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Long-Haul COVID-19: Putative Pathophysiology, Risk Factors, and Treatments

Author: Shin Jie Yong[1]*

[1]Department of Biological Sciences, Sunway University, Petaling Jaya, Selangor, Malaysia

*Correspondence: Shin Jie Yong

E-mail: shin.y7@imail.sunway.edu.my; phone: +60178487513

Abstract

Long-haul COVID-19 illness first gained widespread recognition among social support groups and later in scientific and medical communities. This illness is mysterious as it affects COVID-19 survivors at all levels of disease severity, even younger adults and children. While the precise definition may be lacking, the defining symptoms are fatigue, dyspnea, and headache that last for months after hospital discharge. The less typical symptoms may include cognitive impairments, chest and joint pains, myalgia, smell and taste dysfunctions, cough, mood changes, and gastrointestinal and cardiac issues. Presently, there is limited literature discussing the possible pathophysiology, risk factors, and treatments in long-haul COVID-19, which the current review aims to address. In brief, long-haul COVID-19 may be driven by long-term lung and brain damage and unresolved inflammation from multiple sources. The associated risk factors may include female sex, more than five early symptoms, early dyspnea, and specific biomarkers like D-dimer. While only rehabilitation training has been useful for long-haul COVID-19, therapeutics repurposed from mast cell activation syndrome, myalgic encephalomyelitis/chronic fatigue syndrome, and pulmonary fibrosis also hold potential. In sum, this review hopes to provide the current understanding of what is known about long-haul COVID-19.

Keywords: COVID-19, SARS-CoV-2, long-haul, inflammation, tissue damage, drug repurposing

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1. 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 (B. Hu et al. 2020a). However, months later, 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, in a phenomenon called "medical gaslighting" (Rubin 2020).

However, that soon changed. The term long-haul COVID-19 (or post-acute COVID-19, chronic COVID syndrome, or long-COVID) started gaining recognition in the scientific and medical communities (Baig 2020; Callard and Perego 2020; Nath 2020). While the actual definition may be lacking, the defining symptoms of long-haul COVID-19 are fatigue, dyspnea (i.e. shortness of breath), and headache that persist for at least two to three months after hospital discharge (Table 1). It may also come with other less typical symptoms, such as cognitive impairments, myalgia, chest and joint pains, smell and taste dysfunctions, mood changes, cough, and cardiac and gastrointestinal issues. Notably, a positive SARS-CoV-2 is not a prerequisite to long-haul COVID-19 (Greenhalgh et al. 2020).

One puzzling feature of long-haul COVID-19 is that it is not predicted by initial disease severity. Long-haul COVID-19 affects even mild-to-moderate cases and younger adults that do not require respiratory support or intensive care (Lu et al. 2020; Miyazato et al. 2020; Townsend et al. 2020; van den Borst et al. 2020; Y. M. Zhao et al. 2020). It also happens to recovered patients that were no longer positive for SARS-CoV-2 and discharged from the hospital (Nath 2020; Rubin 2020). More concerningly, long-haul COVID-19 also targets children in a similar manner as adults, showing symptoms such as dyspnea, fatigue, myalgia, cognitive impairments, headache, heart palpitations, and chest pain for 6-8 months since COVID-19 clinical diagnosis (Ludvigsson 2020).

However, one known aspect of long-haul COVID-19 is that similar post-viral syndrome happened with prior human coronavirus diseases. For example, symptoms of fatigue, myalgia, and psychiatric impairments have inflicted survivors of Middle East respiratory syndrome (MERS)

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and severe acute respiratory syndrome (SARS) for up to four years (Das et al. 2017; Lam et al. 2009; Ngai et al. 2010; Rogers et al. 2020). 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 (P. Zhang et al. 2020b; F.-C. Zhao et al. 2012). This is rather unsettling as it implies that long-haul COVID-19 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-haul COVID-19. The current review, hence, seeks to fulfill these gaps.

Table 1. Demographics, clinical outcome, symptoms, prevalence, and blood profile of long-haul COVID-19 survivors.

Study	Participant and clinical characteristics	Follow-up duration	Symptom (% prevalence)	Associated biomarkers (levels)
Arnold et al. (2020)	N = 110; median age = 60; 44% females; 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%) • Dyspnea (39%) • Fatigue (39%) • Insomnia (24%) • Myalgia (22%) • Cough (11%) • Anosmia (11%) • Arthralgia, headache, abdominal pain, diarrhea (<5%).	• Not tested.
Carfi et al. (2020).	N = 143; 56.5 ± 14.6 years; 37.1% females; 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%) • Dyspnea (43.4%) • Worsened quality of life (44.1%) • Joint pain (27.3%) • Chest pain (21.7%)	• Not tested.

Cirulli et al. (2020).	N = 21,359 (only 233 were COVID-19 survivors); 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, dyspnea, headache, heart palpitations, chest pain, tachycardia, and cough.	• Not tested.
Lu et al. (2020).	N = 60; 45.88 ± 13.90 years; 43.3% females; 78.3% had mild disease; 20% had severe disease; 1.7% had critical disease; Anhui Province, China.	3 months after hospital discharge.	• ≥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%)	• Not tested.
Mandal et al. (2020).	N = 384; 59.9 ± 16.1 years; 38% females; 59.8% needed supplemental O_2; 14.5% admitted to ICU; 7.1% needed intubation; London, U.K.	Median of 54 days after hospital discharge.	• Fatigue (69%) • Dyspnea (53%) • Cough (34%) • Depression (15%)	• ↓ lymphocytes • ↑ D-dimer • ↑ CRP • No changes in WCC, platelets, ferritin, creatine, ALT, AST, or glucose.
Miyazato et al. (2020)	N = 63; 48.1 ± 18.5 years; 33.3% females; 27% needed supplemental O_2; 7.9% needed MV; Tokyo, Japan.	60 days after symptom onset.	• Dyspnea (17.5%) • Dysosmia (16.1%) • Fatigue (15.9%) • Cough (7.9%) • Dysgeusia (4.8%)	• Not tested
		120 days after symptom onset.	• Fatigue (9.5%) • Cough (6.3%) • Dysosmia (9.7%) • Dysgeusia (1.6%)	

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Petersen et al. (2020)	N = 180; 39.9 ± 19.4 years; 54% females; 4.4% were hospitalized; Faroe Islands, Denmark.	125 days after symptom onset.	• ≥1 symptom (55%) • Fatigue (28.9%) • Anosmia (27.2%) • Ageusia (15.6%) • Joint pain (11.1%) • Rhinorrhea (8.9%) • Dyspnea (8.3%) • Headache (7.2%) • Myalgia (7.2%) • Nausea (6.1%) • Chest tightness (6.1%) • Chills (4.4%) • Cough (4.4%) • Diarrhea (4.4%)	• Not tested
Shah et al. (2020)	N = 60; median age = 67; 32% females; 46% needed supplemental O_2; 20% needed mechanical ventilation; Vancouver, Canada.	12 weeks after symptom onset.	• Dyspnea (20%) • Cough (20%) • Other symptoms were not tested.	• Not tested.
Sollini et al. (2020).	*N = 10; 58 ± 13 years; 70% females; 20% admitted to ICU; Milan, Italy.	>30 days after hospital discharge.	• Dyspnea (70%) • Fatigue (70%) • Ageusia (20%) • Joint pain (20%) • Chest pain (10%) • Headache (10%) • Trembling hands (10%)	• Not tested.
Stavem et al. (2020)	N = 434; 49.8 ± 15.2 years; 56% females; 22.8% had mild disease; 38.5% had moderate disease; 38.7% had severe disease; Lørenskog, Norway.	1.5-6 months after symptom onset.	• ≥1 symptom (38.7%) • Dyspnea (15%) • Smell dysfunction (12%) • Taste dysfunction (10%) • Arthralgia (9%) • Myalgia (8.5%) • Headache (6%) • Dry cough (6%) • Sore throat, chills, runny nose, vision disturbance, skin	• Not tested.

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			rash, conjunctivitis, ear pain, cramps, wheeze, confusion, gastrointestinal symptoms (<5%)	
Sudre et al. (2020)	N = 4182; 42.8 ± 13.4 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	• Not tested.
Townsend et al. (2020)	N = 128; 49.5 ± 15 years; 54% females; 36.7% needed supplemental O_2; 14.1% admitted to ICU; Dublin, Ireland.	Median of 10 weeks after symptom onset.	• Fatigue (52.3%) • Other symptoms not tested.	• No changes in leukocytes, neutrophils, lymphocytes, LDH, CRP, IL-6, or CD25.
van den Borst et al. (2020)	N = 124; 59 ± 14 years; 40% females; 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%)	• Not tested.
Wong et al. (2020)	N = 78; 62 ± 16 years 36% females; Vancouver, Canada.	3 months after symptom onset.	• ≥1 symptom (76%) • Worsened quality of life (51%) • Dyspnea (50%) • Cough (23%)	• Not tested.
Y. M. Zhao et al. (2020)	N = 55; 47.5 ± 15.5 years; 41.8% females; 7.3% had mild disease, 85.5% had pneumonia without needing O_2 supplementation; 7.3% had severe pneumonia; 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%)	• ↑ BUN • ↑ D-dimer • No changes in CRP, albumin, or glucose.

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Note: Years refer to age presented as mean ± standard deviation, unless otherwise stated as median. * refers to sample size that specifically recruited long-haul COVID-19 participants. Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CRP, C-reactive protein; ICU, intensive care unit; IL-6; interleukin-6; LDH, lactate dehydrogenase; MV, mechanical ventilation; O_2, oxygen; WCC, white cell count.

2. Putative Pathophysiology

2.1. Long-term tissue damage

In a three-month follow-up study of 55 survivors, of which over 90% needed no oxygen support, pulmonary radiological abnormalities and functional impairments were still detected in 71% and 25% of participants, respectively (Y. M. Zhao et al. 2020). Another study has also observed reduced lung diffusion capacity that correlated with radiological abnormalities in 42% (i.e. 52 out of 124) of COVID-19 survivors at three-month post-hospital discharge, regardless of initial disease severity (van den Borst et al. 2020). Moreover, other reports have found radiological evidence of lung fibrosis among COVID-19 survivors after hospital discharge (D. Liu et al. 2020b; Wei et al. 2020). These studies collectively indicate that pulmonary scarring or fibrosis may be a common sequela of patients with COVID-19. As pulmonary scarring impairs the lung's gas exchange capacity indefinitely, it may be responsible for persistent dyspnea in long-haul COVID-19 (Krishna et al. 2020; Swigris et al. 2014).

However, a separate study has also found that symptoms of long-haul COVID-19 persist even in those with improvements in pulmonary radiological and functional examinations (Arnold et al. 2020). Thus, other or additional pathophysiology may be involved in long-haul COVID-19 besides pulmonary lesions. Indeed, the brain may be affected by long-haul COVID-19. At three-month post-discharge, brain structural and metabolic abnormalities were reported in a group of 60 COVID-19 survivors, which correlated with persistent neurological symptoms such as memory loss, anosmia, and fatigue (Lu et al. 2020). 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, hemorrhage, and stroke) has also found that initial COVID-19 severity plays little role in predicting these brain diseases (Paterson et al. 2020).

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In more severe cases of COVID-19 that lead to delirium in about 20-30% of hospitalized patients, long-term neurological symptoms are more plausible (L. Mao et al. 2020a; O'Hanlon and Inouye 2020). This is because delirium is a strong predictor of long-term cognitive impairments, especially among older adults (Girard et al. 2010; Gross et al. 2012). Delirium is defined as impaired attention, awareness, and cognition, leading to confusion and psychotic symptoms (European Delirium Association and American Delirium Society 2014). A meta-analysis examining neuropsychiatric outcomes of SARS, MERS, and COVID-19 survivors has found that delirium is a common complication in the acute phase of disease, leading to neuropsychiatric sequelae, such as depression, anxiety, post-traumatic stress disorder, memory loss, and fatigue (Rogers et al. 2020). Indeed, COVID-19-related fatigue has been suggested to result from autonomic nervous system dysfunction (Rubin 2020).

Given that SARS-CoV-2 is a respiratory virus, its propensity to injure the lungs is not surprising. In contrast, it was only months into the pandemic that evidence started confirming the neurological tropism and replication of SARS-CoV-2 in neuronal cultures, brain organoids, mice, and human brain autopsies (Ackermann et al. 2020; Chu et al. 2020; Sun et al. 2020; von Weyhern et al. 2020; B. Z. Zhang et al. 2020a). Furthermore, damage of the brainstem's respiratory center, which expresses high levels of angiotensin-converting enzyme 2 (ACE2; receptor of SARS-CoV-2), has been proposed to worsen respiratory symptoms of COVID-19 (Bulfamante et al. 2020; Gandhi et al. 2020; Y. C. Li et al. 2020b). Likewise, respiratory complications such as dyspnea may limit oxygen availability to the brain, which may lead to sub-par neurological functions (Fiani et al. 2020; Greenhalgh et al. 2020). Thus, COVID-19 may perpetuate a vicious cycle of long-term pulmonary and neurological injuries, resulting in long-haul COVID-19 (Figure 1).

There is inconclusive evidence that persistent cardiac injury may also be a part of long-haul COVID-19 pathophysiology (Del Rio et al. 2020). A radiological study of 100 recovered patients from COVID-19 has found evidence of cardiac abnormalities and myocardial inflammation in 78% and 60% of participants, respectively (Puntmann et al. 2020). In this study, initial COVID-19 severity was not associated with the cardiac imaging results, and symptomatic assessments were not performed. In another study of 26 college athletes with asymptomatic SARS-CoV-2 infection, 46% of them also presented with myocardial inflammation (Rajpal et al. 2020).

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However, the long-term clinical significance of these radiological findings remains unknown (Del Rio et al. 2020). Assuming long-haul COVID-19 involves cardiac injury, it may explain some of its rarer symptoms, such as chest pain, heart palpitations, and tachycardia (Carfi et al. 2020; Cirulli et al. 2020; Sollini et al. 2020).

2.2. Unresolved inflammation

There have been instances of patients with COVID-19 who remained positive for SARS-CoV-2 by reverse transcription real-time polymerase chain reaction (RT-PCR) test for up to three months (Carmo et al. 2020; Kandetu et al. 2020; X. Wang et al. 2020b). Other studies have documented cases of prolonged SARS-CoV-2 shedding in the respiratory tract via quantitative RT-PCR for up to four months (Hirotsu et al. 2020; Q. Li et al. 2020a). Interestingly, extended SARS-CoV-2 shedding has also been detected in the feces, regardless of gastrointestinal symptom manifestation, for up to two months (Park et al. 2020; Wu et al. 2020). These studies showed that, in certain cases, people could carry and shed SARS-CoV-2 for several months, indicative of viral persistence that may lead to some level of immune activation.

As long-haul COVID-19 and autoimmune diseases affect females disproportionately (also see section 3.2), it has been suggested that T-cells dysfunction may promote long-haul COVID-19 pathophysiology in a similar manner in autoimmune diseases (Karlsson et al. 2020). It has been proposed that SARS-CoV-2 may make antigen-presenting cells present antigens to auto-reactive T-cells in a process called bystander activation. This is consistent with autopsy examinations of deceased patients with COVID-19 showing that infiltrates in the lungs and other organs were enriched with CD8+ T cells, one of the most crucial mediators of autoimmune reactions (Ehrenfeld et al. 2020). Surprisingly, thyroid dysfunction has been detected in 15-20% of patients with COVID-19 (Lui et al. 2020; Muller et al. 2020). As the thyroid is closely linked to T-cell-mediated autoimmunity, thyroid dysfunction may play a role in the autoimmunity pathophysiology of long-haul COVID-19 (Q. Li et al. 2019; Lui et al. 2020).

B-cells may also be involved in long-haul COVID-19 autoimmunity, as evidenced by the presence of self-reactive autoantibodies in patients with COVID-19. In a study analyzing serum samples from 172 hospitalized patients with COVID-19, antiphospholipid autoantibodies were detected in 52% of samples, which further associated with pro-inflammatory neutrophil

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hyperactivity and more severe clinical outcomes (Y. Zuo et al. 2020c). 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 (Bastard et al. 2020; Vlachoyiannopoulos et al. 2020; Y. Zhou et al. 2020a). While it is unconfirmed if such autoantibodies are long-lasting in COVID-19, these autoantibodies have been strongly linked to chronic autoimmune diseases, such as antiphospholipid and Sjogren syndromes, lupus erythematosus, and rheumatoid arthritis (Elkon and Casali 2008). Notably, lupus and rheumatoid arthritis also bear symptomatic resemblances to long-haul COVID-19: fatigue, joint pain, concentration difficulties, and headache (Cojocaru et al. 2011; Guo et al. 2018).

Besides, evidence exists that severe COVID-19 causes lymphopenia (i.e. B-cell and T-cell lymphocytes deficiency) that causes hyperinflammation (Fathi and Rezaei 2020; Tavakolpour et al. 2020). This is because lymphocytes, particularly T-cells, participate in inflammation resolution following infection (Y. Cheng et al. 2019; Kong et al. 2020). Following this, meta-analyses have determined lymphopenia and high pro-inflammatory neutrophil count as independent risk factors of COVID-19 severity and mortality (Danwang et al. 2020; Malik et al. 2020; Ou et al. 2020). Therefore, as B-cell and T-cell lymphocytes are renewed, elevated inflammation from unresolved hyperinflammation may ensue and contribute to long-haul COVID-19 (Kong et al. 2020; Tavakolpour et al. 2020). 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-haul COVID-19 (F. Hu et al. 2020b; B. Liu et al. 2020a) (Figure 1).

Indeed, lymphopenia and increased levels of pro-inflammatory C-reactive protein (CRP) have been detected in about 7.3% and 9.5% of COVID-19 survivors, respectively, at a median of 54 days after hospital discharge. Over half of these survivors also suffer symptoms of long-haul COVID-19 (Mandal et al. 2020). However, other studies of COVID-19 long-haulers did not find any differences in lymphocytes, neutrophils, or CRP levels (Townsend et al. 2020; Y. M. Zhao et al. 2020). Yet, a radiological study of COVID-19 long-haulers has revealed an increase in [18^{F}]FDG uptake, which signifies persistent inflammation, in the bone marrow and blood vessels in 80% and 60% of participants, respectively (Sollini et al. 2020). These reports imply that unresolved inflammation may partly account for long-haul COVID-19 pathophysiology,

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particularly the inflammation-related symptoms such as myalgia, joint pain, and fatigue (Kucuk et al. 2020) (Figure 1).

Another possible source of unresolved inflammation in long-haul COVID-19 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, leading to increased fecal shedding of SARS-CoV-2 in patients (Lamers et al. 2020; Xiao et al. 2020; Zang et al. 2020). As follows, meta-analyses have estimated that gastrointestinal manifestations (e.g. appetite loss, nausea, vomiting, diarrhea, and abdominal discomfort) affect 10-20% of patients with COVID-19 (Cheung et al. 2020; R. Mao et al. 2020b). Importantly, gastrointestinal symptoms have also been reported in a third of COVID-19 survivors at three-month post-discharge (Y. M. Zhao et al. 2020). Thus, SARS-CoV-2 persistence in the gastrointestinal tract may underlie the gastrointestinal manifestations of long-haul COVID-19.

Furthermore, gut microbiome disruption (i.e. gut dysbiosis) has been observed among patients with COVID-19, which persisted for at least ten days after hospital discharge (T. Zuo et al. 2020a; T. Zuo et al. 2020b). In these studies, gut dysbiosis also correlated with increased COVID-19 severity and prolonged SARS-CoV-2 fecal shedding. However, it is unclear if such gut dysbiosis extends beyond 10 days. Notwithstanding this uncertainty, since the gut is closely intertwined with the immune system, the accompanying gut microbiome has been implicated in numerous diseases related to chronic inflammation (Belkaid and Hand 2014). The gut microbiome also modulates the gut's and brain's neurotransmitter circuitries via the microbiota-gut-brain axis (Yong et al. 2019). Hence, persistent gut dysbiosis may contribute to the gastrointestinal and neurological symptoms of long-haul COVID-19.

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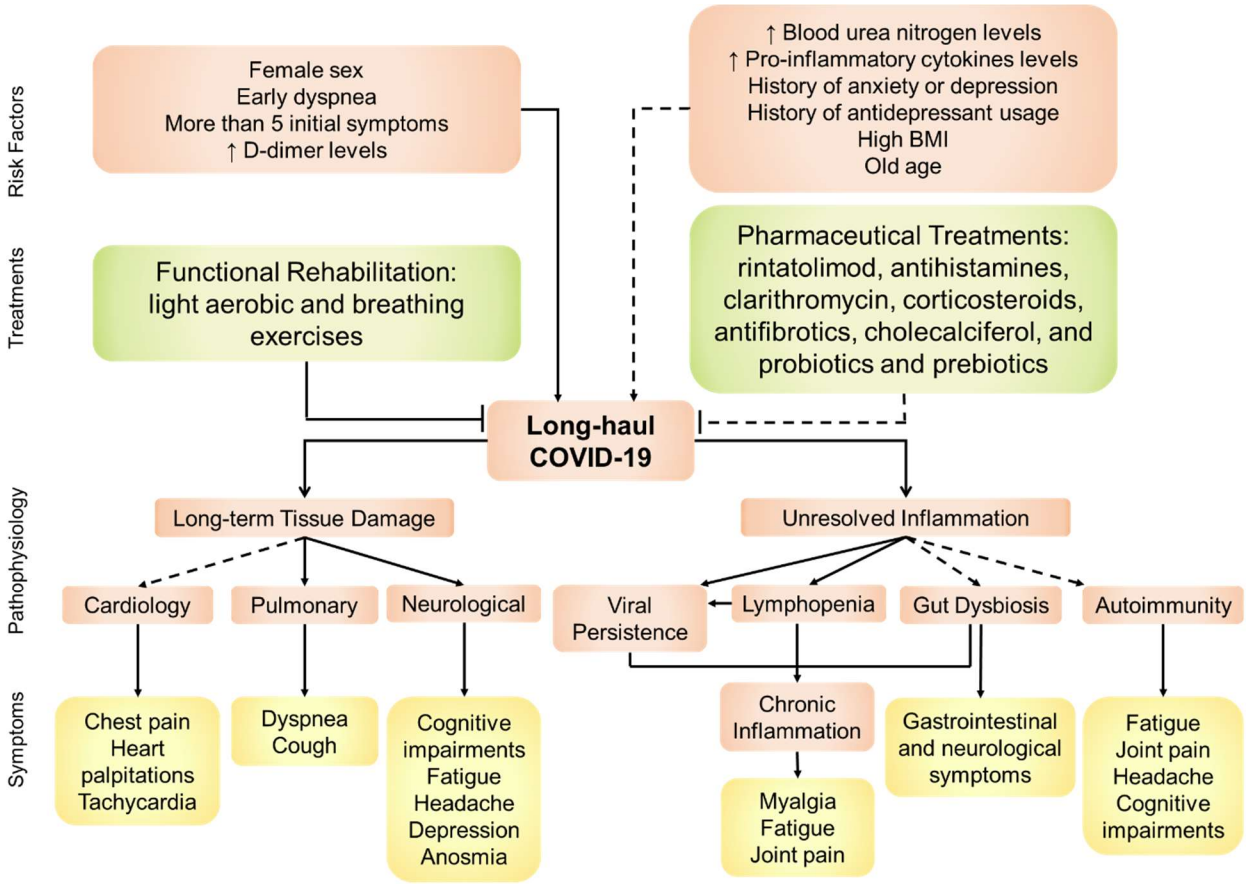

Fig. 1. An overview of the pathophysiology, symptoms, and potential treatments involved in long-haul COVID-19. Note: Dashed lines represent areas where evidence is relatively lacking compared to non-dashed lines. (Color online only)

3. Possible Risk Factors

3.1. Biomarkers

Elevated blood urea nitrogen (BUN) and D-dimer levels were found to be independent risk factors for pulmonary dysfunction among survivors of COVID-19 at three-month post-hospital discharge (Y. M. Zhao et al. 2020). In another study, increased levels of D-dimer and CRP and decreased lymphocytes were more common in long-haul COVID-19 survivors than their fully recovered counterparts (Mandal et al. 2020). However, other studies have not found any differences in pro-inflammatory biomarkers (e.g. CRP, interleukin-6, CD25, and neutrophil and lymphocyte counts) between long-haul and typical COVID-19 cases (Townsend et al. 2020; Y. M. Zhao et al. 2020).

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The reason why D-dimer (two studies) and, to a lesser extent, BUN (one study) associate with long-haul COVID-19 more consistently than other biomarkers remains unclear. A possible explanation may be that BUN and D-dimer signify not only inflammatory disorder but also kidney injury and blood clotting disorder, respectively, which may play important roles in long-haul COVID-19 (Halaby et al. 2015; Seki et al. 2019). Notably, BUN and D-dimer are also independent predictors of COVID-19 mortality and greater severity (A. Cheng et al. 2020; Ghahramani et al. 2020). Another reason may be the heterogeneous nature of long-haul COVID-19, as evident by its multifaceted symptomatic presentations (Table 1). This hints at the possible involvement of multiple pathophysiology, with each type possessing a unique set of biomarkers.

3.2. Patient and Clinical Characteristics

One study has found that over half of discharged patients reported persistent fatigue for about ten weeks post-COVID-19 (Townsend et al. 2020). The fatigue was severe enough to hinder 31% of them from returning to work. This study further revealed that survivors who developed long-haul COVID-19 were more likely females and persons with a history of anxiety or depression diagnosis or antidepressant usage (Townsend et al. 2020). Interestingly, in the first published case series of five children with long-haul COVID-19, four were females (Ludvigsson 2020).

A more extensive study tracked over 4000 COVID-19 survivors and found that 13% of them developed long-haul COVID-19 for at least 28 days. Further statistical analyses identified several factors that predicted long-haul COVID-19, which include old age of over 70 years, more than five symptoms during the first week of illness, BMI of over 27.5, presence of hoarse voice and dyspnea, and female sex (Sudre et al. 2020). In another study examining 233 survivors, 42% had long-haul COVID-19 for at least 30 days and 24% after 90 days from clinical diagnosis. This study also found that more than five initial presenting symptoms and dyspnea were risk factors for long-haul COVID-19, as well as blood type A+ and chest pain, but not BMI, sex, or comorbidities (Cirulli et al. 2020). Similarly, a study of 180 survivors found that 53.1% developed symptoms of long-haul COVID-19 for at least 125 days since symptom onset, which was not associated with sex, comorbidities, or medication use (Petersen et al. 2020).

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Therefore, some of the more prominent risk factors of long-haul COVID-19, supported by at least two studies, are female sex, more than five early symptoms, and early dyspnea. Reasons for the ambiguity in long-haul COVID-19 risk factors may be due to 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. As mentioned, an alternate possibility could also be the multifaceted pathophysiology of long-haul COVID-19 that may target populations with particular phenotypes.

4. Potential Treatments

4.1. Rehabilitation

Functional rehabilitation is the only current recommendation that has worked for treating long-haul COVID-19 (Greenhalgh et al. 2020). 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 dyspnea are seen, which is 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 minutes sessions throughout the day (Greenhalgh et al. 2020; T. J. Wang et al. 2020a).

Indeed, such rehabilitation training has been used to relieve dyspnea and improve lung function and exercise capacity in patients with chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), and acute COVID-19 (Gloeckl et al. 2018; Hsieh et al. 2018; T. J. Wang et al. 2020a). Complementary behavioral modification and psychological support may also help improve survivors' well-being and mental health (Greenhalgh et al. 2020).

4.2. Pharmaceutical treatments

The mechanisms of these mentioned potential pharmaceutical treatments, in relation to long-haul COVID-19 pathophysiology, are detailed in Table 2.

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Recently, rintatolimod is the first immunomodulatory drug to successfully pass phase II/III clinical trial to treat myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Specifically, rintatolimod improved the quality of life and exercise duration by 25% in the majority (i.e. 51%) of patients with ME/CFS for two to eight years (Strayer et al. 2020). ME/CFS is defined as disabling fatigue that lasts for at least six months with other symptoms, such as myalgia, sleep and cognitive impairments, and malaise. While ME/CFS often develops following infections, its pathophysiology still remains unclear; plus, there are no approved drugs for ME/CFS (Castro-Marrero et al. 2017). Evidently, symptoms of ME/CFS overlap with that of long-haul COVID-19, and the two conditions have been closely associated (Callard and Perego 2020; Perrin et al. 2020). Therefore, rintatolimod that improved symptoms of ME/CFS patients has potential for treating long-haul COVID-19 as well (Strayer et al. 2020).

Others have also suggested that long-haul COVID-19 bears striking similarities to mast cell activation syndrome (MCAS). MCAS is a multisystem inflammatory and allergic disorder represented by fatigue, headache, chest pain, dyspnea, cough, myalgia, cognitive impairments, gastrointestinal symptoms, and rashes (Afrin et al. 2020; Kazama 2020). Mast cells serve as a fibroblast-activating factor that could lead to pulmonary fibrosis seen in survivors of COVID-19 (D. Liu et al. 2020b; Wei et al. 2020). Notably, SARS-CoV-2 has been reported to trigger mast cell responses alongside other immune cells (Z. Zhou et al. 2020b). While whether long-haul COVID-19 and MCAS share similar underlying disease mechanisms remain unconfirmed, existing treatments for MCAS may hold potential as repurposed drugs for long-haul COVID-19. Such drugs include anti-allergic antihistamines (e.g. olopatadine and ketotifen), anti-inflammatory antibiotics (e.g. clarithromycin), and corticosteroids (e.g. hydrocortisone and dexamethasone) (Afrin et al. 2020; Kazama 2020).

As discussed above, SARS-CoV-2 persistence may be one contributing factor to long-haul COVID-19. Interestingly, a pilot clinical trial has shown that vitamin D3 treatment in the form of oral cholecalciferol promoted viral clearance, where it shortened the duration of SARS-CoV-2 positivity (Rastogi et al. 2020). In this study, oral cholecalciferol also decreased fibrinogen levels among persons infected with SARS-CoV-2, which may improve pulmonary fibrosis (Ma and Peng 2019; Rastogi et al. 2020). Following this, antifibrotic drugs (e.g. nintedanib and pirfenidone) have

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been proposed as potential therapeutics for long-term pulmonary fibrosis that may result from COVID-19 (Chaudhary et al. 2020; George et al. 2020). Lastly, while not classified as pharmaceutical drugs, probiotics and prebiotics have been proposed as supplements for COVID-19, owing to its favorable safety profile with benefits of systemic immunomodulation and gut-lung axis regulation (Olaimat et al. 2020).

Table 2. The potential drugs that may be repurposed for long-haul COVID-19.

Drug	Mechanisms of action	Possible mechanistic intervention in long-haul COVID-19
Rintatolimod	Double-stranded RNA molecule acting as TLR3 agonist to suppress the production of pro-inflammatory cytokines via the MyD88-independent cytosolic TRIF pathway (Mitchell 2016).	Improved symptoms of ME/CFS, a condition similar to long-haul COVID-19, in terms of disabling fatigue, myalgia, and cognitive impairments (Strayer et al. 2020). It may help alleviate unresolved inflammation.
Olopatadine	Mast cell stabilizer and histamine H1 receptor antagonist to inhibit histamine release (Kaliner et al. 2010).	Improved symptoms of MCAS, a condition similar to long-haul COVID-19, in terms of fatigue, dyspnea, headache, myalgia, and cognitive impairments (Afrin et al. 2020; Kazama 2020). It may help alleviate unresolved inflammation.
Ketotifen	Mast cell stabilizer, eosinophil inhibitor, and histamine H1 antagonist (Grant et al. 1990).	
Clarithromycin	Antibiotic, mast cell stabilizer, and inhibitor of neutrophil and eosinophil respiratory burst (Borszcz et al. 2005; Kazama et al. 2016).	
Hydrocortisone	Cortisol that inhibits GR-dependent pro-inflammatory pathways (Olnes et al. 2016).	
Dexamethasone	Long-lasting glucocorticoid that inhibits GR-dependent pro-inflammatory pathways (Czock et al. 2005).	
Nintedanib	Small molecule antagonist of FGFR, PDGFR, and VEGFR to inhibit the proliferation of fibroblasts (Wollin et al. 2015).	It may help alleviate pulmonary fibrosis (George et al. 2020).
Pirfenidone	Small molecule inhibitor of TGF-β1-dependent stimulation of pro-inflammatory cytokines and fibroblast proliferation (Ruwanpura et al. 2020).	It may help alleviate unresolved inflammation.

Cholecalciferol	Vitamin D3 that regulates the immune system and RAS to prevent excessive inflammation and bradykinin accumulation, respectively (Aranow 2011; Garvin et al. 2020).	It may help restore SARS-CoV-2-induced dysfunction of the immune system and RAS. It may help promote viral clearance and resolve viral persistence (Rastogi et al. 2020). It may help alleviate pulmonary fibrosis (Ma and Peng 2019; Rastogi et al. 2020).
Probiotics and prebiotics	Probiotics are live microorganisms that provide health benefits when consumed at adequate amounts, owing to their modulatory effects on the gut microbiome. Prebiotics refer to substrates that support the growth of commensal gut bacteria (Olaimat et al. 2020).	It may help alleviate persistent gut dysbiosis (T. Zuo et al. 2020a; T. Zuo et al. 2020b). It may help improve functions of the immune and pulmonary systems via the gut-lung axis (Olaimat et al. 2020).

Abbreviations: FGFR; fibroblast growth factor receptor; GR, glucocorticoid receptor; MCAS, mast cell activation syndrome; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; MyD88, mouse myeloid differentiation primary response 88; PDGFR; platelet-derived growth factor receptor; RAS, renin-angiotensin system; TLR3, toll-like receptor 3; TRIF, TIR-domain-containing adapter-inducing interferon-β; TGF-β1; transforming growth factor-beta 1; VEGFR, vascular endothelial growth factor receptors.

5. Concluding remarks

This review presents the current understanding of long-haul COVID-19, a relatively new and puzzling condition that may affect 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-haul COVID-19, particularly its risk factors with inconsistent data thus far. This may be due to its multiple symptomatic presentations and pathophysiology, ranging from long-term damage of the pulmonary, nervous, and possibly cardiac systems to unresolved inflammation from viral persistence, hyperinflammation, autoimmunity, or gut dysbiosis. Hence, future research might be interested in phenotyping subtypes of long-haul COVID-19 according to their respective pathophysiology of symptomatic manifestations. Presently, only functional rehabilitation has been useful for improving symptoms

of long-haul COVID-19, whereas the potential pharmaceutical drugs repurposed from ME/CFS, MCAS, and pulmonary fibrosis still require future clinical trials to validate.

Evidently, it is apparent that the pandemic has brought us a wave of a new chronic, disabling condition called long-haul COVID-19 that deserves serious attention among the scientific and medical communities to resolve. 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-haul COVID-19.

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