

Review

Revisiting the COVID-19 Pandemic: An Insight into Long-Term Post-COVID Complications and Repurposing of Drugs

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Abstract: SARS-CoV-2 is a highly contagious and dangerous coronavirus that has been spreading around the world since late December 2019. Severe COVID-19 has been observed to induce severe damage to the alveoli, and the slow loss of lung function led to the deaths of many patients. Scientists from all over the world are now saying that SARS-CoV-2 can spread through the air, which is a very frightening prospect for humans. Many scientists thought that this virus would evolve during the first wave of the pandemic and that the second wave of reinfection with the coronavirus would also be very dangerous. In late 2020 and early 2021, researchers found different genetic versions of the SARS-CoV-2 virus in many places around the world. Patients with different types of viruses had different symptoms. It is now evident from numerous case studies that many COVID-19 patients who are released from nursing homes or hospitals are more prone to developing multi-organ dysfunction than the general population. Understanding the pathophysiology of COVID-19 and its impact on various organ systems is crucial for developing effective treatment strategies and managing long-term health consequences. The case studies highlighted in this review provide valuable insights into the ongoing health concerns of individuals affected by COVID-19.

Keywords: COVID-19; long COVID; drug repurposing; pandemic; lung disease; heart disease



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1. Introduction

It is already known that the positive-strand RNA virus named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which belongs to the same family as SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus), was instrumental to the COVID-19 pandemic [1–3]. SARS-CoV-2 was found to have similar genetic material to SARS-CoV, encoding components such as RNA-dependent RNA polymerase (Nsp12, non-structural protein 12), 3C-like protease (3CLpro), and the papain-like protease (PL pro) [4].

In the Coronaviridae family, there are four different genera (Alpha-CoV, Beta-CoV, Gamma-CoV, and Delta-CoV members) that make up the Orthocoronavirinae subfamily, among which subgroups α and β are mainly accountable for infections in humans. MERS-CoV and SARS-CoV are members of the β subfamily and have been found to be responsible for earlier epidemics; they were found to have ~50% and ~79.5% sequence similarity, respectively, with the SARS-CoV-2 genome [5,6], which indicates the close phylogenetic relationship of SARS-CoV-2 with SARS-CoV. Both are associated with the ACE2 (angiotensin-converting enzyme 2) receptor of humans with their spike protein. Zhou et al., in 2021, reported that temperature largely influences SARS-CoV-2 spike protein binding to the ACE2 receptor, with optimal binding occurring at 37 °C and gradually decreasing

with an increase in temperature over 40 °C because of the enhanced variation in the RBD (receptor-binding domain) [7].

It is now clear that viral load (SARS-CoV-2 exposure) is one of the key factors that significantly influence how quickly a disease develops in a person [8]. Several patients that have recovered from COVID-19 have been reported to acquire long-term health hazards even after a negative RT-PCR result 3-4 weeks after its detection. Patients suffer from joint pain, cough, fatigue and muscular weakness, persistent oxygen need, and other symptoms [9].

The common indicators of the SARS-CoV-2 infection include fever, anosmia, cough, headache, diarrhea, etc. Predominant studies have described its association with lung problems in people from all age groups, especially those who have several comorbidities. Multi-organ failure, interstitial pneumonia, and acute respiratory distress syndrome (ARDS) also contribute to the high death rates due to the effect of SARS-CoV-2 [10]. The outbreak of COVID-19 was proclaimed to be a pandemic by the World Health Organization (WHO) in March 2020 due to the high infectivity along with the mortality rate of the disease. As a consequence, scientists from all over the globe devoted their efforts to developing specific drugs or vaccines for treatment, as no gold-standard drugs were available against this virus during that period. Patients were being treated with known drugs that were not designed to protect against COVID-19 but offered a little ray of hope [11].

It was evident from previous studies that the SARS-CoV-2 virus affects human hosts as well as animals. Cats, ferrets, and dogs are prone to COVID-19 as the ACE2 receptor is present in these organisms [12,13]. In ferrets, it has been reported that a considerable number of ACE2 receptors are present in the tracheobronchial submucosal glands where the spike protein binds [14]. The receptor-binding domain of the spike protein in ferrets is very similar to that in cats, only differing by two amino acid residues [15]. Ferrets and monkeys have a greater chance of infection compared to rabbits, pigs, ducks, and chickens, as indicated by RBD domain analysis. The higher infectivity rate in ferrets and monkeys is due to the enhanced affinity of the spike glycoprotein towards the ACE2 receptor [15,16]. Looking at SARS-CoV's epidemiology, it can be said that animals can be infected by the virus and may transfer it to human hosts.

There have been a few new reports describing COVID-19 patients who had mucormycosis, died in strange ways, and went blind. Most patients had uncontrolled blood sugar levels or were severely diabetic, which made their cases challenging to treat. In the second wave of COVID-19 with SARS-CoV-2 variants, clinical data also show that children under 18 were more likely to have a mild or asymptomatic infection [17–20].

During the second and third surge of COVID-19, the transfer of the virus from asymptomatic carriers to secondary patients was commonly seen in younger age groups (less than 20 years) [21–25]. Patients affected by asymptomatic carriers were more likely to develop severe symptoms if they had a co-morbidity or if they were immune-compromised while some patients even needed hospitalization [22]. Scientists have found that the UK, South African, and Brazilian mutant coronaviruses are more infectious than the first-wave variants. The increased infectiousness of these new variants could lead to a surge in cases and put more strain on healthcare systems, highlighting the urgent need for continued efforts to control the spread of the virus through various measures.

2. Post-COVID Complications

2.1. Short-Term Health Issues

The short-term or immediate health issues include fever (moderate to high), shortness of breath, cough, chestpain, jointpain, nausea, diarrhea, sore throat, fatigue, rashes on the skin, headache, loss of odor or taste, conjunctivitis, and a tendency towards acute respiratory distress syndrome (ARDS) [26]. These are some clinical consequences encountered by the patients once they are infected. If the patient has mild symptoms, no hospitalization is required. Home isolation, proper food, and medication are sufficient for the patient's recovery. When the symptoms are severe, especially when the patient has acute pneumonia,

he or she needs hospitalization. However, post-COVID complications may arise in both of these groups; the ones with mild symptoms and the ones with acute symptoms [27].

According to recent studies, COVID-19 affects women less frequently than it does men [28]. This can be understood in terms of sex hormones, which are very important for controlling how the immune system responds to viruses. The major sex hormones are namely progesterone, oestrogen, and testosterone [29]. Oestrogen is a female sex hormone that stimulates the immune system against viral infection. On the contrary, the testosterone secreted by the men's gonads suppresses the immune system against COVID-19 infection. Female sex hormones may reduce the ACE2 mRNA expression, and thus men are more prone to any viral attack than females, which is predominant in the case of SARS-CoV-2 [30,31].

2.2. Long-Term Health Complications

Table 1 shows the results of different analyses from around the world about the incident and how conditions after COVID-19 still exist. A few other data points are likewise discussed in Sections 2.2.1–2.2.8.

Table 1. Case study findings on the occurrence of post-COVID-19 syndrome (1–6 months of post-COVID follow-up).

Total No. of Participants under Case Studies	Age Group in Years (Mean/Median)	% of the Male Population	% of Patients Admitted to ICU	Patients Had Shortness of Breathing (%)	O ₂ Support Needed (%)	Patients Diagnosed with Chest Pain (%)	Loss of Taste/Smell in Patients (%)	Patients Had Acute Joint Pain (%)	Patients Detected with Cough and Cold (%)	The Study Conducted by (References)
143	Mean (s.d.) = 56.5 (14.6)	62.9	12.6	43.4	53.8	21.7	15	27.3	15	Italy [32]
100	Median (ward/ICU) = 70.5/58.5	54	32	40	78	17.2	NR	NR	NR	UK [33]
150	Mean (s.d.) = 45 (15)	44	NR	30	NR	13.1	22.7	16.3	NR	France [34]
110	Median (IQR) = 60 (44–76)	61.8	16.4	39	75.4	12.7	11.8	4.5	11.8	UK [35]
277	Median (IQR) = 56 (42–67.5)	52.7	8.7	34.4	NR	NR	21.4	19.6	21.3	Spain [36]
355	Mean (s.d) = 39.8 (13.4)	58.3	11.5	45.7	36.3	4.8	38.9	18.8	68.1	Bangladesh [37]
120	Mean (s.d.) = 63.2 (15.7)	62.5	20	41.7	NR	10.8	13.3	NR	16.7	France [38]
1733	Median (IQR) = 57 (47–65)	52	4	23	75	5.0	17	9	NR	China [39]
145	Mean(s.d) = 63.23	55	22	36	50	24	NR	NR	17	Austria [40]
137	Median (IQR) = 27	61.6	NR	51.5	NR	14	46	22.2	16.7	Rome [41]
636	Median (IQR) = 67.61 (49–70)	54	56	12.6	NR	40.5	16	NR	63.4	Turkey [42]
33	Mean (s.d) = 64	67	NR	33	82	18	12	NR	33	Germany [43]
287	Mean (s.d) = 32.3 (8.5)	35.88	4.9	28.2	14.9	28.9	NR	31.4	NR	Egypt [44]

s.d.: standard deviation; NR: not reported; IQR: interquartile range.

2.2.1. Cardiovascular Complications

Patients who became sick with SARS-CoV-2 had heart problems after they got better, such as low blood pressure, a slow heart rate, and atrial fibrillation [45], and about 20% of COVID-19 patients who became better reported chest pain up to 60 days later [46]. The myocardial tissues, including the alveoli and the lungs, consist of an ACE2 receptor where the virus binds to the receptor and decreases expression of ACE2, which is a cardio-protective transmembrane protein widespread in many tissues such as the kidney, lungs, heart, and intestine. Moreover, following SARS-CoV-2 infection, many people are diagnosed with cardiac arrhythmias with an increased troponin level [47–51].

Several reports highlighted that pneumonia is a predominant symptom seen in SARS-CoV-2-affected patients, some of whom may require hospitalization. These patients have a high chance of having cardiovascular complications after recovery. Corticosteroids are infrequently suggested for COVID-19 patients with lung damage. However, in severe cases, corticosteroids were applied, which in turn affected the cardiovascular tissues [52]. Reported cases also highlighted those patients with no history of cardiac problems who developed malignant arrhythmias and acute respiratory failure, leading to death. Moreover, the increased troponin level also resulted in the cardiac arrest of the patients after recovery. Based on the cases reported in previous outbreaks like SARS-CoV and MERS-CoV, 40% of recovered subjects have had persistent cardiovascular problems for a long time [53]. The same scenario is expected in the case of COVID-19.

Those who survived COVID-19 have a higher cardiometabolic demand, just like those who survived SARS. This can happen when the heart's reserve capacity is low, when corticosteroids are used, or when the renin–angiotensin–aldosterone system doesn't work well [54]. Weerahandi and co-workers reported a study conducted in New York that indicated 74% out of 152 subjects faced difficulty breathing [11]. Another population study with 200 patients in the UK also indicated the prevalence of cardiorespiratory trouble encountered by 40% of the subjects after 30 days of negativization [55].

2.2.2. Respiratory Complications

SARS-CoV-2 mostly affects the lungs. The severe attack on the lungs develops critical manifestations such as respiratory failures and pneumonia, constituting a prime reason for COVID-19-associated mortality [56]. Inflammation and pulmonary fibrosis are the two main effects of a viral lung infection. This inflammation affects the tiny air sacs called alveoli, which help in the diffusion of respiratory gases. Post-mortem analysis of several COVID patients has shown an extreme level of lung congestion, and the parenchymal cells present in the lungs are highly inflamed and appear to be bluish-red [57]. The histopathological reports of lung tissue samples indicated the congestion of the small and large airways, including the pleural tissue and capillaries. These examinations also gave evidence of acute bronchopneumonia, emphysema, asthma, etc. [58]. These severe complications have a high chance of being prevalent in the long run after the patient's recovery.

Most survivors of COVID-19 have pulmonary symptoms such as dyspnea, which have been reported in 42% to 66% of cases at 60 to 100 days of follow-up [59]. When standard radiological imaging has been used to find respiratory problems, they have been described as having segmentation of the lungs and opacities that look like glass. The lung segmentation pattern shows how viral loads can damage the lungs and make them less able to hold air. In some patients (about 5%), the CTs (computed tomography scan) findings indicated lymphadenopathies, pleural effusions, and cavitations. These findings are more prominent in positive RT-PCR patients with respiratory troubles than in those with non-respiratory symptoms [60,61]. Patients with COVID-19 use high doses of steroids to treat their lung inflammation. According to research by scientists, there is evidence that such steroid application for other coronavirus infections has also contributed to the development of lung fibrosis, a chronic health condition [62,63].

The aging process in people also results in some cellular dysfunctions; as a result, the immune system in such people fails to control the viral encounter, leading to some lung-related problems, including lung fibrosis [64]. However, the post-COVID complications due to SARS-CoV-2 have not yet been evident on a large scale, but owing to the evidence from other cases of coronavirus infections, similar complications may likely appear. Additionally, pulmonary vascular microthrombosis as well as macrothrombosis have been perceived in almost 20% to 30% of COVID-19 patients with endothelial injury [65–67].

When the SARS-CoV-2 virus first gets into a person's body, it comes into contact with the mucous membranes in the eyes, mouth, and nose. First, the virus moves into a healthy cell and starts making copies of itself. This creates new virus particles that spread to all healthy cells nearby. Recent reports say that this new coronavirus can infect the whole respiratory system of a person [68]. Once it goes through our airways and gets to our alveoli, the lining could become red and irritated. This novel coronavirus infection is new, and doctors and scientists are constantly learning more and more every day about the pathophysiology of this disease, which has similar effects on the human body to other coronavirus-related diseases, such as SARS and MERS. A retrospective study in Wuhan, China, demonstrated that the CTs showed that about 98% of people had impaired lung functions [69].

Alveoli are tiny air sacs in the lungs responsible for gas exchange between the air and the blood. There are three parts to the alveolar wall: (a) the alveolar epithelium with the basement membrane; (b) the capillary endothelium with the basement membrane; and (c) an interstitium with the fused basement membranes and fibroblasts, elastic fibers, macrophages, and collagen fibrils. The SARS-CoV-2 virus is responsible for the respiratory illness COVID-19, which primarily affects the alveoli and respiratory system. The role of alveolar injuries in the disease progression of COVID-19 is crucial. The alveolar injuries and the subsequent inflammation cause a reduction in the oxygen exchange capacity of the lungs, leading to hypoxemia (low blood oxygen levels). Hypoxemia can further exacerbate the inflammation and damage to the alveoli, creating a vicious cycle of lung injury. Alveolar injuries also play a role in the development of blood clots in COVID-19 patients, which can lead to complications such as pulmonary embolism and stroke. Therefore, alveolar injuries are a crucial component of the disease progression of COVID-19, leading to severe respiratory complications such as ARDS (acute respiratory distress syndrome) and hypoxemia, as well as potentially life-threatening blood clotting disorders. Effective management of COVID-19 requires a comprehensive approach that addresses both the viral infection and the resulting lung injury [70].

2.2.3. Gastrointestinal Complications

The fact that the ACE2 receptor is found in the GI (gastrointestinal) tract makes it easy for SARS-CoV-2 to take over [71]. Patients who became better had higher levels of SGPT (serum glutamic-pyruvic transaminase), SGOT (serum glutamic-oxaloacetic transaminase), bilirubin, and other enzymes that the liver needs to work well. The elevated levels had given clear evidence of the problem in the liver [72]. Other than the liver, the other gastrointestinal complications include dysbiosis, visceral hypersensitivity, and enhanced intestinal permeability, which leads to inadequate absorption of bile acid together with problems related to some metabolic pathways. Moreover, evidence suggests that viral attacks may lead to functional gastrointestinal disorders or disorders in the gut-brain interaction, although this symptom does not persist for a very long time [73]. In about 20% of patients, it is observed that the virus was found in the stool even after getting negative results. Authorities have also decided to discharge a hospitalized patient only after getting negative results from the RT-PCR of stool [74]. Interestingly, a few patients developed GI symptoms rather than any respiratory complications [75,76].

Most drugs used to treat SARS-CoV-2 infections have major side effects on the GI tract, liver, stomach, and pancreas, which change the environment in the gut [77]. These complications of the GI tract (hepatobiliary, bowel ischemia, hypomotility, and others)

are more likely to happen during COVID-19 and after recovery in people who had GI symptoms at the start of their viral symptoms [78]. According to the reports published by Arnold et al., 2020, and Moreno-Pérez et al., 2021, case studies in the United Kingdom (110 people) and Spain (277 people) reported that 0.9% and 10.5% faced diarrhea problems after 3 months of negativization [35,36].

2.2.4. Neurological Complications

Spike protein–ACE2 receptor interaction leads to the dysfunction of cell signaling processing, which in turn affects the functioning of the olfactory and gustatory organs. This may lead to adverse neurological complications in the long run due to the entry of the virus into the brain via the nasal cavity [79,80]. Stroke, encephalitis, and other cerebrovascular diseases are among the leading causes of human suffering [81]. Post-Covid neurological problems that are seen in a large number of patients include anosmia, headaches, and stroke in some cases. The pathway of the virus toward the brain leads to olfactory dysfunction (namely, anosmia) [82].

Normal neurological effects of this impairment fall into three groups: problems with the central nervous system, problems with the peripheral nervous system, and injuries to the bones and muscles. These manifestations together lead to headaches, dizziness, anosmia, vision problems, etc. [83]. The virus is also found in the cerebrospinal fluid (CSF) of many people. Many pieces of evidence suggest that the positive patients only had headache and anosmia as their only symptoms. According to the last report, 96 patients with stroke have been reported following an increased level of ferritin, D-dimer, and C-reactive protein. In addition, another exclusive case study was conducted on a 56-year-old man who tested positive for the virus in March 2020. Later, he was examined for certain neurological complications after 6 months of recovery. He required a routine EEG examination and overcame momentary epileptic seizures [84]. A case was reported on the prevalence of long-term anosmia in a 40-year-old Brazilian lady even after 85 days of recovery [85].

2.2.5. Psychiatric Complications

The SARS-CoV-2 distresses the brain, which houses several neuronal circuits, just like the other two infectious members of the Coronaviridae family [86–90]. A viral infection in the brain stem lowers the number of ACE2 receptors. This kills neurons and changes how several baroreceptors work [91,92]. In the long run, post-traumatic stress disorder (PTSD) will be a common problem. This is not only due to the viral attack in the brain but also to this severe pandemic and a high mortality rate associated with many complications [93]. Several neuropsychiatric problems, including auditory and visual hallucinations, schizophrenia, PTSD, epilepsy, etc., are reported after COVID-19 recovery [51].

Furthermore, COVID-19 patients passed through an extremely stressful period. Some of them even had very severe complications and needed hospitalization. They even required the support of ventilators. They were isolated for 14 days, kept away from their near and dear ones, their workplace, society, etc. This isolation and detachment have created trauma or anxiety. After getting back to their normal lives, they are unable to overcome this problem; they need to consult psychiatrists [94]. The pandemic forced the government (both state and central) to initiate a complete lockdown over 3 months, culminating in the unemployment of many people in 2020, especially in India. These changes somehow created psychological problems, which are likely to persist. India suffered greatly from the second COVID-19 surge even in 2021, which had a greater impact than it had in the previous year [95–97]. A potential study of 91 patients conducted in Santiago, Spain, found evidence of post-COVID anxiety and depression among 46% of the subjects [98]. A collective study conducted in Hall, UK, with a total of 134 subjects, also showed the prevalence of sleep disturbances (35.1%) and mood disturbances (37.3%) after recovering from SARS-CoV-2 infection [99].

2.2.6. Dermatological Complications

The urticarial lesions, maculopapular lesions, vesicular lesions, necrosis, and liver lesions that have been reported are caused by the interaction between the spike protein and the ACE2 receptor in the basal cells of the epidermis [100]. Many of the patients even had oral ulcers and blisters. Another very common symptom observed in the case of children was rashes on the skin [101,102]. Adverse dermatological manifestations included varicella-like exanthems, which can persist for 12 days [103]. No cases with severe dermatological manifestations were found to prevail in the long run during previous coronavirus outbreaks, which may not remain the same in the present scenario. The most common dermatological complication observed among 20% of the patient population after recovering from COVID was reported hair loss [9].

2.2.7. Renal Complications

Acute kidney injury (AKI), electrolyte disturbances, and renal replacement therapy (RRT) are some of the most common renal complications that have been associated with COVID-19 patients [104]. A prominent cause of COVID-19-related death other than proteinuria and haematuria is AKI [105]. Long-term renal complications in patients are also caused by AKI, potentially causing microalbuminuria and chronic kidney diseases; as a result, they require routine dialysis, and about 40% of patients who had AKI needed intensive care [106]. Renal problems will prevail in the long run because the involvement of the kidneys was also prevalent in the cases of SARS and MERS. A prospective study in Oxford, UK, showed that 29% of 58 subjects developed acute post-COVID renal complications [107].

2.2.8. Gonadal Complications

The ACE2 receptor is principally present in the Leydig cells and Sertoli cells of males. Spermatogenesis will be dysfunctional in the case of ACE2-positive spermatogonia [108]. Infection of Sertoli cells leads to dysfunctioning of the spermatogenesis cycle because the viral entry destroys the seminiferous epithelium barrier of the cells, which provides a barrier to the spermatogonia from the cytotoxic products of the blood [109]. Destruction of this obstacle, in turn, affects the process of spermatogenesis.

The decrement of the ACE2 receptor due to the viral attack decreases sperm motility because the ACE2-angiotensin-(1–7)-Mas receptor maintains sperm mobility by activating the PI3K/AKT pathway [110,111]. Recent studies have also indicated the alteration of the levels of several androgens and gonadotrophins in male patients. The considerable diminution in the level of LH (luteinizing hormone) indicates that the SARS-CoV-2 virus has less effect on Sertoli cells than Leydig cells [112].

3. Immunological Changes in the Course of Long COVID

Post-COVID-19 symptoms (long COVID) can affect people with a history of SARS-CoV-2 infection regardless of age and gender, and the fact that long COVID may appear in people with mild symptoms is also worrying the authorities even more. COVID-19 recurrence is reported to increase the probability of long COVID symptoms even more [113]. The menace and liability of sequelae due to SARS-CoV-2 reinfection were significantly higher compared to persons who did not get reinfection. This has concerned the authorities even more, as strategies for the prevention of reinfection are of the utmost importance in managing long COVID.

Dr. Janet Diaz, Unit Head, Clinical Management, WHO Health Emergencies Programme, explains that it is still not clear how many days long COVID may remain as cases have been reported to continue even after nine months. Still, we have not been able to fully understand the reason and the mechanism of long COVID. At the same time, common indications of long COVID include dyspnoea, lethargy, and/or cognitive dysfunction. However, more than 200 other symptoms have also been reported for long COVID [114], the majority of which are associated with the malfunctioning of the visceral organs like the heart, lungs, liver, pancreas, and spleen. The mechanism for long COVID is still unclear,

and different studies are still going on that emphasize different plausible mechanisms that have been discussed below.

The broad mechanisms proposed for explaining the activation of autoimmune disease are bystander activation, molecular mimicry, and epitope spreading.

3.1. Bystander Activation and Long COVID

Bystander activation is linked to T-cell and/or B-cell activation that does not involve their receptors. When antigens interact with their corresponding receptors, they usually cause the receptors to become active. A series of activities that result in the production of cytokines, cell differentiation, cell growth, and/or cell death happens next [115]. Unlike what was thought before, not all self-reactive lymphocytes go through apoptosis. Some naive lymphocytes may be able to get around the central tolerance [116,117]. Bystander activation is related to the activation of autoimmune diseases. Viral infection near the sites of these bystander cells or the migration of these bystander cells towards the inflammation sites may trigger unspecific activation of these lymphocytes without the involvement of B-cell receptors and/or T-cell receptors [115]. Gregorova et al., 2020, have proposed bystander T-lymphocyte activation in post-acute COVID-19 complications. They saw an abundance of CD8+ TEMRA (terminally differentiated effector memory cells re-expressing CD45RA) cells among the spike-1-specific CD8+ cell population. CD8+ TEMRA cells may be activated in the presence of cytokines only, without involving TCR (T-cell receptor) [118,119]. T cells mediate the connection between the thyroid gland and autoimmunity, and long COVID-19 cases have reported inappropriate thyroid gland functioning with autoimmune pathophysiology [120]. Autoimmune consequences of long COVID also involve B cells, as evidenced by the presence of autoantibodies against phospholipids, cyclic citrullinated peptides, connective tissue, neutrophils, and interferons [121–124].

3.2. Molecular Mimicry and Epitope Spreading in Long COVID

If the pathogen and the host share antigens, the host may have an autoimmune response. It is called “molecular mimicry” when an antigen from an outside pathogen causes the body to attack itself. A bioinformatics study predicted the presence of such shared antigens in SARS-CoV-2 spike glycoprotein with that of the adrenal cortex, pituitary, thyroid surface proteins, and beta cells of the islets of Langerhans. This is most likely what causes neuroendocrine dysfunction in long COVID. However, more in vivo studies need to be done to further verify this [125]. Another plausible mechanism underlying the autoimmune-pathological condition of long COVID may be due to epitope spreading [126]. Our immune system not only targets a particular antigen of a pathogen, but temporal diversification of the immune system to target multiple epitopes of a pathogen may also take place. In a study, it was seen that people who could not suppress SARS-CoV-2 early might have a higher virus load for a prolonged period, which may lead to antibody evolution and epitope spreading [127].

4. Drug Repurposing

The global public health emergency caused by COVID-19 sped up research on SARS-CoV-2 to learn more about the virus’s evolution and how it causes disease, as well as to find a cure. Researchers are looking into how SARS-CoV-2 has changed at the genome and protein levels to track the spread of the pandemic using phylodynamic and epidemiological models. They are also looking for possible drug targets.

From an original idea, it takes a lot of time and money to come up with a new drug and bring it to market. The most crucial step in drug discovery is drug-target identification, followed by validation [128]. Among the things that make a biomolecule a good drug target are its unique structure and function, its role in important biological pathways, etc. [129]. The target biological entities are large proteins and may also be nucleic acids, proteins, ribosomes, as well as physiochemical mechanisms, which should be validated by biomarker analysis, in vitro animal as well as cell-based disease models, disease associa-

tion and computational genetics, expression profiling, together with bioinformatics and pharmacological tools, and a literature survey [130].

There are not many efficient disease-management strategies available to immediately reduce morbidity and/or mortality in light of the disease's rapid spread and high reproductive index caused by an entirely new pathogen. Considering the slowness of conventional drug discovery along with the expenses incurred, a drug-repositioning approach was needed to fulfill public health-related queries. Moreover, the complications pertaining to long COVID symptoms also require immediate remediation, for which drug repositioning was again further demanded. The concept of drug repositioning, also known as drug repurposing, has emerged as a popular alternative strategy in biopharmaceutics with the prospect of identifying novel applications for prevailing drugs with well-established pharmacological and safety profiles and for developing new drugs due to its fast and low-cost approaches over the traditional *de novo* ones [131]. As an initial screening step for appraising a wide variety of medications, drug profiling is effective for selecting drugs that allow further assessment and experimental authentication. As an outcome of long COVID infection, there can be a multitude of consequences alone or in combinations, namely, hyper-inflammatory or allergic reactions, the propensity of infection by opportunistic pathogens, as well as cardiac, neurological, and gastrointestinal impediments, etc.

The hyper-inflammatory responses seen in people with long-term COVID may be due to the inflammatory and allergic responses seen in people with mast cell activation syndrome (MCAS) [132,133]. Mast cell activation may already be occurring (with or without symptoms) and may be a result of immune disturbances brought on by COVID-19 or cytokine storms brought on by emotional or physical stressors [132–134]. Patients with long COVID are said to have fewer CD8+ and CD4+ effector memory cells, while programmed cell death protein-1 expression is higher in central memory cells. People who did not have any symptoms, on the other hand, only had fewer CD8+ effector memory cells, while CD28 expression was higher in central memory cells [134]. Long-term COVID symptoms are treated with drugs that block histamine and histamine receptors, such as diphenhydramine HCl, hydroxyzine pamoate, nizatidine, famotidine, etc. [134–136]. If people use drugs in the wrong way, they may end up with too many histamine antagonists in their blood, which can lead to dementia over time [136].

Viral infections often weaken the immune system, making it easier for other types of infections to take hold. Antibiotics such as azithromycin and antiviral agents such as remdesivir and favipiravir are being studied for their usefulness in diminishing the symptoms of long COVID [137,138]. Widespread inflammatory conditions from COVID-19 infection can be confronted with antibody-based immunotherapy with monoclonal antibodies such as infliximab, tocilizumab, siltuximab, anakinra, and leronlimab. These therapeutic monoclonal antibodies are promising for the treatment of ARDS in COVID-19-afflicted people by controlling the cytokine storms and restoring lung homeostasis [139–142].

In the case of long COVID, when the disease condition persists for more than 3 months after the onset of COVID-19 symptoms, paracetamol and NSAIDs (non-steroid anti-inflammatory drugs) are prescribed to relieve specific symptoms. Neurological, cardiac, or gastrointestinal complications arising from COVID-19 may lead to fatigue and dyspnea. In cases of tachycardia or palpitations, the use of ivabradine is recommended [143].

Long COVID syndromes and medical indicators of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), such as sleep disturbances, post-exercise malaise, fatigue, sore throat, cognitive impairment, tender lymph nodes, and so on, have been found to be strangely similar [144,145]. In a review study of 1146 COVID-19 survivors with ongoing symptoms, 13.5% were diagnosed with POTS (postural orthostatic tachycardia syndrome), and 10.3% were diagnosed with ME/CFS. This means that they could be good candidates for repurposing drugs. Immunomodulating vaccines such as rintatolimod and Staphypan Berna, along with oral coenzyme Q10 and NADH, are good options for treating CFS [146].

In the interim, long COVID symptoms are said to be lessened by antidepressants that restore the functionality of the immune system by diminishing peripheral inflammatory

markers. Vortioxetine, a discerning serotonin reuptake inhibitor and serotonin receptor modulator, is under clinical trial for the treatment of long COVID [147].

People who have long COVID, which is the long-term effect of the SARS-CoV-2 infection, may still have their original symptoms or get new ones after getting better from COVID-19. However, these symptoms, such as being tired, short of breath, having trouble thinking, and having other long-term health problems, are similar to or overlap with the clinical profiles of other diseases. Because the symptoms of COVID are similar to those of other conditions, it is not necessary to come up with long-term COVID-specific treatment plans. Instead, it is better to use the drugs and other treatments for other conditions whose symptoms overlap with COVID. Drugs that have been used as antivirals, anti-inflammatory agents, monoclonal antibodies, and immunomodulators in other diseases can speed up the treatment of the disease.

4.1. Data Resources Used for Drug Repurposing

Drug repurposing has several advantages over developing a new drug from scratch. Firstly, repurposing an existing drug saves time and money as it eliminates the need for extensive preclinical and clinical testing. Secondly, it can be easier to gain regulatory approval for repurposed drugs since their safety profile is already known.

Remdesivir, dexamethasone, and hydroxychloroquine are among the drugs that were originally made to treat other diseases but are now used to treat COVID-19 (<https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/remdesivir>, accessed on 1 December 2022).

These drugs have shown varying degrees of efficacy and have been used in different stages of the disease. From time to time, new studies are started and published to look at the pathomechanics of COVID-19 and possible ways to treat it. Aside from experimental datasets, the most important of these are in silico efforts to use existing methods and resources in new ways. This viral disease outbreak had a big effect on how virus bioinformatics tools work and whether they can be used to answer important research questions [148].

The basic ideas behind drug repurposing are: (i) drugs that are prescribed for one disease may also work for other diseases because they have similar pathomechanisms, and (ii) a drug may have multiple targets and signaling pathways that depend on each other. So, strategies employed in drug redesign can be (a) drug-based or (b) disease-based. While drug-based strategies depend on available molecular, biomedical, chemical, pharmaceutical, and genomic facts related to the drug, information related to phenotypic traits, side effects, and indications is fundamental to disease-based strategies to forecast therapeutic possibilities and unique signatures for prevailing drugs [149].

Most of the data resources used for the computational repurposing of COVID-19 drugs were already available before the worldwide outbreak of SARS-CoV-2. They include information about networks and interactions, drugs and trials, and molecular properties.

4.1.1. Molecular Data

Genome, transcriptome, and proteome-based sequence data about SARS-CoV-2 and its host can be procured from databases like GenBank, the GISAID (Global Initiative on Sharing Avian Influenza Data) initiative, or UniProt [150,151]. The findings of the human genome sequencing project permit an enhanced understanding of the mode of action of drugs as well as diseases, and the genes/gene products contributing to it may be a promising target for governments and pharmaceutical industries. This information, complemented by clinical databases, provides an opportunity to explore new uses of existing drugs. In silico studies of diverse types of functional and structural members of the SARS-CoV-2 proteome have significantly enriched protein information in structural resources like the Protein Data Bank (PDB) [152]. Many unique functional gene interactions contributing to the generation of novel disease subtypes, together with the characterization of disease pathomechanisms or modes of drug response, have been elucidated by computational

studies of drug repurposing using data on gene regulation, based on the presumption that drugs aim to bind the same proteins with equivalent gene expression profiles [153]. Lastly, gene-expression data from transcriptome resources like the Genotype-Tissue Expression (GTEx) program and the LINCS L1000 database have also been referred to in several COVID-19 drug-repurposing approaches [154,155]. While the former deals with tissue-specific gene expression, the latter outlines alterations in gene expression patterns under certain drug treatment conditions. It is mention-worthy that microarray-based gene expression analysis is the most popular tool among genetic profiling methods that have been used for drug reprofiling as it reveals cellular dynamics and transcriptional activity of a multitude of genes at the same time.

4.1.2. Network and Interaction Resources

Protein–protein interaction (PPI) networks can be used to think of and evaluate interactions between proteins in the host and the virus. PPI networks also let you make specific changes and search strategies, and drug resources can back up what you find. VirHostNet [156,157], which was already a virus–host PPI resource, has been added to 167 more SARS-CoV-2-centered interactions. Between SARS-CoV-2 (26 of 29 proteins) and human proteins, there are 332 statistically significant protein–protein interactions. Of these, 66 host proteins were found to be targeted by 69 compounds that were strong enough to be used in people [158]. This is a promising new resource for SARS-CoV-2. Host-specific PPIs such as STRING v11, used for COVID-19 drug redesign, are also pre-existing resources devoid of any virus specificity [159]. Envisioning the interaction of chemicals, genes, and phenotypes through knowledge graphs such as the Global Network of Biomedical Relationships (GNBR) provides insights into the mechanisms behind complex biochemical processes like drug–drug interaction and drug response variability across individuals [160].

4.1.3. Drug and Trial Resources

Drug resources like DrugBank, ChEMBL, and ZINC15 that are continually supplemented with novel drugs from a time much before the pandemic era are effectively applied to correlate different experimental observations to druggable compounds that are either approved or under clinical trial [161–164]. Trial databases such as ClinicalTrials.gov and the EU Clinical Trials Register (<https://www.clinicaltrialsregister.eu/>, accessed on (new update released on 28 March 2023)) also aid the approaches of drug remodeling through validation of the applicability of predicted drugs.

Proteins such as nuclear hormone receptors, proteases, kinases, and GPCRs (G protein-coupled receptors) are the most promising biomolecule targets for successful drug development [165]. While determining potential drug targets, the 3D structure of proteins is evaluated to model and understand the binding compartments of target proteins that can bind molecules or drugs of low molecular weight [166,167]. Several strategies for drug discovery are being implemented to broaden the scope of treatment alternatives against the virus, as summarized below.

4.2. Drug Reprofiting Approaches

4.2.1. Targeting Virus

Drug screening procedures based on the 3D structures of target proteins are fundamental from drug-redesigning approaches to targeting the virus through the prediction of affinity binding of chemical compounds to target proteins of both host and viral origin. There are two major workflows:

(a) Structure-based drug screening: Here, a drug library needs to be selected that may be restricted to antiviral drugs or maybe elaborate with databases like DrugBank that can combine compounds with information from the KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway [168]. Drugs with high scores are selected with the help of virtual screening software like Autodock 4 version (v4.2.6) and Glide (Schrödinger Release 2023-1) and validated for application with molecular dynamics simulations [169–171].

(b) Repurposing strategies based on deep learning (DL): The binding affinities of billions of chemicals can be predicted and assigned scores by DL models based on numerous physio-chemical properties, enhancing the range of the compounds examined and the prospect of detecting alternative compounds [172]. Some drug–target interaction prediction models have been developed (dependent or independent of docking software) that, in conjunction with DL algorithms, study drug–target protein complex structures and predict binding affinities of the drug–protein complex, namely, DeepDocking, MathDL, and Molecule TransformerDrug–Target Interaction [173,174].

4.2.2. Targeting Host

Redesigning drugs could be aimed at the parts of the host that start the process of viral pathogenesis. Since SARS-CoV-2 contagions are associated with the unregulated release of pro-inflammatory chemokines and cytokines, COVID-19 patients who are critically affected can benefit from the application of drugs that can target specific dysregulated pathways of the immune system [175–177]. The same can be addressed in two ways:

(a) Signature-based approaches: Looking at how the genes in samples that have been infected with viruses are expressed can help find drug candidates. Connectivity map databases are based on figuring out how drug-induced expression signatures can cause disease signatures to change [178,179]. Otherwise, comparative analysis of the expression profiles of afflicted and unaffected people can also be utilized in the pathway-guided drug-redesigning workflow [180].

(b) Network-based approaches: Several sources of data, like those on host–virus interactions, co-expression networks, PPIs, functional connotations, or drug–target interactions, may be integrated, followed by the application of suitable random-walk-based algorithms such as Save RUNNER to identify appropriate host-protein targets or interactome to be besieged by therapeutic approaches [180–183]. A modified version of the PageRank algorithm, called TrustRank, is applied by CoVex to rank host proteins that may be drug targets based on scores from a user-defined reference point [184,185]. Estimation of the network proximity of drug targets with coronavirus-associated proteins in the human interactome may be applied to determine the efficiency of candidate drugs as well [186]. The choice of prospective drug combinations dedicated to COVID-19 is grounded on the closeness of targets between two drugs as estimated by network proximity [187]. A multi-modal integration of network proximity with graph convolutional networks (GCNs) and diffusion-state distance has been reported to be applied to the virus–host interactome together with tissue specificity and probable disease comorbidities for the identification of drugs perturbing the properties of host proteins associated with COVID-19 [188].

CoVex is a web platform for the discovery of virus–host–drug interactomes concerning both SARS-CoV-1 and SARS-CoV-2, where drug candidates along with their targets may be predicted using different graph-analysis methods such as Key Pathway Miner [185].

It has been said that sometimes a method is used that combines matching signatures and network dependencies. Identification of gene products that are induced by drugs altering the COVID-19 infection signature profile using auto-encoders was followed by the application of the Steiner tree and causal network-discovery algorithms to characterize the pathomechanism manifested by SARS-CoV-2 [189].

4.3. Drugs under COVID-19 Clinical Trials

By mapping the FDA drug database with the PubChem repository, we have summarized the drugs considered for clinical trials for SARS-CoV-2 contagion. Molecular mechanisms that are considered for being targeted by drugs in clinical trials are RNA mutagens, protease inhibitors, virus entry blockers, and anti-inflammatory cytokine storm inducers.

4.3.1. RNA Mutagens

RNA-dependent RNA polymerase-regulating SARS-CoV-2 replication can be prospective targets for designing treatments for COVID-19, for which RNA mutagens such as

favipiravir, remdesivir, and ribavirin are conventional drugs of choice that are being reviewed through clinical trials [190].

A nucleotide-analog prodrug named remdesivir that can contend with ATP being incorporated into the Ebola virus and all known infectious coronaviruses is anticipated to be a strong candidate to treat COVID-19 by triggering RNA mutations in SARS-CoV-2 [191]. Several clinical trials have been conducted to examine the effectiveness of remdesivir on COVID-19, although no definite conclusion regarding the clinical benefit of the drug could be deduced [192,193]. Although it reduces the time of recovery with promising effects on clinical outcomes in terms of oxygen support, it did not receive approval from the FDA as a drug against COVID-19 [27].

Favipiravir–triphosphate and ribavirin are analogs that mimic ATP and GTP in combination with RdRp, although their efficiency is less than that of remdesivir. The favipiravir family showed markedly less virus clearance time, better imaging of the chest, and a smaller quantity of antagonistic reactions. However, favipiravir provides a quicker reprieve from symptoms such as cough and pyrexia. A literature survey reveals that the application of ribavirin in a combination of lopinavir/ritonavir, IFN- α , or lopinavir/ritonavir, IFN- β -1b, and ribavirin may be helpful to SARS-CoV-2 patients [194].

4.3.2. Protease Inhibitors

Ritonavir–lopinavir and darunavir are antagonists of protease activity that can be used as drugs of choice as targeted proteases are essential for the proteolytic treatment of polypeptides into functional proteins such as enzymes that are dedicated to the regulation of gene expression and replication in coronaviruses [195]. The combination medication for inhibiting HIV protease, ritonavir–lopinavir, was also tested for its effectiveness against SARS-CoV2 infection. Several clinical trials revealed that the amalgamation of ritonavir–lopinavir and adjuvant drugs markedly reduced the timespan for virus clearance in comparison to the singular use of adjuvant drugs [196,197]. Administration of darunavir did not show any effect in preventing SARS-CoV2 patients from developing the disease or in reducing the severity of the disease [198].

4.3.3. Viruserentry Blockers

As the gateway for SARS-CoV-2 in the mammalian cell is through interaction with cell membrane receptors, interference with the entry of the virus with drugs like chloroquine, hydroxychloroquine, and arbidol, along with anti-virus spike protein antibodies, namely, LY3819253, JS016, and REGN-COV2, may have the likelihood to fight virus infection.

The antiviral effect of the classical anti-malarial drug chloroquine and its hydroxylated form, hydroxychloroquine, are yet to be deciphered, with only a few studies implicating their role in intruding in the glycosylation of the human cell membrane receptor ACE2 and other gangliosides, thus impeding binding of the virus to the target receptor [199]. Although some small-scale studies showed the effectiveness of the hydroxylated version for mild COVID-19 treatment with or without azithromycin, this could not be validated in larger-scale studies [198]. Additionally, the additional therapy of hydroxychloroquine to ritonavir–lopinavir may show multiple harmful effects, including neurological, cardiac, and metabolic symptoms, and therefore should be used cautiously [200].

Broad-spectrum antiviral Arbidol restricts various steps of the lifecycle of viruses such as HCV and influenza [201]. Some clinical-study reports suggest a role for Arbidol monotherapy and combination therapy with ritonavir–lopinavir in reducing the period of the disease compared to the sole use of ritonavir–lopinavir, which was further contradicted by several other studies that failed to demonstrate the efficacy of the drug in eradicating SARS-CoV-2 infection [202]. Monoclonal antibodies such as LY3819253 (commercialized by Eli Lilly), JS016 (commercialized by pharmaceutical company Shanghai Junshi Bioscience), and REGN-COV2 (a combination therapy of REGN10933 and REGN10987 Abs) directed against the target spike (S) protein are under clinical trials.

4.3.4. Virus-Release Blockers

Medications designed as virus-release blockers, exemplified by oseltamivir, inhibit virus transmission from the infected cell. In influenza viruses, oseltamivir is reported to inhibit neuraminidase, thus blocking virus release from the infected cell [203]. A similar effect is being examined in the treatment of COVID-19.

4.3.5. Non-Virus-Targeting Treatments

A cytokine storm in COVID-19 can cause ARDS and multiple organ failure, which can suddenly make the patient's condition worse or even kill them. This storm can be stopped with drugs such as IL-6 inhibitors (tocilizumab) and cytokine suppressors (such as CD24Fc) [203,204]. Additionally, metabolic modulators such as the corticosteroid drug dexamethasone, which prevents naive T cell proliferation and differentiation, and sodium-glucose cotransporter-2 (SGLT2) inhibitor dapagliflozin, which prevents the fall of pH in the cell, are expected to reduce disease severity [205]. However, the use of metabolic modulators should be critically scrutinized for metabolic side effects such as the slight elevation of blood sugar content, hypertension of the eye, cataracts, neuropsychological side effects in the case of dexamethasone, and diabetic ketoacidosis in the case of dapagliflozin [206].

5. Prevention/Precautionary Measures of Long COVID—Bioactive Compounds from Natural Sources and Functional Foods against Long COVID

Everyone affected by COVID-19 does not require to get hospitalized, but they possess a broad range of several symptoms and severity levels. The nature of long-lasting problems raised by COVID-19 may be very wide-ranging and can include various symptoms such as fatigue, breathlessness, anxiety, depression, different thinking problems, loss of appetite or weight, as well as other problems [207]. In most cases, it is really difficult to find out which variant of the virus is responsible for the onset of the disease [208]. The hasty alterations in SARS-CoV-2 strains have led to differentiated forms of medicine as well as dietary profiles for monitoring the infection risk [209]. Bioactive compounds isolated from natural sources and functional foods are a major contributor to the modulation of the host-immune response by spawning antiviral activities within the host and creating biologically active agents that are generally active against long COVID [210].

Bioactive compounds from natural sources, nutraceuticals, and dietary supplements or functional foods have been recognized as a rich source of various amino acids, water-soluble vitamins, fat-soluble vitamins, minerals, and different types of alkaloids and flavonoids that can readily be used for the improvement of cognitive performance during stressful conditions that occur during long COVID [211]. The conventional method of treatment for COVID-19 includes medicine, vaccines, etc.; along with that, the application of nutraceuticals or functional foods has been considered most beneficial in the treatment or prevention of post-COVID-19 symptoms [212–214]. Different data support the potential advantages of various bioactive compounds' regulatory role as immunomodulant during COVID-19 infection [215,216].

Chourasia et al., 2020, wrote about how a specific peptide is made when *Lactobacillus delbrueckii* WS4 ferments soy cheese. This peptide has antiviral properties [217]. Thyme, turmeric, lime, cardamom, lemon, coriander, and beetroot juice are decent sources of water-soluble vitamins, i.e., vitamin C. Vitamin C scavenges reactive oxygen species and averts lipid peroxidation along with protein alkylation, and this way it safeguards cells from impairments induced by oxidative stress. Therefore, functional foods with vitamin C can aid in symptom relief, as well as provide immunity improvement and an antioxidant effect against the SARS-CoV-2 infection [217,218].

Although evidence from experimental studies is very scarce, FrattaPasini et al., 2021, have established correlations between antioxidant intake and recovery from viral infection by performing clinical trials in patients with SARS-CoV-2 infection [219]. Soy beverages, milk, goat's milk, salmon, mackerel, eggs, and cod liver oil are all potent sources with enhanced amounts of fat-soluble vitamins, i.e., vitamin D, which plays a key role in both

immunomodulatory and antiviral responses. It is found that vitamin D suppresses virus-induced inflammation, which is indeed helpful for overpowering the cytokine storm in SARS-CoV-2 infection [220,221].

Different foods, such as fish, meat, egg yolk, walnut seeds, pumpkin, wheat germ, oats, nuts, and sesame, are the source of dietary zinc (Zn). Zn can stop SARS-CoV-2 RNA polymerase from working, so it is important for controlling COVID-19. However, it is not yet established whether a supplemental dose of these nutraceuticals administered to patients without their deficiency would result in a benefit. Specific clinical trials are now being conducted on the intravenous delivery of vitamin C to hospitalized COVID-19 patients. Vitamin D deficiency has been associated with increased susceptibility to respiratory infections; therefore, it is reasonable, even in the absence of specific data, to administer vitamin D to healthy individuals and COVID-19 patients. While diet, nutraceuticals, and similar interventions show promising improvement for preventing and managing COVID-19, it is also true that strong clinical research data are required to support any such claim. As a means of supportive treatment, Majnooni M. B. et al. have established that quinine, berberine, ergotamine, cepharanthine, crambescidin, palmatine, noscapine, lycorine, and tetrandrine are alkaloids, and they can serve as potential therapeutic targets with prominent antiviral effects. So, these nutraceuticals can be utilized as immunomodulatory and protective against long COVID symptoms. Quercetin, fisetin, jusanin, luteolin, kaempferol, and apigenin are a group of compounds found in natural resources termed flavonoids. These compounds generally target several inflammatory pathways associated with SARS-CoV-2, which will lead to variation in the immune response [221–226].

6. Conclusions

Millions of people suffered badly due to COVID as well as post-COVID lung infections that were hard to comprehend. Thus, in conclusion, we would like to enlighten you on the fact that lung diseases are prevalent medical conditions among COVID-19 patients globally, and patients with asthma and COPD are highly susceptible to getting infected. In this review, we focused on various lung diseases associated with COVID-19 patients, their causes, symptoms, diagnosis, and treatments. COVID-19 mainly causes respiratory tract infections in humans. The symptoms usually vary from mild flu-type sickness to ARDS [8,227]. Secondary fungal and bacterial infections in the lungs have been diagnosed earlier in patients affected by other coronaviral diseases. However, this type of secondary pulmonary infection has not been reported well to date and warrants further clinical intervention. It is important to note that not everyone who contracts COVID-19 will experience these long-term complications, and the severity of the symptoms can vary widely. However, it is crucial to take precautions to prevent the spread of COVID-19, such as wearing a mask, washing your hands frequently, and getting vaccinated, to reduce the risk of both short-term and long-term health effects.

Long COVID, also called post-acute sequelae of SARS-CoV-2 infection (PASC), is a condition in which COVID-19 symptoms last for weeks or months after the initial infection has gone away. Most people become better from COVID-19 within a few weeks, but some keep having a variety of symptoms that can have a big impact on their quality of life. It is unclear what causes long COVID, but it is thought to be related to the immune system's response to the virus. Some experts believe that the virus may trigger an autoimmune response in some people, which can lead to ongoing symptoms. Long COVID can affect people of all ages, including those who had mild or even asymptomatic cases of COVID-19. It is important to note that the condition is not well understood, and research is ongoing to better understand the causes and potential treatments. Immunological changes (e.g., T-cell dysfunction, autoimmunity, impaired antibody responses in individuals, persistent inflammation in the body, immune response dysregulations, etc.) have been observed in individuals with long COVID, although the exact mechanisms are still being studied.

It is important to keep in mind that the tests used to find complications after COVID-19 can vary depending on the person's symptoms and medical history. So, surveillance and

medical trials are important parts of finding and effectively treating complications after COVID-19. They also help us learn more about these complications. As more research is done, doctors will be better able to deal with COVID-19's long-term effects on health and help people fully recover from the disease. Hence, this present review article has provided comprehensive information on two very important topics, i.e., long COVID and the need for drug repurposing.

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