19 (*N* = 28), 39% required a new need of oxygen therapy. • In patients with asthma before COVID-19 (*N* = 39), 21% need treatment intensification. • In patients with diabetes before COVID-19 (*N* = 109), 9% need treatment intensification and 5% need new insulin prescription.	• 43% discharged from hospital from severe COVID-19 • Persistent symptoms were associated with hospital admission

Note: **N* refers to sample sizes with selection or recruitment bias that specifically looked for participants with persistent symptoms. Studies were arranged in the order of appearance in the text.

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; BPM, beats per minute; CCC, Canadian Consensus Criteria; CDC, Centres for Disease Control and Prevention; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CT, computed tomography; CVD, cardiovascular disease; DLCO, diffusing capacity of the lung for carbon monoxide; DVT, deep vein thrombosis; FVC, forced vital capacity; GI, gastrointestinal; HR, hazard ratio; HRCT, high-resolution computed tomography; ICU, intensive care unit; LRT, lower respiratory tract; MCS, medical or clinical sequelae; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; MRI, magnetic resonance imaging; MV, mechanical ventilation; O_2, oxygen; OR, odds ratio; PE, pulmonary embolism; PEM, post-exertional malaise; POTS, postural orthostatic tachycardia syndrome; PTSD, post-traumatic stress disorder; RR, rate ratio; TLC, total lung capacity; URTI, upper respiratory tract infection; UTI, urinary tract infection.

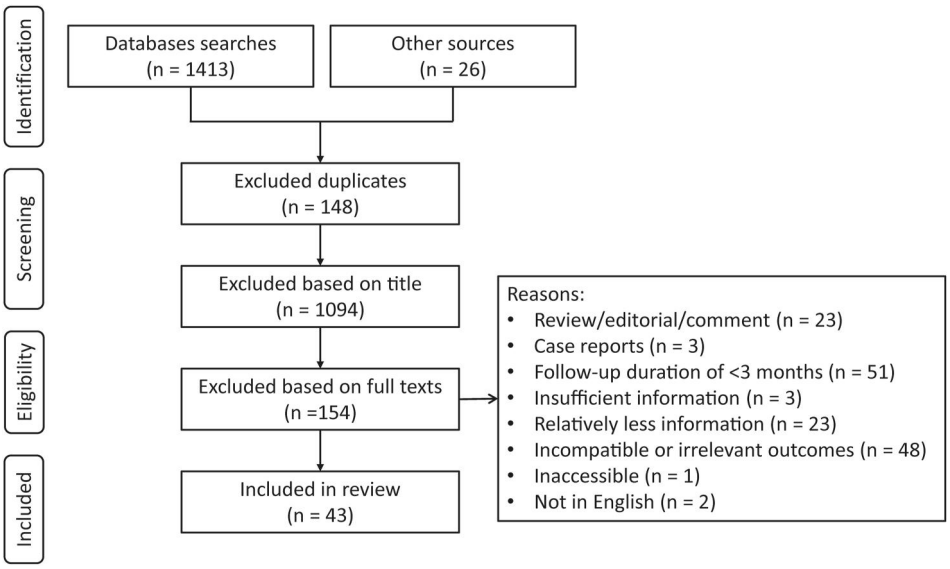

FIGURE 3 Flowchart of the literature search following the PRISMA guidelines

Several studies have found that survivors of mild COVID-19 that needed no hospitalisation could develop multi-organ impairments and symptomatic manifestations, especially fatigue, dyspnoea, and cognitive impairments, at 3- to 8-month follow-up.[22,24,25] Other studies have also reported that survivors of mild-to-moderate COVID-19 can develop PCS with multi-organ symptoms, regardless of the initial disease severity or hospitalisation status, at 6- to 12-month follow-up.[26–28] More concerningly, even children with non-severe COVID-19 may develop PCS with multi-organ manifestations.[29,30] These studies indicate that even non-severe COVID-19 (NSC) could lead to PCS with MOS; hence, the NSC-MOS subtype. Descriptions of these key studies supporting this subtype are summarised in Table 1A.

Studies investigating post-COVID-19 single-organ impairment have also been performed. For example, pulmonary radiological abnormalities and impaired lung function have been found among COVID-19 survivors, regardless of initial disease severity, at 3- to 12-month follow-up.[67–70] One study has detected brain structural and metabolic abnormalities, which also correlated with persistent neurological and fatigue symptoms, among survivors of COVID-19 (mostly mild) at 3-month post-discharge.[71] Radiological abnormalities have also been detected in the frontoparietal regions extending into the brainstem among COVID-19 survivors with persistent neurological symptoms.[72,73] Cardiac radiological abnormalities have also been documented among young survivors of asymptomatic or mild COVID-19.[74–77]

To date, there are no widely accepted pharmaceutical recommendations for PCS, let alone the NCS-MOS subtype. However, rehabilitation programs have been reported to improve symptoms of PCS, although such PCS cases probably do not belong to the NSC-MOS subtype as they involved older survivors of moderate-to-severe COVID-19.[4,78–80] Nevertheless, in principle, rehabilitation can be recommended for NSC-MOS due to its holistic approach, which need not be catered to specific pathophysiology. As there can be different rehabilitation programs (e.g., pulmonary, cardiac, musculoskeletal and neurological and multidisciplinary), rehabilitation may need to be personalised to individual NSC-MOS subtype cases, for example, by basing it on which organ systems are most affected upon assessments.[79,81]

3.2 | Pulmonary fibrosis sequelae (PFS)

In severe-to-critical COVID-19, multi-organ failure and acute respiratory distress syndrome (ARDS) are common, which require prolonged hospitalisation and intensive care unit (ICU) admission.[1,82] Survivors of ARDS or severe respiratory infections usually face long-term pulmonary sequelae, namely pulmonary fibrosis, characterised by excessive extracellular matrix deposition within the lung interstitium and pulmonary parenchyma lesions.[83,84] Moreover, patients with ARDS in the ICU are often subjected to invasive mechanical ventilation, which imposes mechanical stress that may contribute to pulmonary fibrosis and lung injury.[85,86] Common symptoms of pulmonary fibrosis sequelae (PFS) are dyspnoea, dry cough, and fatigue.[87] Ambardar et al.[88] has also proposed post-COVID-19 pulmonary fibrosis as a sequela that comprises a subset of PCS cases.

At 2- to 3-month post-discharge, most COVID-19 survivors exhibited persistent symptoms (especially dyspnoea and fatigue) and multi-organ radiological abnormalities (particularly the lungs), which were associated with initial disease severity.[32] This suggests that more severe COVID-19 may lead to MOS that are pulmonary-centred. In a 4-month follow-up study of discharged COVID-19 patients, although 63% had radiological lung abnormalities, only 19% had fibrotic lung lesions that occurred exclusively in former ICU patients.[33] Other studies have also found that survivors of more severe COVID-19 were more likely to develop lung fibrosis and other

pulmonary radiological abnormalities, as well as impaired lung function, up to 6- to 7-month post-discharge. A few of these studies also reported that long-term pulmonary fibrosis was associated with comorbidities, male sex and older age.[34–41] Details of these studies are summarised in Table 1B. Therefore, in contrast to NSC-MOS, the PFS subtype of PCS is dependent on the initial severity of acute COVID-19.

As PFS is not an entirely novel condition, a few existing approved pharmaceutical drugs may aid PCS recovery due to PFS, namely antifibrinolytic agents like nintedanib and pirfenidone.[89] A non-randomised clinical trial has found that nintedanib minimised the frequency of lung injury in mechanically ventilated COVID-19 patients (n = 30) compared to matched controls without nintedanib (n = 30) from 39% to 26%, with non-significant differences in adverse events.[90] Moreover, several randomised clinical trials (RCTs) are ongoing that are inspecting other medications (i.e., pirfenidone and tetrandrine), traditional Chinese medicine (i.e., FuzhengHuayu formula and Anluohuaxian), and interventions (i.e., mesenchymal stem cells and hyperbaric oxygen) for any potential therapeutic effects on COVID-19-associated pulmonary fibrosis[87] (Table 2).

The Swiss Society for Pulmonology and other experts have suggested that pulmonary rehabilitation may help treat COVID-19 survivors with PFS, post-ARDS sequelae, or persistent pulmonary symptoms.[91–93] In brief, pulmonary rehabilitation entails breathing and aerobic exercises, airway clearance techniques, oxygen and nutritional support, and other aspects described in Siddiq et al.[91] and Yang and Yang.[94] Several uncontrolled, observational studies have also supported the efficacy of pulmonary rehabilitation in improving exercise and lung function capacities, as well as symptoms of fatigue, dyspnoea, and mental health, among COVID-19 survivors.[95–98] In a prospective cohort study, pulmonary rehabilitation improved the physical and lung function of survivors of severe COVID-19 (n = 99) compared to the control group of lung disease patients (n = 419).[99] One RCT has also shown that a 6-week pulmonary rehabilitation programme gradually improved lung function and exercise capacity in elderly survivors of COVID-19 (n = 36) compared to no rehabilitation (n = 36).[100]

3.3 | Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has three commonly used diagnostic criteria. The 1994 Centres for Disease Control and Prevention's (CDC) one entails severe fatigue lasting for at least 6 months with at least four of the following symptoms: cognitive impairments, tender cervical or axillary lymph nodes, headache, muscle and multi-joint pain, sore throat, post-exertional malaise (PEM) and unrefreshing sleep.[101] The 2003 Canadian Consensus Criteria (CCC) for ME/CFS involves fatigue, PEM, unrefreshing sleep, pain, at least two neurocognitive manifestations, and at least two of either autonomic, neuroendocrine, or immune manifestations that persist for 6 months or longer.[102] The 2015 Institute of Medicine (IOM) diagnoses ME/CFS by four symptomatic manifestations lasting for at least 6 months: severe fatigue (not relievable with rest), PEM, unrefreshing sleep and either cognitive impairment or orthostatic intolerance.[103]

An estimated 1% of the general population has ME/CFS.[104] Although symptoms of ME/CFS may improve over the years, full recovery is achieved in about 5% of cases only.[105] The precise biological aetiology of ME/CFS remains undetermined with several proposed theories such as hypometabolism, autoimmunity, chronic inflammation, and dysautonomia.[106,107] Common risk factors of ME/CFS include female sex, major stressful life event, and infections, such as *Coxiella burnetii*, Epstein-Barr virus, Ebola virus, Ross River virus, Chikungunya virus, West Nile virus, SARS-CoV-1, and now SARS-CoV-2.[108,109] Due to the overlapping symptoms and possible mechanisms, many have predicted that PCS may eventually lead to ME/CFS.[110–112]

Indeed, a proportion of PCS survivors have been diagnosed with ME/CFS. For example, in a study of COVID-19 survivors discharged 6 months prior, 14.3% (i.e., 3 out of 21) of those who still had fatigue qualified for a ME/CFS diagnosis.[42] Another study found that among 802 COVID-19 survivors who received a medical diagnosis due to persistent symptoms lasting for 6–7 months, 14.7% were ME/CFS.[21,22] In another study of COVID-19 survivors with fatigue that persisted for at least 6 months, 45% of them fulfiled the criteria for ME/CFS; the remaining 55% had PEM for less than 14 h and did not meet the neurocognitive criteria for ME/CFS. This study showed that certain PCS cases are ME/CFS, and some may be borderline or subclinical ME/CFS.[43] Moreover, one study found that PCS survivors with post-infectious fatigue syndrome, a condition highly similar to ME/CFS, had (i) higher scores of physical and mental fatigue, (ii) more abnormal neurophysiological assessments and (iii) more severe acute COVID-19 compared with controls (i.e., COVID-19 survivors without PCS).[47]

Another study reported that depending on the diagnostic criteria, 13%–18% of discharged COVID-19 patients developed ME/CFS at 6-month.[44] Similarly, in another study, 23% of SARS-CoV-2-positive persons with no history of fatigue and cognitive dysfunction developed ME/CFS at 6-month.[45] In these studies, most participants were 30–60 years, and female sex was often a risk factor, whereas initial disease severity played little role in the development of ME/CFS (Table 1C). Interestingly, a study using a machine learning approach has identified several phenotypes in a sample of 57,622 patients who underwent SARS-CoV-2 testing, of which 20% were positive. One of the phenotypes is ME/CFS, which was two-fold more likely to happen to COVID-19-positive than—negative patients, especially among women younger than 65 years, at 6- to 9-month post-infection.[46] Further details of these studies are summarised in Table 1C.

For this subset of PCS survivors who develop ME/CFS, existing ME/CFS therapies may provide clinical benefits. A systematic review of 56 RCTs has identified five non-pharmaceutical (i.e., involving cognitive behavioural therapy; CBT, graded-exercise therapy; GET, rehabilitation, and acupuncture and abdominal tuina) and three

TABLE 2 An overview of the symptoms, main pathophysiology, and potential interventions of the five proposed subtypes of the post-COVID-19 syndrome (PCS)

Subtype	Proposed diagnostic guide	Main pathophysiology	Potential interventions
NSC-MOS	Multi-organ symptoms lasting for ≥3 months after acute COVID-19 (regardless of disease severity), especially fatigue, dyspnoea and cognitive impairments	Tissue damage across multiple organs or system-wide dysregulation	• Personalised, multidisciplinary rehabilitation
PFS	Pulmonary fibrosis and other pulmonary sequelae (i.e., impaired lung function or respiratory symptoms) lasting for ≥3 months after acute COVID-19, especially severe COVID-19.	Extensive tissue damage, especially in the lungs	• Pulmonary rehabilitation • Hyperbaric oxygen • Nintedanib (antifibrotic drug) • Pirfenidone (antifibrotic drug) • Tetrandrine (calcium channel blocker) • FuzhengHuayu formula (antifibrotic traditional Chinese medicine) • Anluohuaxian (antifibrotic traditional Chinese medicine) • Mesenchymal stem cells • Galectin-3 inhibitor • Poly-(ADP-ribose) polymerase inhibitor • Cobrotoxin (nicotinic acetylcholine receptors antagonist)
ME/CFS	Disabling fatigue, unrefreshing sleep, PEM, and either cognitive impairment or orthostatic intolerance lasting for ≥6 months after acute COVID-19. More specific diagnostic criteria may follow the 1994 CDC, 2003 CCC or 2015 IOM criteria for ME/CFS	Dysfunction of the immune and nervous systems	• CBT (debatable) • GET (debatable) • Rehabilitation • Acupuncture • Abdominal tuina • Acupuncture • Staphypan Berna vaccine (staphylococcal toxoid) • Rintatolimod (immunomodulator) • Coenzyme Q10 + NADH (mitochondrial modulator) • Pain medications • Sleep medications • Antidepressants
POTS	Increased heart rate of >30 beats per minute within 5–10 min of standing or upright tilt without orthostatic hypotension. This condition lasts for ≥6 months after acute COVID-19, which may occur with dizziness, palpitations, blurred vision, headache, generalised weakness, exercise intolerance, and fatigue.	Dysfunction of the autonomic nervous system	• Increased fluid and salt intake • Compression garments/stockings • Non-upright exercises • Propranolol (beta-blocker) • midodrine (vasopressor) • ivabradine (I_f ion channel blocker) • fludrocortisone (corticosteroid) • antihistamines • intravenous saline • verapamil (calcium channel blocker) • pyridostigmine (acetylcholinesterase inhibitor) • clonidine (hypotensive agent) • methyldopa (hypotensive agent) • droxidopa (norepinephrine precursor)
PICS	Physical (e.g., muscular weakness, weakened handgrip, and poor mobility), cognitive (e.g., memory and concentration), and mental (e.g., anxiety, depression, and PTSD) sequelae lasting for ≥3 months after acute COVID of ICU level of severity.	Severe-to-critical illnesses in need of ICU level of care, from which full recovery is difficult	• Statin (lipid-lowering agent) • Dabigatran (anticoagulant) • RAAS inhibitors (modulator of the cardiovascular and renal systems) • SGLT2 inhibitors (glucose-lowering agent) • Metformin (glucose-lowering agent) • GLP-1RA (glucose-lowering agent) • β-Adrenoceptor blockers (beta-blocker) • Neuromuscular electrical stimulation • Virtual reality therapy • Rehabilitation programs

TABLE 2 (Continued)

Subtype	Proposed diagnostic guide	Main pathophysiology	Potential interventions
MCS	Acute or chronic diseases or other clinical sequelae that require medical care. Examples include respiratory, cardiovascular, gastrointestinal, kidney, liver and neurological diseases, diabetes, infectious diseases and mental health disorders	Health deterioration or unmasking of chronic diseases	• Standard therapy for the medical or clinical diagnosis.

Note: In the intervention column, non-pharmaceutical approaches are presented first, followed by pharmaceutical therapies. The relevant references are incorporated in the main text.

Abbreviations: CBT, cognitive behavioral therapy; CCC, Canadian Consensus Criteria; CDC, Centres for Disease Control and Prevention; GET, graded exercise therapy; GLP-1RA, glucagon-like peptide-1 receptor agonist; ICU, intensive care unit; IOM, Institute of Medicine; MCS, medical or clinical sequelae; ME/CFS, myalgic encephalomyelitis or chronic fatigue syndrome; NSC-MOS, non-severe COVID-19 multi-organ sequelae; PEM, post-exertional malaise; PFS, pulmonary fibrosis sequelae; PICS, post-intensive care syndrome; POTS, postural orthostatic tachycardia syndrome; PTSD, post-traumatic stress disorder; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose co-transporter-2.

pharmaceutical (i.e., Staphypan Berna vaccine, rintatolimod and co-enzyme Q10 + NADH) therapies that significantly improved symptoms of ME/CFS[113] (Table 2). Reviews and clinical practice have also suggested using other pharmaceuticals to treat specific symptoms of ME/CFS, rather than the syndrome itself, such as sleep and pain medications and antidepressants.[114,115] For CBT and GET, their effectiveness and even potential harm in ME/CFS have been debated, possibly due to the flawed RCTs and incompatibility with underlying pathophysiology.[116–118] Recently, the UK NICE has ceased recommending GET and CBT for treating ME/CFS, although CBT may still be used to manage patients' psychological symptoms.[119] Thus, similar precautions may be needed for patients with PCS.

3.4 | Postural orthostatic tachycardia syndrome (POTS)

Postural orthostatic tachycardia syndrome (POTS) is a common autonomic disorder lasting for 6 months or more, diagnosed by an increased heart rate of >30 beats per minute (BPM) within 5–10 min of standing or upright tilt without orthostatic hypotension. This condition may also occur with dizziness, palpitations, blurred vision, headache, generalised weakness, exercise intolerance, and fatigue.[120,121] The prevalence of POTS stands at 0.2%–1% in developed countries, with about 80% of cases affecting younger females and 50% of cases recovering spontaneously within 1–3 years. Possible aetiologies of POTS include dysautonomia, hypovolaemia, and hyperadrenergic stimulation; possible triggers include surgery, pregnancy, psychological stress, concussion, and, most commonly, infections of the gastrointestinal and respiratory tracts.[121,122]

Therefore, COVID-19, being a respiratory viral disease, may trigger POTS, which has been documented in several case series. The majority of these cases involved female survivors and were not associated with initial COVID-19 severity.[48,123–125] In a large-scale survey of 3762 COVID-19 (mostly mild) survivors, 30% of those who had persistent tachycardia also reported an increase of >30 BPM upon standing, and 19% of those who sought medical diagnosis received POTS.[21,22] Another study of 27 COVID-19 survivors referred for autonomic nervous system testing for possible dysautonomia found that 22% fulfiled the criteria for POTS and another 11% with borderline POTS.[49] Borderline or sub-clinical POTS has also been seen in other studies, where a proportion of COVID-19 survivors with persistent symptoms (most commonly fatigue) also showed orthostatic intolerance.[50,51] Details of these studies are summarised in Table 1D.

A case series of 15 persons with post-COVID-19 POTS has reported symptomatic relief with pharmaceutical (i.e., propranolol, midodrine, ivabradine, fludrocortisone and antihistamines) or non-pharmaceutical (i.e., increased fluid and salt intake, compression stocking and non-upright exercise) approaches commonly used for POTS.[48] However, no comparison group was involved in this case series, so further controlled studies are warranted. Interestingly, ivabradine has been shown to relieve racing heart rate more effectively than carvedilol in a small study of 24 COVID-19 survivors with palpitations or tachycardia.[126] Other pharmaceutical options for POTS include intravenous saline, pyridostigmine, clonidine, methyldopa, verapamil and droxidopa,[121,122] which may be useful for treating the POTS subtype of PCS as well (Table 2). However, the Heart Rhythm Society has recommended non-pharmaceutical approaches for POTS first, followed by pharmaceutical options if necessary; therapies also need personalisation as there are no universally accepted approaches for POTS.[121]

3.5 | Post-intensive care syndrome (PICS)

Complete recovery may not be possible following a bout of severe-to-critical illness (e.g., multi-organ failure, sepsis or ARDS), particularly when prolonged ICU level of care was needed. This is widely known as the post-intensive care syndrome (PICS) that has three major hallmarks: long-term cognitive (e.g., memory and concentration), mental (e.g., anxiety, depression and post-traumatic stress disorder; PTSD), and physical (e.g., muscular weakness, weakened handgrip and poor mobility) sequelae that substantially impair the

quality of life.[127,128] Although PICS is a well-known syndrome, the lack of diagnostic codes has impeded medical intervention efforts.[129] About 14% and 5% of COVID-19 cases are severe and critical, respectively, especially among older adults and individuals with multiple medical comorbidities, which may require extended hospitalisation and ICU admission.[1,82] As follows, several have proposed that a proportion of PCS cases may be PICS.[130,131]

In a small study of survivors of severe COVID-19, everyone had impaired life quality related to physical status and general health, with 42% of participants also experiencing cognitive and mental health impairments at 3-month post-ICU discharge.[52] Another 3-month follow-up study of post-ICU COVID-19 survivors also found a high prevalence of PICS-related impairments, with an additional symptom of persistent dyspnoea.[53] Similarly, other studies involving ICU survivors of COVID-19 have noted that 90% or more had at least one symptom of PICS, namely impairments in physical, cognitive, or mental health functioning at 3- and 6-month.[54,55] In one of those studies, survivors with COVID-19-related PICS also had additional health complications of weight loss, dyspnoea, and impaired lung function.[55] These studies indicate that PICS with possible pulmonary sequelae may constitute a subset of PCS with a history of ICU admission. Further accounts of these studies are documented in Table 1E.

As PICS is not an entirely novel condition, a few existing pharmaceutical drugs with good safety profiles may aid PCS recovery due to PICS. To this end, Bangash et al.[130] have proposed that if chronic inflammation, thrombosis or fibrosis are present in COVID-19 survivors with PICS, antagonists of these pathological processes may help. These antagonists include statin, dabigatran, renin-angiotensin-aldosterone system inhibitors, sodium-glucose co-transporter-2 inhibitors, glucagon-like peptide-1 receptor agonist, metformin and β-adrenoceptor blockers[130,132,133] (Table 2). However, it should be noted that these medications have not been tested in clinical trials involving post-COVID-19 PICS patients, so further discretions are necessary.

Several studies have emphasised the necessity of PICS screening and rehabilitation needs assessments in post-ICU survivors of COVID-19.[134,135] However, a meta-analysis of 10 RCTs has reported that post-ICU physical rehabilitation may not necessarily improve health and mental quality of life at 6- to 12-month.[136] Nonetheless, more RCTs are ongoing that sought to test other potential non-pharmaceutical therapies (e.g., neuromuscular electrical stimulation, virtual reality and rehabilitation programs) for post-ICU survivors of COVID-19.[137–141]

3.6 | Medical or clinical sequelae (MCS)

Nath[142] is arguably the first to hypothesise that one possible aetiology of PCS is the 'unmasking of underlying comorbidities'. Similarly, Hacker et al.[143] noted three ways in which COVID-19 may be linked to chronic diseases: (i) COVID-19 may exacerbate the health of those with or at risk of chronic diseases; (ii) pandemic circumstances may have interrupted routine management, diagnosis, and prevention of chronic diseases; (iii) COVID-19 sequelae may have caused additional chronic diseases or formed a new group of patients with chronic conditions. In other words, acute COVID-19 may have the capacity to deteriorate the health of survivors, leading to medical or clinical sequelae (MCS) in need of medical attention, such as diabetes, respiratory, cardiovascular, gastrointestinal and neurological diseases and mental and behavioural disorders. MCS is also unique from the other PCS subtypes as it involves a broad spectrum of actual diseases, rather than symptoms or radiological abnormalities seen in other subtypes.

In a study of 47,480 COVID-19 survivors (previously hospitalised) and 47,780 matched controls, the risks of new diagnoses of respiratory disease, cardiovascular disease, chronic liver disease, chronic kidney disease, and diabetes were several times greater in the COVID-19 group at 140-day.[56] An outcome-specific cohort study has also found increased risks of various diseases and symptoms involving the neurocognitive, respiratory, cardiovascular, and metabolic systems, as well as medications (e.g., bronchodilators, anticoagulants, antilipidemic agents, etc.), among 73,435 COVID-19 survivors (non-hospitalised) compared to matched controls and influenza patients at 4-month.[57] Another controlled cohort study involving 236,379 COVID-19 patients also found that the risks of neurological and psychiatric diseases were higher than matched controls with other respiratory tract infections at 6-month, especially among those with more severe acute COVID-19.[58] In another large-scaled controlled cohort study, SARS-CoV-2-infected persons (N = 266,586) had elevated risks of multiple sequelae (i.e., ranging from acute and chronic neurological, psychiatric, respiratory, cardiovascular and metabolic conditions) that required medical care compared to matched controls (N = 266,586) up to 4-month follow-up. Such risks were also higher for those over 50 years old, with comorbidities, and previously hospitalised for COVID-19.[59] These findings indicate that the MCS subtype may be associated with, but not limited to, more severe COVID-19. Further descriptions of these studies are presented in Table 1F.

Another controlled cohort study, however, found that various new diagnoses (e.g., neurological, psychiatric, musculoskeletal and respiratory disorders) happened at 1- to 2-month rather than 3- to 4-month post-COVID-19.[60] Similarly, an uncontrolled cohort study noted that 69% of non-hospitalised COVID-19 survivors required additional outpatient visits at 28- to 180-day post-diagnosis, of which 65% received a new medical diagnosis.[61] Thus, the MCS subtype of PCS may also occur earlier than 3 months after acute COVID-19 in some instances. Moreover, not every MCS may be as prominent as some studies reported. This is shown in a population-based study of SARS-CoV-2-positive non-hospitalised individuals, where only risks of hospital diagnoses of dyspnoea and venous thromboembolism were found heightened compared to SARS-CoV-2-negative controls at 6-month; other persistent symptoms (e.g., fatigue and cough), diseases (e.g., neurological, respiratory and cardiovascular diseases), and drug prescriptions (e.g., anti-inflammatories, anticoagulants and antihypertensives) were not statistically different between groups.[62]

Lastly, one cohort study reported that COVID-19 survivors at 1-year post-discharge may also experience exacerbations of pre-existing and new onset of medical conditions.[63] Further details of these pertinent studies are summarised in Table 1F.

Therefore, these cohort studies show that acute COVID-19 (even when mild) may qualify as a risk factor for MCS that require medical attention. As such, increased use or prescriptions of various medications for those MCS were also reported in some of these studies. The lack of specific MCS in these studies indicates that (i) COVID-19 induces MCS via a myriad of disease-specific mechanisms or (ii) COVID-19 exacerbates existing health conditions, or both. Nonetheless, MCS may also qualify as a PCS subtype given that concrete evidence has emphasised COVID-19 as an initiator of MCS up to 9-month follow-up (Table 1F). Accepting this notion may also mean that clinicians have to monitor the health of COVID-19 survivors more closely for risks of MCS to determine whether further management and interventions may be required.

4 | DISCUSSION

PCS (or initially called long-COVID or long-haul COVID) is arguably the first medical condition brought to the attention of scientific and medical communities from patients' advocacy in social support groups.[144] Although sufferers of PCS faced disbelief initially, with their symptoms dismissed as mental health issues related to stress and anxiety, PCS research has since made substantial progress. As scientific knowledge on PCS is rapidly evolving, we have better understood the spectrum, prevalence, and duration of symptoms that characterise PCS, as well as the six putative subtypes and their respective potential therapies described in this review.

The medical and research prospects of PCS also seem promising. The UK National Health Service (NHS) has allocated £10 million to support the recovery process of PCS sufferers through specialised clinics and telerehabilitation. Moreover, the UK National Institute for Health Research (NIHR) has dedicated £20 million to fund research on biomarkers and therapies of PCS.[15] The US National Institute of Health (NIH) is also investing US$1.15 billion into the research on its epidemiology, pathophysiology, long-term effects, therapies and prevention of post-acute sequelae of SARS-CoV-2 (PASC); PASC includes PCS.[14] Although the COVID-19 pandemic may end in the coming years, its sequela will linger indefinitely. It is, therefore, not only reasonable but highly commended that research initiatives into PCS be taken seriously.

This review is not without limitations. First, the case definition of PCS remains unstandardised throughout the studies cited. Using informatics tools to analyse the literature, a study has concluded that studies on PCS thus far do not conform to a unified definition.[145] For instance, studies have identified PCS based on a varying follow-up duration (ranging from 2 weeks to 9 months) after diagnosis, discharge, or symptom onset. Not all studies screened for the same symptoms, which may explain the absence of certain common PCS symptoms such as neurocognitive impairments and PEM in some studies.[145] Second, studies also differ in how they recruit COVID-19 survivors, which could be based on polymerase chain reaction (PCR), serum antibody tests, or suspected (i.e., molecularly unconfirmed) COVID-19.[145–d147] For this reason, a study has developed the first symptom and impact tools (ST and IT) specific for PCS, which have also been validated with a nascent cohort of COVID-19 survivors and other health-related questionnaire tools.[148] Such a standardised assessment method would enable more effective identification and monitoring of PCS, warranting more research efforts on this aspect.

Furthermore, the pathophysiological mechanisms of PCS and its subtypes were only briefly discussed as such information has been reviewed in detail elsewhere.[8,17,65,66] From these reviews, it appears that the pathophysiology of PCS is highly multifaceted that differ in terms of immunology, neurobiology, endocrinology, physiology (e.g., pulmonary, cardiology, neurology, nephrology, gastroenterology and haematology). Henceforth, future research may seek to classify endotypes (i.e., distinct pathophysiological subtypes) of PCS, adding another layer of precision into the current review of PCS subtypes that are mainly based on symptomatic phenotyping. Properly defined phenotypes and endotypes of PCS would consequently open research avenues for biomarker exploration important for precision medicine.[149] Lastly, one prominent limitation in PCS research is the lack of non-COVID-19 control groups in most studies (Table 1), obscuring cause-and-effect relationships and possible influences of confounding factors.

5 | CONCLUSION

In summary, this narrative review has characterised six subtypes of PCS based on the current literature: NSC-MOS, PFS, ME/CFS, POTS, PICS and MCS. Each subtype differs in its symptomatic manifestations, pathophysiological mechanisms, and interventional approaches, although some degree of overlap may be present (Table 2). Equipped with this summarised understanding of PCS subtypes and their respective potential interventions, this review hopes to advance medical and public health efforts in alleviating PCS that has imposed a hefty health and economic burden. PCS is arguably the most common post-viral syndrome or sequelae, judging from the sheer number (by the hundreds of millions) of COVID-19 cases alone worldwide.

ACKNOWLEDGEMENTS

Not applicable.

CONFLICT OF INTEREST

No conflict of interest declared.

AUTHOR CONTRIBUTION

SJY wrote the manuscript and SL critically revised the manuscript. Both approved the manuscript for publication.

ETHICS STATEMENT

Not applicable.

PATIENT CONSENT STATEMENT

Not applicable.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

DATA AVAILABILITY STATEMENT

Not applicable.

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How to cite this article: Yong SJ, Liu S. Proposed subtypes of post-COVID-19 syndrome (or long-COVID) and their respective potential therapies. *Rev Med Virol*. 2021;e2315. https://doi.org/10.1002/rmv.2315