

Post-COVID Complications

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Millions of people suffered badly due to COVID as well as post-COVID lung infections that were hard to comprehend. It is 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.

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

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) [1]. 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 [2].

According to recent studies, COVID-19 affects women less frequently than it does men [3]. 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 [4]. 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 [5][6].

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 this section.

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 Conductor by (Reference) |
|--|----------------------------------|--------------------------|-------------------------------|---|-----------------------------------|--|-------------------------------------|-----------------------------------|---|------------------------------------|
| 143 | Mean (s.d.) = 56.5 (14.6) | 62.9 | 12.6 | 43.4 | 53.8 | 21.7 | 15 | 27.3 | 15 | Italy [7] |
| 100 | Median (ward/ICU) = 70.5/58.5 | 54 | 32 | 40 | 78 | 17.2 | NR | NR | NR | UK [8] |
| 150 | Mean (s.d.) = 45 (15) | 44 | NR | 30 | NR | 13.1 | 22.7 | 16.3 | NR | France [9] |
| 110 | Median (IQR) = 60 (44–76) | 61.8 | 16.4 | 39 | 75.4 | 12.7 | 11.8 | 4.5 | 11.8 | UK [10] |
| 277 | Median (IQR) = 56 (42–67.5) | 52.7 | 8.7 | 34.4 | NR | NR | 21.4 | 19.6 | 21.3 | Spain [11] |
| 355 | Mean (s.d.) = 39.8 (13.4) | 58.3 | 11.5 | 45.7 | 36.3 | 4.8 | 38.9 | 18.8 | 68.1 | Banglade: [12] |

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|--|----------------------------------|--------------------------|-------------------------------|---|-----------------------------------|--|-------------------------------------|-----------------------------------|---|------------------------------------|
| 120 | Mean (s.d.) = 63.2 (15.7) | 62.5 | 20 | 41.7 | NR | 10.8 | 13.3 | NR | 16.7 | France ^[1] |
| 1733 | Median (IQR) = 57 (47–65) | 52 | 4 | 23 | 75 | 5.0 | 17 | 9 | NR | China ^[14] |
| 145 | Mean(s.d) = 63.23 | 55 | 22 | 36 | 50 | 24 | NR | NR | 17 | Austria ^[1] |
| 137 | Median (IQR) = 27 | 61.6 | NR | 51.5 | NR | 14 | 46 | 22.2 | 16.7 | Rome ^[16] |
| 636 | Median (IQR) = 67.61 (49–70) | 54 | 56 | 12.6 | NR | 40.5 | 16 | NR | 63.4 | Turkey ^[1] |
| 33 | Mean (s.d) = 64 | 67 | NR | 33 | 82 | 18 | 12 | NR | 33 | Germany ^[1] |
| 287 | Mean (s.d) = 32.3 (8.5) | 35.88 | 4.9 | 28.2 | 14.9 | 28.9 | NR | 31.4 | NR | Egypt ^[15] |

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

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 ^[20], and about 20% of COVID-19 patients who became better reported chest pain up to 60 days later ^[21]. 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 ^{[22][23][24][25][26]}.

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 ^[27]. 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 ^[28]. 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 ^[29]. Weerahandi and co-workers reported a study conducted in New York that indicated 74% out of 152 subjects faced difficulty breathing ^[30]. 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 ^[31].

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 ^[32]. 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 ^[33]. 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. ^[34]. 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 ^[35]. 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 [36][37]. 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 [38][39].

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 [40]. 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 [41][42][43].

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 [44]. 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 [45].

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 [46].

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 [47]. 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 [48]. 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 [49]. 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 [50]. Interestingly, a few patients developed GI symptoms rather than any respiratory complications [51][52].

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 [53]. 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 [54]. 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 [10][11].

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 [55][56]. Stroke, encephalitis, and other cerebrovascular diseases

are among the leading causes of human suffering [57]. 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) [58].

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. [59]. 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 [60]. A case was reported on the prevalence of long-term anosmia in a 40-year-old Brazilian lady even after 85 days of recovery [61].

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 [62][63][64][65][66]. A viral infection in the brain stem lowers the number of ACE2 receptors. This kills neurons and changes how several baroreceptors work [67][68]. 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 [69]. Several neuropsychiatric problems, including auditory and visual hallucinations, schizophrenia, PTSD, epilepsy, etc., are reported after COVID-19 recovery [26].

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 [70]. 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 [71][72][73]. A potential study of 91 patients conducted in Santiago, Spain, found evidence of post-COVID anxiety and depression among 46% of the subjects [74]. 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 [75].

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 [76]. 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 [77][78]. Adverse dermatological manifestations included varicella-like exanthems, which can persist for 12 days [79]. 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 [80].

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 [81]. A prominent cause of COVID-19-related death other than proteinuria and haematuria is AKI [82]. 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 [83]. 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 [84].

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 [85]. 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 [86]. 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 [87][88]. 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 [89].

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 [90]. 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, researchers 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 [91], 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 [92]. 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 [93][94]. 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 [92]. 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) [95][96]. 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 [97]. 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 [98][99][100][101].

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 [102]. Another plausible mechanism underlying the autoimmune-pathological condition of long COVID may be due to epitope spreading [103]. 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 [104].

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