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REVIEW ARTICLE

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Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments

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ABSTRACT

Long COVID or post-COVID-19 syndrome first gained widespread recognition among social support groups and later in scientific and medical communities. This illness is poorly understood as it affects COVID-19 survivors at all levels of disease severity, even younger adults, children, and those not hospitalized. While the precise definition of long COVID may be lacking, the most common symptoms reported in many studies are fatigue and dyspnoea that last for months after acute COVID-19. Other persistent symptoms may include cognitive and mental impairments, chest and joint pains, palpitations, myalgia, smell and taste dysfunctions, cough, headache, and gastrointestinal and cardiac issues. Presently, there is limited literature discussing the possible pathophysiology, risk factors, and treatments in long COVID, which the current review aims to address. In brief, long COVID may be driven by long-term tissue damage (e.g. lung, brain, and heart) and pathological inflammation (e.g. from viral persistence, immune dysregulation, and autoimmunity). The associated risk factors may include female sex, more than five early symptoms, early dyspnoea, prior psychiatric disorders, and specific biomarkers (e.g. D-dimer, CRP, and lymphocyte count), although more research is required to substantiate such risk factors. While preliminary evidence suggests that personalized rehabilitation training may help certain long COVID cases, therapeutic drugs repurposed from other similar conditions, such as myalgic encephalomyelitis or chronic fatigue syndrome, postural orthostatic tachycardia syndrome, and mast cell activation syndrome, also hold potential. In sum, this review hopes to provide the current understanding of what is known about long COVID.

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Introduction

Early into the coronavirus disease 2019 (COVID-19) pandemic, announced in March 2020 by the World Health Organization (WHO), hardly anyone would have thought that the disease might be chronic. The causative agent of COVID-19 is the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As the 'A' in the name implies, the respiratory disease is acute [1]. However, longer-lasting COVID-19 cases started gaining traction among social support groups. At first, doctors dismissed their concerns as symptoms related to mental health, such as anxiety or stress, in a phenomenon called 'medical gaslighting' [2,3]. However, that soon changed. The term long COVID (or post-COVID syndrome or long-haul COVID-19) started gaining recognition in the scientific and medical communities [4]. Different descriptions of long COVID have already been proposed, and the most common description is symptoms lasting for more than three months after the first symptom onset (Table 1).

While the actual definition is lacking, a review identified that the most frequent symptoms of long COVID are fatigue and dyspnoea (i.e. shortness of breath) [17,18]. Other less typical symptoms include cognitive and mental disorders, headache, myalgia, chest and joint pains, smell and taste dysfunctions, cough, hair loss, insomnia, wheezing, rhinorrhea, sputum, and cardiac and gastrointestinal issues. These symptoms may persist for up to six months and counting after hospital discharge or symptom onset (Table 2). Less common symptoms of pernio, chills, flushing, ear pain, and visual impairments associated with long COVID have also been documented [36,45,47]. This illustrates the multifaceted nature of long COVID that involves multiple organ systems.

Evidently, studies have also reported different persistent symptoms in contrasting durations and frequencies among long COVID survivors (Table 2). This may be due to distinct sample characteristics and data collection methods each study employed or the fact that long COVID is a highly heterogeneous condition [11,48]. Therefore, the precise symptomatic manifestations of long COVID remains elusive and may involve multiple subtypes or phenotypes [49].

One puzzling feature of long COVID is that it affects survivors of COVID-19 at all disease severity. Studies have discovered that long COVID affects even mild-to-moderate cases and younger adults who did not require respiratory support or hospital or intensive care. Patients who were no longer positive for SARS-CoV-2 and discharged from the hospital, as well as outpatients, can also develop long COVID [24,30,31,41,50]. More concerningly, long COVID also targets children, including those who had asymptomatic COVID-19, resulting in symptoms such as dyspnoea, fatigue, myalgia, cognitive impairments, headache, palpitations, and chest pain that last for at least 6 months [51–53].

One known aspect of long COVID is that similar post-viral syndrome was observed with prior human coronavirus diseases. For example, symptoms of fatigue, myalgia, and psychiatric impairments have inflicted survivors of Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) for up to four years [54–58]. Even at 7-year and 15-year follow-ups, pulmonary and bone radiological complications were still evident among a proportion of SARS survivors who were mostly younger than 40 years [59,60]. This is rather

Table 1. Proposed descriptions of long COVID.

Reference	Terms	Description
[4]	Long COVID	Long-term COVID-19 illness that is cyclical, progressive, and multiphasic.
[5,6,7]	Long-hauler COVID-19	Multi-organ symptoms that persist for months after acute COVID-19.
	Long-COVID	
	Chronic COVID syndrome	
[8]	Long-haul COVID	Symptoms lasting for > 100 days.
	Long-tail COVID	
[9,10]	Long COVID	Symptoms lasting for > 2 months.
[11,12,13]	Late sequelae of SARS-CoV-2 infection	Symptoms lasting for > 4 weeks after the initial infection or diagnosis.
	Long-haulers	
	Long-COVID	
[14]	Post-acute COVID-19 syndrome	Symptoms lasting for > 4 weeks after the first symptom onset.
[15]	Acute post-COVID symptoms	Symptoms lasting for 5-12 weeks.
	Long post-COVID symptoms	Symptoms lasting for 12-24 weeks.
	Persistent post-COVID symptoms	Symptoms lasting for > 24 weeks.
[16, 17,7]	Post-acute COVID-19	Symptoms lasting for 1-3 months from the first symptom onset.
	On-going symptomatic COVID-19	
	Chronic COVID-19	Symptoms lasting for > 3 months from the first symptom onset.
	Long COVID	
	Post-COVID-19 syndrome	

Table 2. Demographics, clinical outcomes, and symptom prevalence of long COVID survivors.

Study	Participant and clinical characteristics	Follow-up duration	Symptom (% prevalence)
[19]	$N = 110$; median age = 60; 44% females; 100% inpatients; 24.5% had mild disease; 59% had moderate disease; 16.4% had severe disease; Bristol, England.	Median of 83 days after hospital discharge.	• ≥1 symptom (74%) • Dyspnoea (39%) • Fatigue (39%) • Insomnia (24%) • Myalgia (22%) • Cough (11%) • Anosmia (11%) • Arthralgia, headache, abdominal pain, diarrhoea (<5%).
[20]	$N = 238$; median age = 61; 40.3% females; 100% inpatients; 72.3% needed supplemental O_2; 11.8% admitted to ICU; 8.8% needed MV; Novara, Italy.	4 months after hospital discharge.	• Post-traumatic stress symptoms (17%) • Arthralgia (5.9%) • Myalgia (5.9%) • Dyspnoea (5.5%) • Ageusia, anosmia, cough, diarrhoea, and chest pain (≤5%)
[21]	$N = 143$; 56.5 ± 14.6 years; 37.1% females; 100% inpatients; 53.8% needed supplemental O_2; 12.6% admitted to ICU; 14.7% needed non-invasive ventilation; 4.9% needed MV; Rome, Italy.	Mean of 60 days after hospital discharge.	• ≥1 symptom (87.4%) • Fatigue (53.1%) • Dyspnoea (43.4%) • Worsened quality of life (44.1%) • Joint pain (27.3%) • Chest pain (21.7%)
[22], preprint.	$N = 21,359$ (only 233 were COVID-19 survivors; 96.6% outpatients); median age = 56; 63.6% females; 83.7% Europeans.	90 days after symptom onset.	• Symptom lasting for >30 days (42.3%). • Symptom lasting for >60 days (33.8%). • Symptom lasting for >90 days (24.1%). • Symptoms: concentration and memory problems, anosmia, ageusia, dyspnoea, headache, heart palpitations, chest pain, tachycardia, and cough.
[23], preprint	*$N = 3,762$; age groups of 18-29 (8%), 30-39 (26.1%), 40-49 (33.7%), 50-59 (27.1%), 60-69 (11%), 70-79 (2.5%), 80+ (0.4%) years; 78.9% females; 56.7% did not seek hospital care; 34.9% outpatients; 8.43% were hospitalized; 56 countries (41.6% from U.S.).	6-7 months after symptom onset.	• Fatigue (80%) • Post-exertional malaise (73.3%) • Cognitive dysfunction (58.4%) • Sensorimotor symptoms (55.7%) • Headaches (53.6%) • Memory issues (51.0%) • Insomnia, heart palpitations, and muscle aches (40-50%) • Dyspnoea, dizziness and balance issues, speech and language issues, joint pain, tachycardia, and other sleep issues (30-40%) • Reduced work schedule (45.2%) • Unable to work (22.3%)
[24]	*$N = 201$; 44 ± 11 years; 71% females; 81.6% outpatients; 18.4% were hospitalized; London, U.K.	Median of 140 days after symptom onset.	• ≥4 symptoms (99%) • ≥10 symptoms (42%) • Fatigue (98%) • Myalgia (86.7%) • Dyspnoea (87.1%) • Headache (82.6%) • Joint pain (78.1%) • Fever (75.1%) • Cough (73.6%) • Chest pain (73.1%) • Sore throat (71.1%) • Diarrhoea (59.2%) • Pain (53.7%) • Wheezing (48.3%) • Inability to walk (40.3%) • Runny nose (33.8%)
[25]	$N = 120$; 63.2 ± 15.7 years; 37.5% females; 100% inpatients; 20% admitted to ICU; Clichy, France.	Mean of 110 days after hospital admission.	• Fatigue (55%) • Dyspnoea (42%) • Memory loss (34%), • Sleep disorders (30.8%) • Impaired concentration (28%) • Hair loss (20%) • Cough (16.7) • Anosmia (13.3%) • Chest pain (10.8%) • Ageusia (10.8%)
[26]	$N = 114$; 54 ± 12 years; 30% females; 100% inpatients; 21% needed MV; Wuhan, China.	Mean of 175 days after symptom onset.	• Dyspnoea (14%) • Expectoration (10%) • Cough (6.1%)
[27]	$N = 1733$, median age = 57; 48% females; 100% inpatients; 67.6% needed supplemental O_2; 4% admitted to ICU; Hubei, China.	Median of 186 days after symptom onset.	• ≥1 symptom (76%) • Fatigue/muscle weakness (63%) • Pain/discomfort (27%) • Dyspnoea (26%)

(*continued*)

Table 2. Continued.

Study	Participant and clinical characteristics	Follow-up duration	Symptom (% prevalence)
			• Sleep difficulties (26%) • Anxiety/depression (23%) • Hair loss (22%) • Smell disorder (11%) • Heart palpitations (11%) • Joint pain (9%) • Low appetite (8%) • Taste disorder (7%) • Dizziness (6%) • Chest pain, sore throat, skin rash, myalgia, and headache ($\leq$5%).
[28]	$N = 103$; median age = 59; 48% females; 100% inpatients; 66% needed supplemental O_2; 15% admitted to ICU; 9% needed MV; Lørenskog, Norway.	3 months after hospital admission.	• Dyspnoea (52%) • Other symptoms not tested.
[29]	$N = 76$; 41.3 ± 13.8 years; 72.4% females; 100% inpatients; 9% admitted to ICU. Wuhan, China.	3 months after hospital discharge.	• Chest tightness and palpitations (62%) • Dyspnoea (61%) • Cough (60%) • Fatigue (59%) • Sputum (43%) • Diarrhoea (26%) • Fever (20%)
[30].	$N = 60$; 44.10 ± 16 years; 43.3% females; 100% inpatients; 78.3% had mild disease; 20% had severe disease; 1.7% had critical disease; Anhui Province, China.	3 months after hospital discharge.	• $\geq$1 symptom (55%) • Memory loss (28.3%) • Myalgia (25%) • Mood changes (16.7%) • Fatigue (6.7%) • Impaired mobility (6.7%) • Numbness in extremities (6.7%)
[31]	$N = 63$; 48.1 ± 18.5 years; 33.3% females; 100% inpatients; 27% needed supplemental O_2; 7.9% needed MV; Tokyo, Japan.	120 days after symptom onset.	• Fatigue (9.5%) • Cough (6.3%) • Dyssomnia (9.7%) • Dysgeusia (1.6%)
[32]	$N = 180$; 39.9 ± 19.4 years; 54% females; 95.6% outpatients; 4.4% were hospitalized; Faroe Islands, Denmark.	125 days after symptom onset.	• $\geq$1 symptom (55%) • Fatigue (28.9%) • Anosmia (27.2%) • Ageusia (15.6%) • Joint pain (11.1%) • Rhinorrhoea (8.9%) • Dyspnoea (8.3%) • Headache (7.2%) • Myalgia (7.2%) • Nausea (6.1%) • Chest tightness (6.1%) • Chills (4.4%) • Cough (4.4%) • Diarrhoea (4.4%)
[33]	$N = 120$; 54.6 ± 16.9 years; 33.3% females; 100% inpatients; 7.5% admitted to ICU; Tehran, Iran.	6 months after hospital discharge.	• Fatigue (17.5%) • PTSD (5.8%) • Other symptoms were not tested.
[34]	$N = 60$; median age = 67; 32% females; 100% inpatients; 46% needed supplemental O_2; 20% needed MV; Vancouver, Canada.	12 weeks after symptom onset.	• Dyspnoea (20%) • Cough (20%) • Other symptoms were not tested.
[35]	$N = 145$; 57 ± 14 years; 43% females; 25% outpatients; 75% were hospitalized; 66% needed supplemental O_2; 27% needed MV; Innsbruck, Austria.	Mean of 103 days after diagnosis.	• $\geq$1 symptom (41%) • Dyspnoea (36%) • Pain (24%) • Night sweat (24%) • Sleep disorders (22%) • Hyposmia/anosmia (19%) • Cough (17%) • Diarrhoea/vomiting (9%)
[36]	$N = 434$; 49.8 ± 15.2 years; 56% females; 100% outpatients; Lørenskog, Norway.	Median of 117 days after symptom onset.	• $\geq$1 symptom (38.7%) • Dyspnoea (15%) • Smell dysfunction (12%) • Taste dysfunction (10%) • Arthralgia (9%) • Myalgia (8.5%) • Headache (6%) • Cough (6%)

(*continued*)

Table 2. Continued.

Study	Participant and clinical characteristics	Follow-up duration	Symptom (% prevalence)
			• Sore throat, chills, runny nose, vision disturbance, skin rash, conjunctivitis, ear pain, cramps, wheeze, confusion, gastrointestinal symptoms (≤5%)
[37]	$N = 4182$; median age = 42 years; 71.5% females; Sweden, U.K, and U.S.	12 weeks after symptom onset.	• Symptom lasting for >4 weeks (13.3%). • Symptom lasting for >8 weeks (4.5%). • Symptom lasting for >12 weeks (2.3%). • Symptoms: Fatigue, headache, dyspnoea, and anosmia
[38]	$N = 242$; 65.9 ± 14.1 years; 40.5% females; 100% inpatients; 18.2% admitted to ICU; 12.8% needed MV; Santiago, Spain.	6 months after hospital discharge.	• ≥1 symptom (31.1%) • Symptoms: dyspnoea, pain, fatigue, muscle weakness, memory loss, depression, and anxiety.
[39]	$N = 128$; 49.5 ± 15 years; 54% females; 44.5% outpatients; 55.5% were hospitalized; 36.7% needed supplemental O_2; 14.1% admitted to ICU; Dublin, Ireland.	Median of 10 weeks after hospital discharge or last acute symptom.	• Fatigue (52.3%) • Other symptoms not tested.
[40]	$N = 22$; 54.6 ± 10.9 years; 27.3% females; 100% ICU patients; 64% needed MV; Brussels, Belgium.	3 months after hospital discharge.	• Dyspnoea (48%) • Other symptoms not tested.
[41]	$N = 124$; 59 ± 14 years; 40% females; 100% inpatients; 21.8% had mild disease; 41% had moderate disease; 21% had severe disease; 16.1% had critical disease; Nijmegen, Netherlands.	3 months after hospital discharge.	• Decreased quality of life (72%) • Fatigue (69%) • Functional impairment (64%) • Cognitive or mental impairments (36%)
[42]	$N = 48$; median age = 63; 31.2% females; 100% ICU patients on MV; Maastricht, Netherlands.	3 months after hospital discharge.	• Dyspnoea (32.5%) • Other symptoms not tested.
[43]	$N = 78$; 62 ± 16 years; 36% females; 100% inpatients; Vancouver, Canada.	3 months after symptom onset.	• ≥1 symptom (76%) • Worsened quality of life (51%) • Dyspnoea (50%) • Cough (23%)
[44]	$N = 18$; 42.2 ± 14.3 years; 57.9% females; 33.3% outpatients; 22.2% needed supplemental O_2; Hamburg, Germany.	Median of 85 days after hospital discharge.	• Attention deficits (50%) • Concentration deficits (44.4%) • Memory deficits (44.4%) • Trouble finding words (27.8%) • Fatigue (16.7%) • Mood swings (11.1%)
[45]	$N = 538$; median age = 52; 54.5% females; 100% inpatients; 33.5% had severe disease; 5% had critical disease; Wuhan, China.	Median of 97 days after hospital discharge.	• ≥1 symptom (49.6%) • Alopecia (28.6%) • Fatigue (28.3%) • Sweating (23.6%) • Post activity polypnoea (21.4%) • Sleep disorders (17.7%) • Chest pain (12.3%) • ↑ resting heart rate (11.2%) • Arthralgia (7.6%) • Cough (7.1%) • Anxiety (6.5%) • Myalgia, chills, dizziness, throat pain, sputum, nonmotor polypnoea, discontinuous flushing, limb oedema, dysphoria, and depression (≤5%)
[46]	$N = 55$; 47.5 ± 15.5 years; 41.8% females; 100% inpatients; 7.3% had mild disease, 85.5% had moderate disease; 7.3% had severe disease; 25.5% needed supplemental O_2; Henan Province, China.	3 months after hospital discharge.	• Gastrointestinal symptoms (30.91%) • Fatigue (16.36%) • Headache (18.18%) • Dyspnoea (14.55%) • Cough and sputum (1.81%)

Years refer to age presented as mean ± standard deviation, unless otherwise stated as median. * refers to sample size that specifically involved long COVID participants. ICU: intensive care unit; IL; MV: mechanical ventilation; O_2: oxygen; PTSD: post-traumatic stress disorder.

unsettling as it implies that long COVID may extend beyond just a few months to years.

Presently, there are limited research papers that have voiced discussions about the possible pathophysiology, risk factors, and treatments for long COVID. The current review, hence, seeks to fulfil these gaps.

Methods

The literature search was conducted on PubMed database using the following algorithm: (SARS-CoV-2[tiab] OR COVID*[tiab]) AND (long-haul[tiab] OR long COVID[tiab] OR post-COVID*[tiab] OR post-viral[tiab] OR recover*[ti] OR survivor*[ti] OR discharge*[ti] OR

sequela*[ti] OR prolong*[ti] OR persistent[ti] OR long-term[ti]) AND English[la]. The sole author screened the titles and abstracts to identify relevant papers. Long COVID was identified with the presence of at least one persistent symptom that includes either fatigue or dyspnoea for at least three months after symptom onset, hospital admission, or diagnosis [17] (Table 1). Since acute COVID-19 may last for a few weeks before hospital discharge, symptoms lasting for at least two months after discharge is also considered as long COVID. Additional references from reviewers' recommendations and reference lists of included articles were also incorporated. The last literature search was performed on 5th February 2021, with another brief search update on 15th April 2021.

Studies on long COVID with information on symptomatic prevalence were summarized in Table 2. Studies detailing probable long COVID with a follow-up duration of fewer than three months after symptom onset or two months after hospital discharge were summarized in Supplementary Table 1. The subsequent putative pathophysiology, risk factors, and treatments sections were based on narrative review expanding on studies in Table 2.

Putative pathophysiology

Long-term tissue damage

In a three-month follow-up study of COVID-19 survivors, pulmonary radiological abnormalities and functional impairments were detected in 71% and 25% of participants, respectively, despite that only less than 10% had severe pneumonia [46]. Another study has also observed reduced lung diffusion capacity that correlated with radiological abnormalities in 42% of COVID-19 survivors at three-month post-hospital discharge, regardless of initial disease severity [41]. Even at six months after symptom onset, lung radiological abnormalities associated with persistent symptoms were still present in about half of COVID-19 survivors [27]. Many other reports have also found radiological evidence of lung fibrosis lasting up to six months among COVID-19 survivors after hospital discharge, which also correlated with initial disease severity [20,26,40,61–63].

Using a more advanced xenon gas radiological technique to study lung function, a study discovered defective pulmonary gas-exchange function among discharged patients who had moderate COVID-19 compared to healthy controls [64]. Moreover, in this study, such pulmonary issues were not detectable with standard chest computed tomography (CT), suggesting that routine radiological examinations might have overlooked such pulmonary complications. Notably, a study found reduced maximal aerobic capacity at about 45-day follow-up among young recruits with symptomatic COVID-19 compared to non-COVID-19 recruits [65]. These studies collectively indicate that pulmonary scarring may be a common sequela of COVID-19, which may be responsible for persistent dyspnoea and cough in long COVID [66,67].

However, a separate study has also found that symptoms of long COVID persist even in those with improvements in pulmonary radiological and functional examinations [19]. Thus, long COVID may involve other pathophysiology besides pulmonary lesions, such as lasting neurological complications. For instance, at three-month post-discharge, brain structural and metabolic abnormalities were reported among COVID-19 survivors, which correlated with persistent neurological symptoms such as memory loss, anosmia, and fatigue [30]. This finding is concerning as most participants had mild COVID-19 at baseline, suggesting that even mild COVID-19 could have persistent effects on the brain. Another study documenting 43 cases of COVID-19-induced serious brain diseases (e.g. encephalopathies, delirium, haemorrhage, and stroke) also found that initial COVID-19 severity plays little role in predicting these brain diseases [68].

In more severe cases of COVID-19 resulting in delirium in about 20–30% of hospitalized patients, long-term neurological symptoms are more probable [69–71]. Delirium is also a strong predictor of long-term cognitive impairments, especially among older adults [72,73]. A meta-analysis examining neuropsychiatric outcomes of SARS, MERS, and COVID-19 survivors has found delirium as a common complication in the acute phase of disease, which can lead to various neuropsychiatric sequelae, such as depression, anxiety, post-traumatic stress disorder, memory loss, and fatigue [58]. Indeed, COVID-19-related fatigue has been suggested to result from autonomic nervous system dysfunction [3,74]. In a registry study of 236,379 COVID-19 survivors, about a third received a neuropsychiatric diagnosis (e.g. stroke, dementia, insomnia, and anxiety and mood disorders) within 6 months after the first symptom onset, which was 44% more common than influenza survivors. Moreover, in this study, ICU survivors were 56% more likely to develop a neuropsychiatric disorder compared to non-ICU survivors [75].

As SARS-CoV-2 is a respiratory virus, lung injury can be expected. However, it was only much later that evidence started confirming the neurotropism and replication capacity of SARS-CoV-2 in neuronal cultures, brain organoids, mice, and human brain autopsies [76–79,80]. Notably, damage to the brainstem's cardiorespiratory centre has been proposed to worsen symptoms of COVID-19 [81,82]. Since neurons rarely regenerate, the resulting brainstem dysfunction may be long-lasting, leading to neurological and cardiorespiratory sequelae that might underlie long COVID [83]. The brainstem expresses higher levels of angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2, than other brain regions [84]. Autopsy reports have also found evidence of SARS-CoV-2 genes and proteins, as well as pathological immune and vascular activations, in the brainstem of deceased COVID-19 victims [85–87]. Therefore, on-going neuroinflammatory processes may drive the neurological symptoms and damage in long COVID.

Evidence of cardiac injury in long COVID also exists. A radiological study of 100 discharged COVID-19 patients has found cardiac abnormalities and myocardial inflammation in 78% and 60% of participants, respectively, which were not associated with initial COVID-19 severity [88]. In another study of 26 college athletes with asymptomatic SARS-CoV-2 infection, 46% of them also presented with myocardial inflammation [89]. Even at three-month post-hospital discharge, radiological abnormalities of ventricular remodelling were still evident in 29% of 79 COVID-19 survivors [90]. However, the long-term clinical significance of these radiological findings remains unclear as symptomatic assessments were not performed, warranting further research and surveillance [91,92]. Nevertheless, cardiac symptoms such as chest pain, heart palpitations, and tachycardia commonly persist among COVID-19 survivors for up to six months, suggesting substantial cardiac sequelae [21,24,27,29].

Lastly, the long-term damage of other organs may also be involved in long COVID. One preprint report has found that young adults, mostly free of risk factors for severe COVID-19, often develop long COVID with multi-organ impairment at four-month follow-up. Specifically, at least one radiological abnormality of the lungs, heart, liver, pancreas, kidneys, or spleen was present in 66% of survivors [24]. Similarly, another study involving moderate-to-severe COVID-19 patients has shown radiological evidence of lung, heart, brain, liver and kidney impairments persisting for at least 2–3 month after hospital discharge [93]. Furthermore, a study of over 40,000 discharged COVID-19 patients found increased risks of new events of respiratory, diabetes, and cardiovascular diseases occurring within the subsequent 140 days compared to controls [94]. Therefore, future research of long COVID should consider possible extrapulmonary or multi-organ involvement that may be less obvious.

Pathological inflammation

There have been instances of COVID-19 patients who remained positive for SARS-CoV-2 by reverse transcription real-time polymerase chain reaction (RT-PCR) test for up to three months [95–97,98]. Other studies have documented cases of prolonged SARS-CoV-2 shedding in the respiratory tract *via* quantitative RT-PCR for up to four months [99,100]. Extended SARS-CoV-2 shedding has also been detected in the faeces, regardless of gastrointestinal symptom manifestation, for up to two months [101,102]. A more recent study has discovered SARS-CoV-2 nucleic acids and proteins in the small intestines of 50% of asymptomatic COVID-19 cases at 4-month post-disease onset [103]. Therefore, these studies showed that SARS-CoV-2 persistence in the body is possible, which may induce some level of immune activation contributing to long COVID.

A review has proposed that T-cells dysfunction may promote long COVID pathophysiology similarly in autoimmune diseases [104]. For instance, SARS-CoV-2 could make antigen-presenting cells present antigens to autoreactive T-cells in a process called bystander activation. This is consistent with autopsy examinations of deceased COVID-19 patients showing that infiltrates in the lungs and other organs were enriched with CD8+ T cells, one of the crucial mediators of autoimmune reactions [105]. Surprisingly, thyroid dysfunction has been detected in 15–20% of patients with COVID-19 [106,107]. As the thyroid is closely linked to T-cell-mediated autoimmunity, thyroid dysfunction may play a role in the autoimmunity pathophysiology of long COVID [106,108].

B-cells may also be involved in long COVID autoimmunity. In a study analysing serum samples from hospitalized COVID-19 patients, antiphospholipid autoantibodies were detected in 52% of samples, which were further associated with neutrophil hyperactivity and more severe clinical outcomes [109]. Other studies have also identified autoantibodies against interferons, neutrophils, connective tissues, cyclic citrullinated peptides, and cell nucleus in 10–50% of patients with COVID-19 [110–112,113]. While it is unconfirmed if such autoantibodies are long-lasting in COVID-19, research review

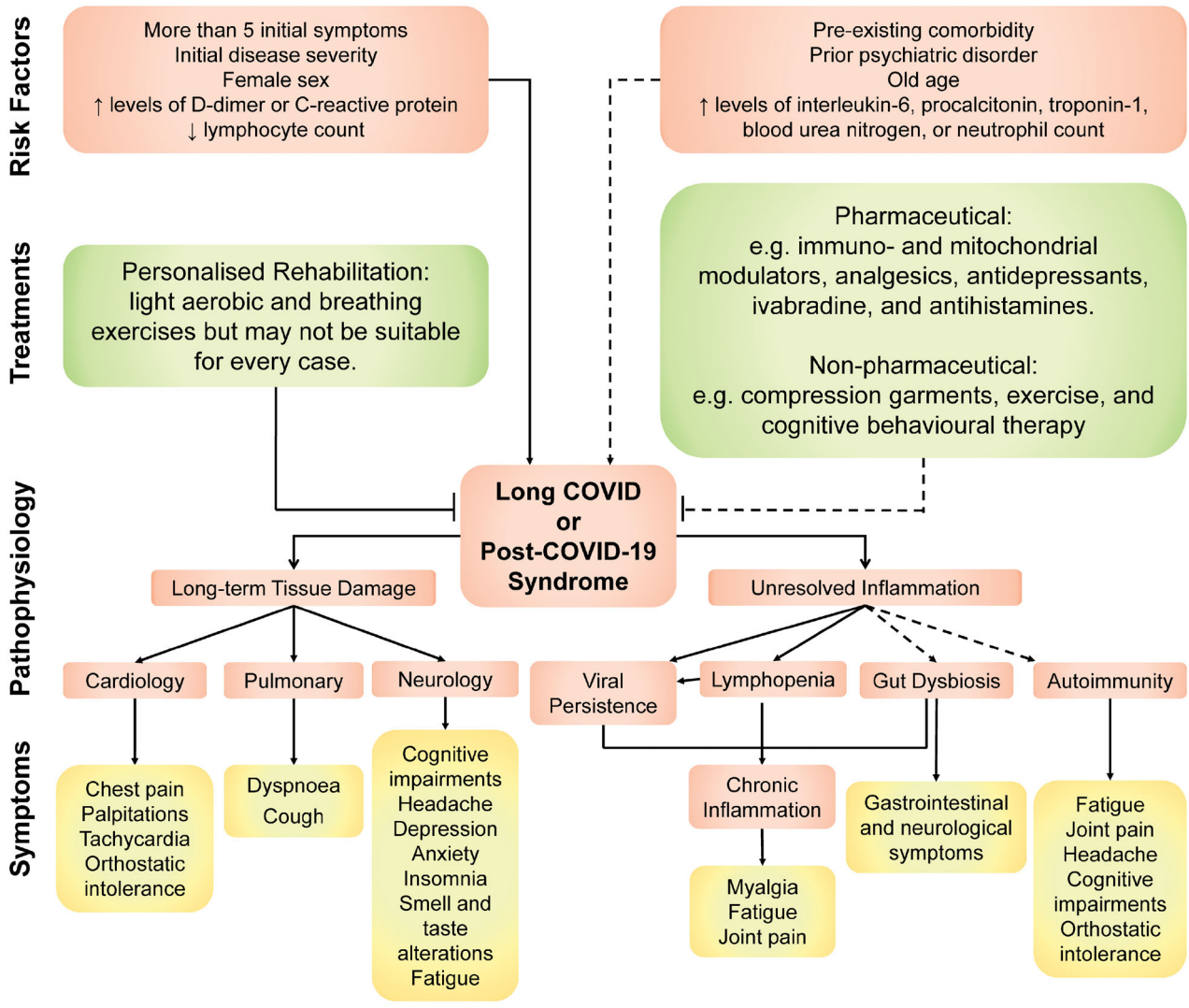

Figure 1. An overview of the symptoms, putative pathophysiology, associated risk factors, and potential treatments involved in long COVID. Note: Dashed lines represent areas where evidence is relatively lacking compared to non-dashed lines. (Color online only).

has strongly linked these autoantibodies to chronic autoimmune diseases, such as antiphospholipid and Sjogren syndromes, lupus erythematosus, and rheumatoid arthritis [114]. Notably, reviews on lupus and rheumatoid arthritis also bear symptomatic resemblances to long COVID: fatigue, joint pain, concentration difficulties, and headache [115,116].

Besides, evidence exists that severe COVID-19 causes lymphopenia (i.e. B-cell and T-cell lymphocytes deficiency) that causes hyperinflammation [117,118]. This is because lymphocytes, particularly T-cells, participate in inflammation resolution following infection [119,120]. Following this, meta-analyses have determined lymphopenia and high pro-inflammatory neutrophil count as independent risk factors of COVID-19 severity and mortality [121–123]. Thus, as B-cell and T-cell lymphocytes are renewed, elevated inflammation from unresolved hyperinflammation may ensue and contribute to long COVID [118,120]. Moreover, decreased T-cell and B-cell numbers have been shown to correlate with persistent SARS-CoV-2 shedding, which may further perpetuate chronic immune activation in long COVID [124,125] (Figure 1).

Furthermore, numerous cases of multisystem inflammatory syndrome (MIS) occurring 2–6 weeks after SARS-CoV-2 infection in children and adults have been documented. These patients do not necessarily have a positive SARS-CoV-2 status or severe respiratory disease. Yet they showed elevated levels of systemic pro-inflammatory markers (e.g. CRP, interleukin-6; IL-6, ferritin, and D-dimer) and severe shock, cardiac, gastrointestinal, or neurological symptoms [126–130]. The delayed manifestation of MIS after SARS-CoV-2 infection suggests the involvement of dysregulated adaptive immune system;

autoantibodies, in particular, have been strongly suspected in research reviews [9,131]. Therefore, it may be possible that residual inflammation and symptoms from post-SARS-CoV-2 MIS could lead to long COVID in children and adults.

Indeed, increased levels of pro-inflammatory markers (e.g. CRP, IL-6, and D-dimer) and lymphopenia have been associated with long COVID (section 'Patient and Clinical Characteristics'). Another radiological study of COVID-19 survivors with symptoms persisting for at least 30 days after discharge has revealed increased [18^F] FDG uptake, signifying persistent inflammation, in the bone marrow and blood vessels [132]. A recent case–control study found elevated levels of vascular-related pro-inflammatory biomarkers, which correlated with pulmonary damage, among COVID-19 patients discharged three months prior [133]. However, other long COVID studies that found no association with pro-inflammatory biomarkers also exist. These reports imply that unresolved inflammation may only partly explain the pathophysiology of long COVID, particularly and perhaps the inflammation-related symptoms such as myalgia, joint pain, and fatigue [134,135] (Figure 1). Notably, chronic fatigue is a complex syndrome that may have other causes besides inflammation, such as channelopathies, inadequate cerebral perfusion, and autonomic nervous system dysfunction, which may also be involved in long COVID [3,136,137].

Another possible source of unresolved inflammation in long COVID could lie in the gut. SARS-CoV-2 has been known to replicate efficiently in gastric and intestinal cells, owing to the high expression of ACE2 receptors therein, leading to increased faecal shedding of SARS-CoV-2 in patients [138–140]. While the prevalence of gastrointestinal symptom may vary between different study designs, meta-analyses have estimated that gastrointestinal manifestations (e.g. appetite loss, nausea, vomiting, diarrhoea, and abdominal discomfort) affect 10–20% of patients with COVID-19 [141,142]. Importantly, gastrointestinal symptoms have also been reported in up to a third of individuals with long COVID [29,32,46]. Thus, SARS-CoV-2 persistence in the gastrointestinal tract may underlie the gastrointestinal manifestations of long COVID.

Gut microbiome disruption (i.e. gut dysbiosis) has been observed among patients with COVID-19, which persisted for at least ten days up to 30 days after disease resolution [143,144,145]. In these studies, gut dysbiosis also correlated with increased COVID-19 severity and inflammatory biomarkers and prolonged SARS-CoV-2 faecal shedding. However, it is unclear if such gut dysbiosis extends beyond 30 days. Notwithstanding this uncertainty, since the gut is closely intertwined with the immune system, a review has implicated the accompanying gut microbiome in numerous diseases related to chronic inflammation [146]. It has also been reviewed that the gut microbiome modulates the neurotransmitter circuitries in the gut and brain *via* the microbiota-gut-brain axis [147]. Hence, persistent gut dysbiosis may also contribute to the gastrointestinal and neurological symptoms of long COVID.

Possible risk factors

Biomarkers

Elevated blood urea nitrogen (BUN) and D-dimer levels were found to be risk factors for pulmonary dysfunction among survivors of COVID-19 at three-month post-hospital discharge [46]. Other studies have shown that COVID-19 pulmonary lesions at two-month post-admission were associated with elevated systemic inflammatory biomarkers, such as D-dimer, interleukin-6 (IL-6), and CRP [62,148]. Systemic inflammatory biomarkers (e.g. CRP, procalcitonin, and neutrophil count) also correlated with radiological abnormalities of the heart, liver, and kidney in a 2- to 3-month follow-up study of discharged COVID-19 patients [93]. In another study, increased D-dimer and CRP levels and decreased lymphocytes were more common in COVID-19 survivors who developed persistent symptoms than their fully recovered counterparts [149]. Another report also found that lymphopenia correlated with chest tightness and heart palpitations, whereas elevated troponin-1 correlated with fatigue, among sufferers of long COVID [29]. Therefore, changes in levels of D-dimer, CRP, and lymphocyte appeared consistent in a few studies, and may serve as potential biomarkers of long COVID.

However, other studies have found no changes in pro-inflammatory biomarkers (e.g. CRP, D-dimer, IL-6, CD25, and neutrophil and lymphocyte counts) between COVID-19 cases with and without persistent symptoms [39,41,150,151,46]. Such discrepancies may be due to different study methods as studies differ in their sample characteristics, measured endpoints, and data collection and analyses. Another reason may be the heterogeneous and relapsing-remitting nature of long COVID with multifaceted symptomatic presentations [15] (Table 2). This hints at the possible involvement of multiple pathophysiology, with each type possessing a unique set of biomarkers that may even fluctuate. Indeed,

inflammatory biomarkers in autoimmune and other chronic inflammatory diseases are known to fluctuate depending on the disease activity and patient's characteristics [152,153].

Patient and clinical characteristics

One study has revealed that COVID-19 survivors who developed persistent fatigue at 10-week post-discharge were more likely females and persons with a history of anxiety or depression diagnosis or antidepressant usage [39]. Similarly, in another study of COVID-19 survivors who developed persistent symptoms, the associated risk factors include female sex and prior psychiatric disorder [154]. More recent studies have also found higher rates of long COVID symptoms in females than males a few months after hospital discharge [27,33,155,156]. Interestingly, in the first published case series of five children with long COVID, four were females [53]. However, some studies have found that males were as likely as females to develop long COVID [32,36,150]. Therefore, female sex may be at higher risk for certain long COVID manifestations, which require further studies to clarify.

Another study tracked over 4000 COVID-19 survivors and identified factors that predicted long COVID, which include old age of over 70 years, more than five symptoms during the first week of illness, presence of comorbidities, and female sex [37]. In another preprint study, more than five initial presenting symptoms was also a risk factor for long COVID, but not sex or comorbidities [22]. The manifestation of at least 10 symptoms during acute COVID-19 was also found as a risk factor for long COVID in another four-month follow-up study of 434 COVID-19 survivors [36].

Most studies did not find any association between long COVID and initial disease severity during acute COVID-19 [30,31,39,41,154]. However, a few have reported that patients who suffered severe COVID-19 in need of invasive mechanical ventilation, intensive care unit (ICU) admission or prolonged hospitalization were more likely to suffer long-term tissue damage associated with persistent symptoms [38,93,155]. Studies have also revealed high rates of severe functional disabilities and impaired quality of life among COVID-19 survivors discharged from the ICU three months ago [40,157]. Indeed, survivors of critical disease generally face post-intensive care syndrome (PICS) involving long-term cognitive, mental, and physical sequelae due to extensive tissue damage [158,159]. The possible additive impact of COVID-19 on top of PICS also warrants more investigations.

Therefore, some of the more prominent risk factors of long COVID, supported by at least three studies, are female sex, more than five early symptoms, and initial acute COVID-19 severity. Reasons for the ambiguity in long COVID risk factors may be variances in reporting, study design, and participants' clinical (e.g. disease severity and treatment received) and demographic (e.g. comorbidities, socioeconomic status, and smoking history) characteristics. Another possibility could be the multifaceted pathophysiology of long COVID, which may target populations with particular phenotypes [49].

Potential treatments

Rehabilitation

The literature thus far has only suggested that rehabilitation may work for treating certain cases of long COVID. According to reviews, in rehabilitation, patients are advised to perform light aerobic exercise paced according to individual capacity. Exercise difficulty levels are increased gradually within tolerated levels until improvements in fatigue and dyspnoea are seen, typically four to six weeks. Rehabilitation also includes breathing exercises that aim to control slow, deep breaths to strengthen respiratory muscles' efficiency, especially the diaphragm. The breath should be inhaled through the nose, expanding the abdominal region, and exhaled *via* the mouth. Such light aerobic and breathing exercises should be performed daily in 5–10 min sessions throughout the day. Complementary behavioural modification and psychological support may also help improve survivors' well-being and mental health [16,160,161]. Reviews have also recommended that rehabilitation programs be personalized since long COVID manifestation and pathophysiology may vary in each case [162,163].

In an observational study of 23 discharged COVID-19 patients with on-going symptoms, a personalized multidisciplinary rehabilitation approach involving breathing, mobilisation, and psychological interventions have improved lung function and physical capacity. However, most participants' lung function did not heal completely, and persistent neurological symptoms remained [164]. A case series of seven discharged COVID-19 patients with on-going symptoms showed that combined breathing and light exercise rehabilitation healed and improved fatigue symptoms in five and two cases, respectively [165]. Thus far, only one randomized controlled trial (RCT) of 72 elderly COVID-19 survivors has demonstrated

Table 3. Descriptions of conditions similar to long COVID with their respective pharmaceutical and non-pharmaceutical treatments.

Condition	Description	Treatment	Reference
Long COVID or post-COVID-19 syndrome	• Condition lasts for ≥3 months after COVID-19 symptom onset. • Fatigue and dyspnoea that may come with neurological, neuropsychiatric, cardiac, or gastrointestinal complications.	• Paracetamol and NSAIDs (for relieving specific symptoms) • Ivabradine (for cases with tachycardia or palpitations). • Personalized rehabilitation	[16,168,17]
ME/CFS	• Condition lasts for ≥6 months after possible triggers such as stress or viral infection. • 1994 CDC criteria: Fatigue with at least four of either headache, myalgia, joint pain, PEM, sore throat, tender lymph nodes, unrefreshing sleep, or cognitive impairment. • 2015 IOM criteria: Fatigue, PEM, and unrefreshing sleep that may come with cognitive impairment or orthostatic intolerance.	• Rintatolimod (TLR3 agonist) • Staphypan Berna vaccine • Coenzyme Q10 + NADH (mitochondrial modulator) • Antidepressants • Analgesics • Antivirals • CBT and GET (debatable)	[169,170,171,172,173]
POTS	• Condition lasts for ≥6 months after possible triggers such as viral infection, surgery, pregnancy, or concussion. • Increased heart rate of >30 beats/minute within 5-10 mins of standing or upright tilt with the absence of orthostatic hypotension, and may come with light-headedness, palpitations, fatigue, generalised weakness, blurred vision, or exercise intolerance.	• Midodrine (α_1-adrenergic agonist) • Fludocortisone (corticosteroid) • Pyridostigmine (cholinergic agonist) • Propranolol (β-blockers) • Ivabradine (I_f ion channel blocker) • Compression garments • ↑ fluid and salt intake • Exercise (may need to avoid upright ones) • Sleep with elevated head of bed	[174,175]
MCAS	• Condition is recurrent and chronic. • Increased serum total tryptase (or other suitable biomarkers) • Multi-organ symptoms of the skin (urticaria, angioedema, or flushing), gastrointestinal (diarrhoea, nausea, vomiting, or abdominal cramp), respiratory (wheezing), cardiovascular (hypotensive syncope, near syncope, or tachycardia), or naso-ocular (conjunctival injection, pruritus, or nasal stuffiness), neuropsychiatric (headache, anxiety, sleeplessness, or cognitive impairments), musculoskeletal (muscle or joint pain), or constitutional (fatigue, asthenia, or fever) systems.	• H1 and H2 antihistamines • Cromolyn (mast cell stabilizer) • Leukotriene antagonists	[176,177]

CBT: cognitive behavioural therapy; GET: graded exercise therapy; CDC: Centres for Disease Control and Prevention; COVID-19: coronavirus disease 2019; IOM: Institute of Medicine; MCAS: mast cell activation syndrome; ME/CFS: myalgic encephalomyelitis or chronic fatigue syndrome; NSAIDs: non-steroidal anti-inflammatory drugs; PEM: post-exertional malaise; POTS: postural orthostatic tachycardia syndrome; TLR3: toll-like receptor 3.

that a 6-week rehabilitation program (i.e. involving breathing, stretching and home exercises) improved lung function, exercise capacity, quality of life and anxiety, but not depression [166].

Risks of physical rehabilitation must also be considered. Systematic and scoping reviews have identified that rehabilitation may not be suitable for survivors of critical COVID-19 with severe pulmonary or cardiac damage. Hence, exclusion criteria for post-COVID-19 rehabilitation have been proposed: high resting heart rate (>100 beats/min), low or high blood pressure (<90/60 or >140/90 mmHg), low blood oxygen saturation (<95%), or other conditions where exercise is a contraindication [167]. Indeed, an international survey study found that 85.9% of participants with long COVID experienced symptom relapse following mental or physical activities [23].

Even persons with similar conditions to long COVID (Table 3) may not always respond favourably to physical rehabilitation, which includes patients with postural orthostatic tachycardia syndrome (POTS) or myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS) with post-exertional malaise [178–180]. Therefore, reviews have emphasised that more RCTs are needed to determine which rehabilitation program would work best for specific groups of long COVID, including those with POTS or ME/CFS [181,182]. The non-pharmaceutical treatment approaches to POTS and ME/CFS may also be repurposed for long COVID cases that share symptoms of POTS and ME/CFS (Table 3). Notably, for ME/CFS, although cognitive behavioural therapy (CBT) and graded exercise therapy (GET) have been the mainstay recommended treatments, they may pose potential harm in some instances [180,183,184].

Pharmaceutical treatments

Presently, no pharmaceutical drug has been shown to ameliorate or attenuate symptoms (or radiological and blood biomarker abnormalities) of long COVID in

controlled or large-scale cohort studies. However, paracetamol and non-steroidal anti-inflammatory drugs may be used to manage specific symptoms such as fever [16]. However, drugs used to treat similar conditions may hold the potential to be repurposed for long COVID, warranting further research to confirm (Table 3).

Specifically, increasing evidence shows that long COVID resembles ME/CFS and POTS. There have been multiple reports of POTS diagnosis following SARS-CoV-2 infection [174,185–187]. Reviews have suggested that long COVID cases would eventually lead to ME/CFS due to the extensive symptomatic resemblance [136,188,189]. In a survey study of 1146 COVID-19 survivors with persistent symptoms who later sought a medical diagnosis, 13.5% and 10.3% of them received POTS and ME/CFS diagnosis, respectively [23]. A six-month follow-up study discovered that 17.5% of discharged COVID-19 patients still had fatigue, of whom 14.2% met the criteria for ME/CFS [33]. Shared pathophysiology may, therefore, be present among long COVID and POTS or ME/CFS, providing a preliminary basis for further research and potential drug repurposing. Interestingly, a small study of 24 COVID-19 survivors with palpitations or tachycardia found that ivabradine (i.e. a POTS medication) effectively relieved racing heart rate compared to carvedilol (i.e. a blood pressure medication) [168].

Reviews have proposed that mast cell activation syndrome (MCAS) may also underlie long COVID pathophysiology [190,191]. Mast cells serve as a fibroblast-activating factor that could lead to pulmonary fibrosis seen in long COVID sufferers [20,26]. Indeed, SARS-CoV-2 has been shown to trigger inflammatory mast cell responses alongside other immune cells in COVID-19 patients [192,193]. Reviews have also been implicated mast cell activation in the pathophysiology of POTS [175,194]. In contrast to POTS and ME/CFS, there have not been any instances of MCAS diagnosis following COVID-19 in the literature thus far. However, this may be due to the heterogeneous nature of MCAS that has been overlooked in long COVID cases [190]. Hence, the possible involvement of MCAS or mast cell activation pathophysiology in long COVID may need further investigations.

Notably, differences between long COVID and other similar conditions also exist. For example, long COVID entails a myriad of symptoms involving multi-organ systems not usually apparent in POTS and ME/CFS. Dyspnoea, a common symptom of long COVID, is rarely seen in and not part of the diagnostic criteria of ME/CFS and POTS (Table 3). Hence, drug repurposing attempts must consider symptomatic and pathophysiological differences between these similar conditions. Another treatment challenge lies in the heterogeneous nature of long COVID, which likely involves multiple subtypes and complicates accurate diagnosis, as also suggested by other reviews [11,48]. Future studies should also explore and possibly solve these challenges in finding therapeutic drugs for long COVID.

Concluding remarks

This review presents the current understanding of long COVID, a relatively new and puzzling condition that may affect COVID-19 survivors, regardless of initial disease severity or age. The symptoms, putative pathophysiology, associated risk factors, and potential treatments have been discussed. However, much remains ambiguous about long COVID, particularly its risk factors with inconsistent data thus far. This may be due to its multiple symptomatic presentations and pathophysiologies, ranging from long-term damage of multiple organ systems to unresolved inflammation from multiple sources. Hence, future research might be interested in phenotyping subtypes of long COVID [49]. Presently, only rehabilitation has been found as possibly effective in improving symptoms of long COVID, whereas the potential pharmaceutical drugs repurposed from ME/CFS, POTS, and MCAS still require future research to validate.

Evidently, the pandemic has brought us a wave of a new chronic, disabling condition called long COVID that deserves serious attention among the scientific and medical communities to resolve. Assuming at least 10% of COVID-19 survivors develop long COVID, which is likely underestimated (Table 2), it is estimated that 5 million people are facing long COVID globally [5]. The information presented in this review, which has not been communicated extensively elsewhere in the literature, may serve as a starting point for further exploration on long COVID.

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