Sri Lankan Journal of Health Sciences

Narrative Review

Post-acute COVID-19 Syndrome and Predicting Factors: A Narrative Review

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Abstract: Accumulating evidence indicates a high prevalence rate of persistent symptoms leading to post-acute COVID-19 syndrome. It has been identified as a multi-organ disease with a wide range of prolonged symptoms that may be reflective of underlying respiratory, cardiovascular, neuropsychiatric, gastrointestinal, dermatological, renal, and endocrine disorders. The most frequent symptoms of post-acute COVID-19 include fatigue, dyspnea, anosmia, ageusia, and cough. Additionally, female gender, older age, pre-existing comorbidities, and initial COVID-19 severity, especially those requiring intensive care unit treatments and mechanical ventilation seem to relate to developing persistent symptoms. Studies also suggest that biological factors such as higher viral load, reactivation of the Epstein-Barr Virus, presence of certain autoantibodies, alterations in the gut microbiome, and other factors such as ambient air pollution, not being vaccinated, and reinfection with COVID-19 increase one's susceptibility to developing lasting symptoms. This narrative review presents an overview of the current understanding of the post-acute symptoms and sequelae, and their potential predicting factors. In addition, this highlights the need for further research to be conducted to improve understanding of the pathophysiological aspects of the post-acute COVID-19 syndrome and develop effective therapies.

Keywords: Post-acute COVID-19 syndrome; Long COVID; Predicting factors; Post-acute sequelae; SARS-CoV-2

Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread across the world. Since its initial appearance in Wuhan, China, it has infected more than 620 billion people globally (1), with fluctuations in cases due to the emergence of novel variants. For most COVID-19 infections, approximately 80-85% are mild or asymptomatic and recover completely and 10-15% of infected individuals may require hospitalization and supplemental oxygen, and around 5% may require intensive care unit (ICU) admission and mechanical ventilation. The average recovery time following an initial COVID-19 infection is 2-6 weeks (2).

With the rising number of survivors, long-term complications following infection with SARS-CoV-2 have drawn increased attention which is referred to as "Post-acute COVID-19 syndrome" or "Long

Citation: Kaushalya L, Bowatte G, Welikannage K, Yasaratne D. Post-acute COVID-19 Syndrome and Predicting Factors: A Narrative Review. Sri Lankan J. Health. Sci. 2022, 1(2): 36-47. https://doi.org/10.4038/sljhs.v1i2.44
Received: 09.12.2022; Accepted: 24.12.2022; Published: 31.12.2022

COVID". The term "Long COVID" was first created by patients in the early months of the pandemic who observed a more complex disease course than was initially described in reports from Wuhan and spread it through social media (3). Thereafter, related terms were adopted to describe the presence of persistent symptoms i.e., long COVID, post-COVID, post-acute sequelae of SARS-CoV-2 (PASC), and post-COVID syndrome (PCS) (4).

Survivors of prior viral diseases, such as severe acute respiratory syndrome (SARS) in 2003 and the Middle East respiratory syndrome (MERS) outbreak in 2012 have shown a similar cluster of persistent symptoms, raising concerns about clinically relevant COVID-19 residual effects (5,6). The post-acute COVID-19 symptoms and sequelae have been found to vary greatly. Even though the spectrum of these long-term consequences is wide, certain clinical, biological, and environmental factors have been observed to be predictive of which symptoms may develop. Findings further revealed that COVID-19 survivors were less healthy compared to the general population without previous SARS-CoV-2 infection, thus some patients may take longer than one year to recover (7). It has resulted in difficulties in returning to the baseline level of health and has caused increased healthcare utilization (8).

As per the proposed clinical case definition by WHO, post-acute COVID-19 occurs in individuals with a history of probable or confirmed COVID-19 infection, generally three months from the onset of infection with symptoms lasting for at least two months, which cannot be explained by an alternative diagnosis (9). This narrative review aims to offer an overview of the current understanding of the post-acute COVID-19 syndrome along with its related predicting factors.

Methods

A comprehensive literature search was performed in Medline PubMed, and Google Scholar using the following search terms, "post COVID", "long COVID", "SARS-CoV-2", "post-acute COVID syndrome", "PACS", "post COVID syndrome", and "PCS". The reference lists of relevant articles were also manually searched. Studies reporting on the prevalence of post-acute COVID-19 symptoms and sequelae, and associated predictors, and studies published in English, not a review were included, and abstracts were screened. After reading the entire text, the relevant articles were selected. The findings were summarized and discussed.

Results

Associated symptoms and sequelae

Post-acute COVID-19 symptoms are encountered as a group of symptoms and can cause dysfunctional issues in any system in the body. Over 200 distinct symptoms associated with different organ systems which include respiratory, cardiovascular, neuropsychiatric, gastrointestinal, dermatological, renal, and endocrine symptoms and sequelae have been identified. A combination of neurological/cognitive and systemic symptoms is the most persistent (8).

Respiratory symptoms and sequelae

Among COVID-19 survivors, a range of pulmonary complications has been described ranging from persistent respiratory symptoms to pulmonary fibrosis. Dyspnea and cough appeared to be the most common respiratory symptoms beyond the acute COVID-19 phase. Of these, dyspnea was the most frequently experienced symptom following recovery and can last for up to months in 23% to 53% of patients (10–12). According to studies reporting persistent respiratory symptoms 1 to 12 months following COVID-19, the prevalence of dyspnea ranges from 13% to 66% in hospitalized patients, (13,14) and approximately 14% in non-hospitalized patients with non-severe COVID-19 (15). Cough can also persist weeks to months after the initial COVID-19 infection and has been reported in 23% to 25% of patients after 30 days and 4 months of hospital discharge, respectively (13,16).

Lung function abnormalities and structural changes have also been observed up to 6 months in mild to severe COVID-19 survivors. The median 6-minute walking distance (6MWD) was reported to be lower than the normal reference value for comparable healthy individuals in around one-quarter of Chinese patients after 6 months (17). Abnormalities in lung function as measured by pulmonary function testing (PFT) have also been identified. In a study of 55 non-severe COVID-19 patients, PFT evaluation over a three-month follow-up period revealed abnormalities in 25% of patients with a decrease in diffusion capacity for carbon monoxide (DLCO) being the most prevalent (18). More than half of the patients in their recovery phase had impaired diffusion capacity, reduced respiratory muscle strength, and lung imaging abnormalities (19).

Cardiovascular symptoms and sequelae

Palpitation and chest pain persisted in 9% and 5% of patients, respectively when examined at 6 months (17). Two to three months following the onset of COVID-19, abnormalities on cardiac magnetic resonance imaging (CMRI) and evidence of myocardial inflammation have also been reported independently of the disease severity (20). Myocarditis was detected in up to 2.3% of young, healthy athletes with CMRI detecting the majority of cases being subclinical myocarditis (21). Following SARS-CoV-2 infection, an increased incidence of postural tachycardia syndrome (POTS) has also been documented (22,23) (Table 1).

Neuropsychiatric symptoms and sequelae

In relation to post-acute COVID-19 syndrome, a wide range of neurological complications involving both the central and peripheral nervous systems have been described. Preliminary evidence revealed that patients with COVID-19 had an increased risk of developing long-lasting neurological symptoms compared with patients with influenza or other respiratory tract infections (24). A longitudinal analysis, 6 months following hospitalization for acute COVID-19, reported that fatigue or muscle weakness (63%) was the most commonly reported symptom followed by sleep disturbances (26%), anxiety or depression (23%), and myalgia was reported by only 2% of patients (17). Nearly 10% of survivors may still experience taste and smell disorders up to 6 months after other symptoms have subsided (11,16,17,25). Cognitive impairment and memory issues have been noted to be common across all age groups among individuals with mild COVID-19 at 7 months follow-up including brain fog, which may impair thinking and concentration, executive functioning, problem-solving, and decision-making (8).

Anxiety, depression, and sleep difficulties were among the most reported psychological symptoms at 6 months follow-up, with approximately 25% reported having experienced those symptoms (17). After 6 months of COVID-19 infection, 34% of patients reported having an incidence of a psychiatric or neurological diagnosis, and 13% of those received their first such diagnosis (24) (Table 1).

Gastrointestinal and dermatological symptoms and sequelae

Significant gastrointestinal symptoms in COVID-19 survivors have not been reported. However, 32% of patients with mild COVID-19 reported diarrhea 60 days after symptom onset (26). After 6 months following hospital discharge, 8% of individuals experienced a decrease in appetite (17).

Hair loss was the most commonly reported dermatological symptom affecting nearly 20% of patients at 6 months and 110 days (16,17). Only 3% of Chinese patients reported having skin rashes at 6 months follow-up (17) (Table 1).

Renal and endocrine symptoms and sequelae

One-third of hospitalized patients with acute kidney injury (AKI) during the initial stage of COVID-19, have not regained full renal function at follow-up (27). At follow-up, 13% of individuals without AKI and with normal estimated glomerular filtration rate (eGFR) at the acute phase had decreased eGFR following discharge (17), newly diagnosed diabetes mellitus was reported (28) (Table 1).

Table 1. Summary of post-acute COVID-19 symptoms and sequelae by major organ system

Organ system	Summary
Respiratory symptoms and sequelae	● Dyspnea, and cough were commonly observed as persistent symptoms (11,13,15) ● Approximately 14% of non-hospitalized patients with non-severe COVID-19 had persistent dyspnea (18) ● A lower 6-minute walking distance has been reported (14) ● Decreased diffusion capacity for carbon monoxide has been observed (20)
Cardiovascular symptoms and sequelae	● Chest pain and palpitation were the commonest cardiovascular symptoms (14) ● Abnormalities on cardiac MRI and myocardial inflammation have also been reported (22)
Neuropsychiatric symptoms and sequelae	● Long-term symptoms may include fatigue, cognitive impairment, headache, sleep disturbance, dizziness, fever, depression, and anxiety (9,14,23) ● Patients with COVID-19 had an increased risk of developing long-lasting neurological symptoms compared with patients with influenza or other respiratory tract infections (23) ● Nearly 10% of survivors still had taste and smell disorders up to 6 months (13,14,19,24)
Gastrointestinal symptoms and sequelae	● Diarrhea, and reduced appetite ● Diarrhea was reported in 32% of patients with mild COVID-19 60 days after symptom onset (12) ● At 6 months follow-up, 8% of individuals experienced a decrease in appetite (14)
Dermatological symptoms and sequelae	● Skin rash and hair loss were observed ● Hair loss is the predominated dermatological symptom reported (14,19)
Renal symptoms and sequelae	● At follow-up, 13% of individuals without AKI and with normal estimated Glomerular Filtration Rate (eGFR) at the acute phase had decreased eGFR
Endocrine symptoms and sequelae	● New onset diabetes mellitus was identified following discharge (28)

Predictors of post-acute COVID-19

Clinical factors

The presence of more than five symptoms, specifically, fatigue, dyspnea, headache, myalgia, and hoarseness of voice during the initial phase of COVID-19 has been associated with an increased likelihood of developing persistent symptoms (29). Female gender and age under 50 years have also been suggested to be predictive for post-acute COVID-19 syndrome (30). Females were found more likely to develop fatigue and anxiety or depression at 6 months follow-up (17). Approximately, 15% of females were reported to have symptoms that lasted for 28 days or more, compared to 9.5% of males, though this gender difference disappeared in those over the age of 70. The greatest gender disparity was observed among those between the ages of 40 and 50, where females were twice as likely as males to develop persistent symptoms (29).

The persistence of certain symptoms such as dyspnea, fatigue or muscle weakness, post-traumatic stress disorder (PTSD), as well as pulmonary complications (impaired diffusion capacities and radiographic pulmonary abnormalities), and decreased scores in health-related quality of life have all been significantly linked to patients with severe acute COVID-19, particularly, those needing a high-flow nasal cannula, and noninvasive or invasive mechanical ventilation during the hospital stay (14,17,25).

More than one-fifth (22%) of individuals over the age of 70 experienced symptoms lasting four weeks or more, compared to one-tenth of those aged 18 to 49 years. Months after contradicting with COVID-19, 35% of people had not returned to their baseline level of health, and the proportion seemed to differ across age groups, with 26%, and 32% in individuals aged 18-34 years, 35-49, respectively, and 47% among ≥ 50 years (31). The presence of comorbidities, asthma, in particular, in patients of all ages, and elderly people over 70 years with cardiopulmonary diseases were found to have persistent symptoms (29). Patients with type 2 diabetes were more likely to develop fatigue, cough, and other persistent respiratory symptoms (32). Having three or more comorbidities including obesity and psychiatric disorders were associated with a delayed recovery compared to normal health status in COVID-19 survivors (31) (Table 2).

Biological factors

A high level of SARS-CoV-2 RNA in patients' blood early in the COVID-19 infection has also been linked to developing post-acute symptoms. Those with higher viral load were likelier to experience memory-related post-acute COVID-19 symptoms. In this same longitudinal cohort of 209 individuals who had autoantibodies were also identified as more likely to be diagnosed with different persistent symptoms. Persons with ongoing neurological symptoms displayed heightened levels of anti-SARS-CoV-2 nucleocapsid protein lgG3, whereas post-acute COVID-19 related gastrointestinal symptoms were associated with higher levels of multiple autoantibodies (32). Lower levels of immunoglobin (lg) antibodies lgM and lgG3, were also found to be more common in patients who developed persistent symptoms compared to those who recovered. When combined with clinical predictors including patients' age, acute COVID-19 symptoms, and presence of pre-existing asthma, this decreased immunoglobin profile may all heighten a person's risk of getting post-acute COVID-19 symptoms (33).

Via antibody titer assessments, the Epstein-Barr virus (EBV) reactivation has been implied to associate with post-acute COVID-19 (34). Individuals with EBV in their blood upon COVID-19 diagnosis showed a heightened chance of memory impairments later on, as well as persistent symptoms specific to EBV viremia including fatigue, and production of sputum in the lungs (32).

A link between alterations to the gut microbiome and post-acute COVID-19 syndrome has also been suggested. COVID-19 patients with healthy gut bacteria and a microbiome similar to that of a healthy individual appeared less likely to acquire post-acute COVID-19, whereas those who developed lasting symptoms following COVID-19 had a less diverse and abundant microbiome (35). At 6 months, the composition of the gut microbiome in individuals with prevalent respiratory symptoms was found to be positively associated with a variety of opportunistic pathogens (S*treptococcus anginosus, Streptococcus vestibularis, Streptococcus gordonii,* and *Clostridium disporicum*). The presence of nosocomial pathogens related to opportunistic infections (*Clostridium innocuum* and *Actinomyces naeslundii*) was associated with fatigue and neuropsychiatric symptoms (35) (Table 2).

Environmental factors

Environment related factors have an impact on the incidence, severity, and mortality of acute COVID-19 (36,37), though their role in persistent symptoms among convalescent COVID-19 patients has not been extensively studied. To explore environmental factors such as the percentage of green areas, air pollution levels, neighborhood population density, and socioeconomic conditions impact on different post-acute COVID-19 symptoms, Ferreira et.al. conducted a 6 months follow-up study in Brazil. The authors found that ambient levels of $PM_{2.5}$ (particulate matter up to 2.5μm diameter) were significantly

associated with persistent dyspnea, fatigue, and lower functional status at follow-up, while population density and individual exposure to green space had no statistically significant association with any of the outcomes assessed (38) (Table 2).

Table 2. Summary of predicting factors for post-acute COVID-19 symptoms

Predicting factors		Summary
Clinical factors	Gender	● Middle-aged females were found more likely to experience post-acute symptoms (17,29,30)
	Age	● Individuals over the age of 70 had an increased risk of getting persistent symptoms (29,31) ● Delayed recovery to the normal status of health increased with the age (31)
	Initial infection severity	● Presence of more than 5 acute symptoms (Fatigue, dyspnea, headache, myalgia, and hoarseness of voice) associated with the emergence of post-acute COVID-19 symptoms (29) ● Patients needing a high-flow nasal cannula, and noninvasive or invasive mechanical ventilation during the hospital stay were more likely to have dyspnea, fatigue or muscle weakness, and pulmonary complications (14,17,25)
	Co-morbidities	● Having asthma, hypertension, cardiopulmonary complications, type 2 diabetes, obesity, and psychiatric disorders increases the risk of experiencing ongoing symptoms (29,31,32)
Biological factors	Viral load	● Patients with higher viral load were likelier to experience memory-related post-acute COVID-19 symptoms (32)
	Autoantibodies	● Different antibodies seemed linked to certain lasting symptoms (32) ● Low levels of antibodies when combined with clinical risk factors increased the risk of developing post-acute COVID-19 symptoms (33)
	Previous EPV infection	● Reactivation of EBV was significantly associated with the development of memory issues, fatigue, and sputum production (32,34)
	Gut microbiomes	● Patients with alterations in the gut microbiome during acute COVID-19 were at higher risk of experiencing persistent symptoms (35)
Environmental factors	Ambient air pollution	● Exposure to ambient air pollution was associated with persistent dyspnea, fatigue, and lower functional status (38)
Other factors	Vaccination status	● Vaccinated individuals were found to have a reduced risk of having persistent symptoms (39,40)
	Reinfection with COVID-19	● Reinfection showed to increase the sequelae in multiple organ systems (42)

Other factors

Vaccination against COVID-19 has been found to be effective in reducing the risk of developing post-acute symptoms. The odds of getting lasting symptoms over 28 days following vaccination were halved in individuals with two vaccination doses (39). Further, adults who had received two doses of a COVID-19 vaccine at least 14 days earlier contracting the virus were observed to have a 41.1% lower likelihood of reporting prevalent symptoms at least 3 months later in reference to not being vaccinated when infected (40). Between 1-6 months post-infection, individuals with breakthrough infections were to have a decreased risk of death and post-acute COVID-19 symptoms compared to those who were not vaccinated, particularly patients hospitalized with COVID-19 (41) (Table 2).

Reinfection with SARS-CoV-2 has been observed to elevate the risk of death, hospitalization, and symptoms and sequelae in multiple organ systems in the acute and post-acute phase at 6 months including pulmonary, hematological, gastrointestinal, diabetes, kidney, musculoskeletal, mental health, and neurological complications regardless of the vaccination status (42).

Discussion

In this narrative review, an overview of the so far documented post-acute COVID-19 symptoms and sequelae and associated predictive factors are presented. In accordance with the presented literature, a substantial proportion of patients continue to experience persistent symptoms beyond the acute phase of COVID-19 infection. These symptoms may affect any part of the human body systems, with the most frequently persistent symptoms among post-acute COVID-19 patients being; fatigue, dyspnea, smell or taste disorders, anxiety, or depression. No studies, however, have examined the duration of post-acute COVID-19 symptoms.

Large variations in prevalence estimates can be seen. A direct comparison is therefore not possible. Fatigue was the most frequently reported symptom across studies. European studies revealed higher prevalence rates of fatigue (50-70%) or dyspnea (30-40%) (16,29), whereas studies from China reported a lower proportion of fatigue (7-16%) (13,18) The methodological differences could explain these discrepancies. This may also be explained by additional variables such as racial differences or genetic makeup, which may impact the development of persistent symptoms.

These identified persistent signs and symptoms resemble those seen in patients impacted by prior outbreaks of viral disease. The survivors of SARS and MERS also had lingering systemic and neurologic issues, decreased lung function, decreased ability to exercise, and mental health issues such as stress, anxiety, and depression (39,40).

A comprehensive interpretation of these findings is, however, presently not possible due to the high heterogeneity of the available studies and due to significant methodological limitations. These include mixed patient populations, varying follow-up lengths, the range of symptoms investigated across studies, the use of different measurement techniques, and the case definition of symptoms. Therefore, caution is warranted in drawing conclusions and characterizing post-acute symptoms and sequelae.

Several pathophysiological mechanisms of the virus could explain these long-term consequences and sequelae. Direct viral tissue damage is one possible mechanism. The SARS-CoV-2 entry receptor, angiotensin-converting enzyme 2 (ACE2), is found throughout the body, allowing the virus to penetrate target cells by activating its spike protein via transmembrane serine protease 2 (41). Epithelial cells, gastrointestinal epithelial cells, nasal goblet cells, renal podocytes, and pancreatic β cells carry these receptors, implying that the SARS-CoV-2 infection may exhibit primarily through direct tissue injury, which may also be a contributor to its long-term consequences (42–44), Endothelial damage, immune system dysfunction, and hypercoagulability, which frequently result in thrombosis, are among other potential routes causing long-term consequences (45–47). Since the precise mechanisms causing post-

acute COVID-19 syndrome are still poorly understood, further research is required to delineate the pathophysiological mechanisms underlying the long-term impacts of COVID-19 on different organ systems, which may ultimately aid in the identification and rational design of effective therapies. Social isolation, decreased physical activity, and social and economic uncertainty may also contribute to post-acute COVID-19 symptoms including physical and psychological consequences. This is an important confounding factor in the included studies that could not be ruled out.

Concerning potential predicting factors of post-acute COVID-19 syndrome, findings of literature indicate some factors that affect certain groups that are differentially affected. Individuals of all ages may experience prolonged symptoms following the initial COVID-19 infection. Middle-aged females, however, were found more likely to be diagnosed with post-acute symptoms. It is not clear why females had adverse outcomes. This could be to do with the higher survival rates for severe acute COVID-19 in females than men. So could have lasting symptoms as a result. A further possibility is the lower tendency in men to disclose symptoms. There is also concern over an overlap of symptoms of post-acute COVID-19 (fatigue, palpitation, muscle pain, cognitive deficit, and sleep disturbance) with those of perimenopause and menopause indicating that sex hormone variations should be further investigated (48).

However, contradictory findings were also identified in the literature on demographic factors' contribution to developing persistent symptoms. Regarding age as a predictor, for instance, several studies revealed that rising age increases one's susceptibility to long-term complications (29). As per some studies, younger patients appeared to be at higher risk of experiencing post-acute symptoms (26), and the risk is not limited to the elderly (49). Similarly, there have been conflicting results on the possible gender predisposition to post-acute COVID-19, with some studies reporting an association between the female gender and persistent symptoms (50,51), and others indicating no association with gender (26,29).

Moreover, the severity of acute COVID-19, especially among those treated in the ICU or mechanically ventilated, has been associated with persistent symptoms (17). However, it is unclear whether, from a pathophysiological perspective, ICU survivors and patients with non-severe COVID-19 who have prolonged symptoms may possess the same traits of post-acute COVID-19 syndrome. Evidence suggests that the long-term effects of ICU COVID-19 survivors exhibit many parallels to post-intensive care syndrome (PICS) (8,52). More research is needed to uncover possible overlaps that differentiate post-acute COVID-19 symptoms and PICS.

Quantifiable predicting factors for post-acute COVID-19 and their associations are poorly identified. Therefore, the fact that certain biological factors including SARS-CoV-2 RNA and EBV viremia predicting prevalent symptoms can be measured at COVID-19 diagnosis, may be of fundamental importance for understanding and developing prospective treatments for post-acute COVID-19. However, these quantifiable factors and other identified predictors need to be validated in large patient cohorts.

Given the high prevalence rate, the wide range of persistent symptoms reported across studies, and the fact that post-acute COVID-19 syndrome comprises a multiorgan disease, extensive patient evaluation, and a multidisciplinary approach involving specialists from various disciplines are critical for providing effective care and management. Based on the findings that respiratory and neuropsychiatric were the frequently reported persistent symptoms related to post-acute COVID-19, health systems and rehabilitation needs can be tailored to give optimal care to patients affected. The cooperation of geriatric specialists is critical for mitigating the persistent symptom burden, particularly, in the frail older population (53). Though the duration of protection remains to be defined, evidence indicates COVID-19 vaccines confer limited but significant protection against post-acute COVID-19 symptoms. However, the burden of lasting symptoms is likely to remain substantial even in fully vaccinated populations. Given that reinfection contributes to health concerns both in the acute and post-acute phase, and the possibility of continued SARS-CoV-2 mutations leading to the emergence of new variants causing reinfections also raises the importance of preventing infections and reinfections through the implementation of mitigation

strategies. Furthermore, the heterogeneity of post-acute COVID-19 symptoms and the diverse variables that have been suggested to be related to it further necessitate the need to comprehensively identify the pathophysiological mechanisms and the evolution of those associations during the course of infection and recovery from SARS-CoV-2 to develop effective therapeutic strategies.

The proper time frame for post-acute COVID-19 is yet unknown. Ongoing research or expansion of included studies in this narrative review may follow up on the individuals until the persistent symptoms disappear, indicating the timeframe of this novel medical condition. A systematic evaluation of emerging data including data from low and middle-income countries is warranted to improve understanding and to have the most up-to-date knowledge on the post-acute COVID-19 syndrome since the present reviews' nonsystematic nature raises the possibility of selection bias. Most included studies were based on higher-income western countries, had small sample sizes, and lacked control groups limiting the generalizability, evaluation of the racial impact on the development of post-acute symptoms, and COVID-19-specific features. The need for more studies in different regions arises with much larger cohorts with control groups to characterize post-acute COVID-19 symptoms that are universal and regional.

Conclusion

The persistence of various symptoms in individuals who recovered from COVID-19 has been identified, leading to post-acute COVID-19 syndrome. Post-acute COVID-19 is conceptualized as a multi-organ disorder with a wide range of persistent symptoms. Fatigue, dyspnea, anosmia, and ageusia were the most frequent symptoms of the post-acute syndrome. Female gender, older age, pre-existing comorbidities, initial COVID-19 severity, higher viral load, reactivation of the Epstein-Barr Virus, presence of certain autoantibodies, alterations in the gut microbiome, ambient air pollution, being unvaccinated, and reinfection with COVID-19 were identified as the post-acute symptoms anticipating predicting factors. Whilst considering the high prevalence, identified persistent symptoms and sequelae of post-acute COVID-19 syndrome, and vulnerable patient populations, a multidisciplinary approach should be adopted to provide optimal patient care and management of the issue. Improving understanding of the pathophysiological aspects of the post-acute COVID-19 syndrome and developing effective therapies will require further study.

Author Contributions: Conceptualization, G.B.; methodology, L.K.; formal analysis, L.K.; data curation, L.K.; writing—original draft preparation, L.K.; writing—review and editing, G.B., D.Y., L.K., and K.W.; supervision, G.B., D.Y.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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