Analysis of post-COVID comorbidities in Pakistani population

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November 2022

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I certify that this research work titled "*Analysis of long-COVID comorbidities in Pakistani population*" is my own work. The work has not been presented elsewhere for assessment. The material that has been used from other sources has been properly acknowledged / referred.

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Abstract

Introduction: Long-COVID, is the collective name given to denote persistence of symptoms for weeks or months in those who have recovered from SARS-COV-2 infection. If the relapsing symptoms are left undetected, can lead to chronic conditions. Still some work needs to be done to determine the correlation of the previous illnesses with the severity of post-COVID symptoms.

Method: A questionnaire survey was spread amongst Pakistani population. About 83 COVID-19 survivors were included in the study, who were asked about any occurrence of symptoms at recovery, the experience and duration of the post-viral symptoms.

Results: Out of 83 participants, 59(71.7%) experienced relapsing symptoms at 3 weeks from the onset of the viral infection, with 34(44.6%) having to face those symptoms for 3-4 weeks (post-acute COVID). Females were significantly more likely to experience fatigue (p=0.014) and severity (p=0.032). The presence of symptoms was not associated with any therapy or activity. The presence of mild symptoms is common after the COVID-19 infection with those already suffering from anxiety, allergies, hypertension, and diabetes.

Conclusion: This study highlights the importance of assessing those recovering from mild COVID-19 with acute-fatigue. Moreover, further longitudinal research in this area can help understand the management of chronic situations.

Keywords; long-covid, fatigue, pacing, comorbidities

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List of abbreviations

1. COVID-19; Coronavirus disease of 2019
2. SARS-COV-2; severe acute respiratory syndrome- Coronavirus 2
3. PCR; Polymerase chain reaction
4. ME/CFS; Myalgic Encephalomyelitis/Chronic fatigue syndrome
5. PEM; Post-exertional malaise
6. CBT; Cognitive behavioral therapy
7. GET; Graded exercise therapy
8. MERS; Middle Eastern Respiratory Syndrome
9. SARS-COV-2; severe acute respiratory syndrome
10. WHO; World Health Organization
11. ACE-2; Angiotensin-converting enzyme 2
12. ARBs; angiotensin receptor blockers

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Chapter 1: Introduction

1.1 Background

The viral infection, causing cold and severe acute respiratory syndrome, known as the coronavirus, is one of the types of viruses. The first viral outbreak was caused in China, in the year 2019. The severe acute respiratory syndrome (SARS-COV-2), caused the disease, was termed as the coronavirus disease 2019 (COVID-19). The World Health Organization (WHO) declared the COVID-19 as a pandemic in March 2020. [3]

The chances of transmission of SARS-COV-2 are higher than SARS-COV and Middle East Respiratory Syndrome (MERS). The droplets released in the form of coughs and sneeze are the most convenient ways of virus' transmission. When in close contact, the particles spread from infected people to others. The transmission is also possible during recovery or incubation since the virus replicates in the epithelial cells of the mouth and the lower respiratory tract where it sheds for a longer time. [4], [5]

The severity of COVID-19 symptoms can vary from mild to severe. Some common symptoms during the infection are fever, cough, and tiredness. Every individual experience the symptoms differently. Some may have only a few or no symptoms. The mild symptoms include loss of taste, shortness of breath, muscle aches, sore throat, runny nose, headache, and nausea/vomiting. [6] There has been some worsening of symptoms experienced too by some, such as shortness of breath and pneumonia. [7]

By June 2022, over 530 million people from around the world are estimated to have experienced COVID-19 infection with more than 6.3 million deaths. [8] Although symptoms are commonly from mild to moderate severity but there is a majority where there is higher risk of getting the disease as severe which would mean hospital admission, worsened outcomes, including long-covid and mortality. [9]

It has been challenging to identify the frequency of symptoms' diagnosis and understanding the duration and severity of long-COVID symptoms. It is still an ongoing process to investigate and implement the preventive and therapy methods. To help explain the post-COVID-19 condition which is termed as 'long-COVID' some defined criteria used are the temporal criteria, the severity of symptoms and clinical criteria (Table 1).

The temporal criteria were considered which concludes in various studies to be the long-COVID experienced for 3 weeks after acute phase of the viral infection from its onset to be the post-acute COVID. While another category defines post-COVID syndrome, 24 weeks after hospitalization with chronic COVID-19 infection. [10] The symptoms' severity, after the onset COVID-19 infection can go to an extent from symptomatic to fatal conditions. The common conditions include fatigue, shortness of breath, headache, coughs. And some worsened symptoms may include multiple organ complications. The last criteria which include four clinical features which differentiate long-COVID symptoms are post-intensive care syndrome, post-viral fatigue syndrome, permanent organ damage and long-term COVID-19 syndrome. [11]

Criteria of diagnosis	**Duration/Symptoms**
Temporal (Duration)	Post-acute COVID : at 3 weeks Post-COVID syndrome : at 24 weeks
Severity of symptoms	Mild/asymptomatic: 2 weeks Severe infection: 3-6 weeks Critical infection: to death [12], [13]
Clinical Criteria	Post-intensive care syndrome Post-viral fatigue syndrome Permanent organ damage Long-term COVID-19 syndrome.

Table 1: Standards for long-COVID diagnosis

COVID-19 infection can be avoided, using a mask, keeping distance and by avoiding any physical contact too. With time, vaccinations have also become necessary to prevent one from getting COVID-19 or even prevent from having a severe illness. The viral infection situation does not end here. The prolonged symptoms experienced even after getting the negative PCR, is the phase known as the Long COVID-19. It is the post-viral condition where an individual undergoes continuous, relapsing or remitting symptoms (the same or the new symptoms of acute COVID) at the time of clinical recovery (Figure 1).

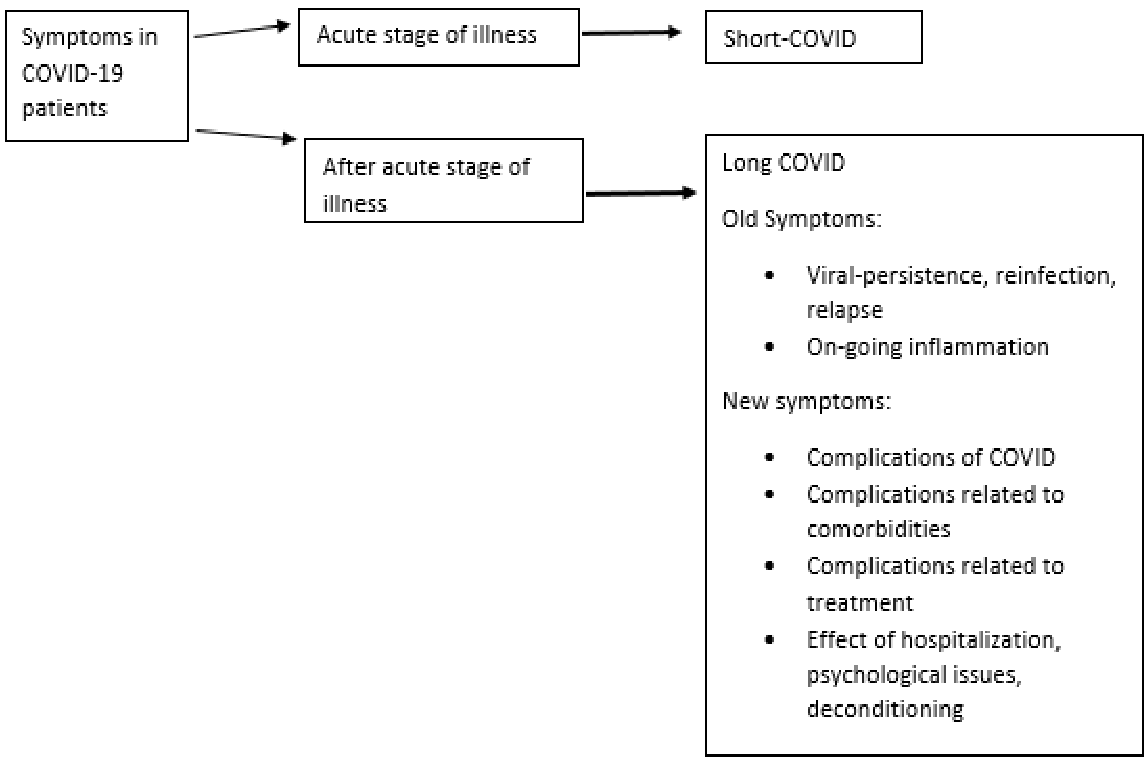


Figure 1. Defining COVID-19 and its post symptoms; Short COVID and Long COVID.

Those individuals suffering with previous medical conditions can be at more risk of serious COVID-19 illness. These include:

- Serious heart diseases
- Cancer
- Diabetes
- Smoking
- Chronic kidney diseases
- Pregnancy

- Weakened immune system

1.2 Immune system response against COVID-19 [2], [14]–[17]

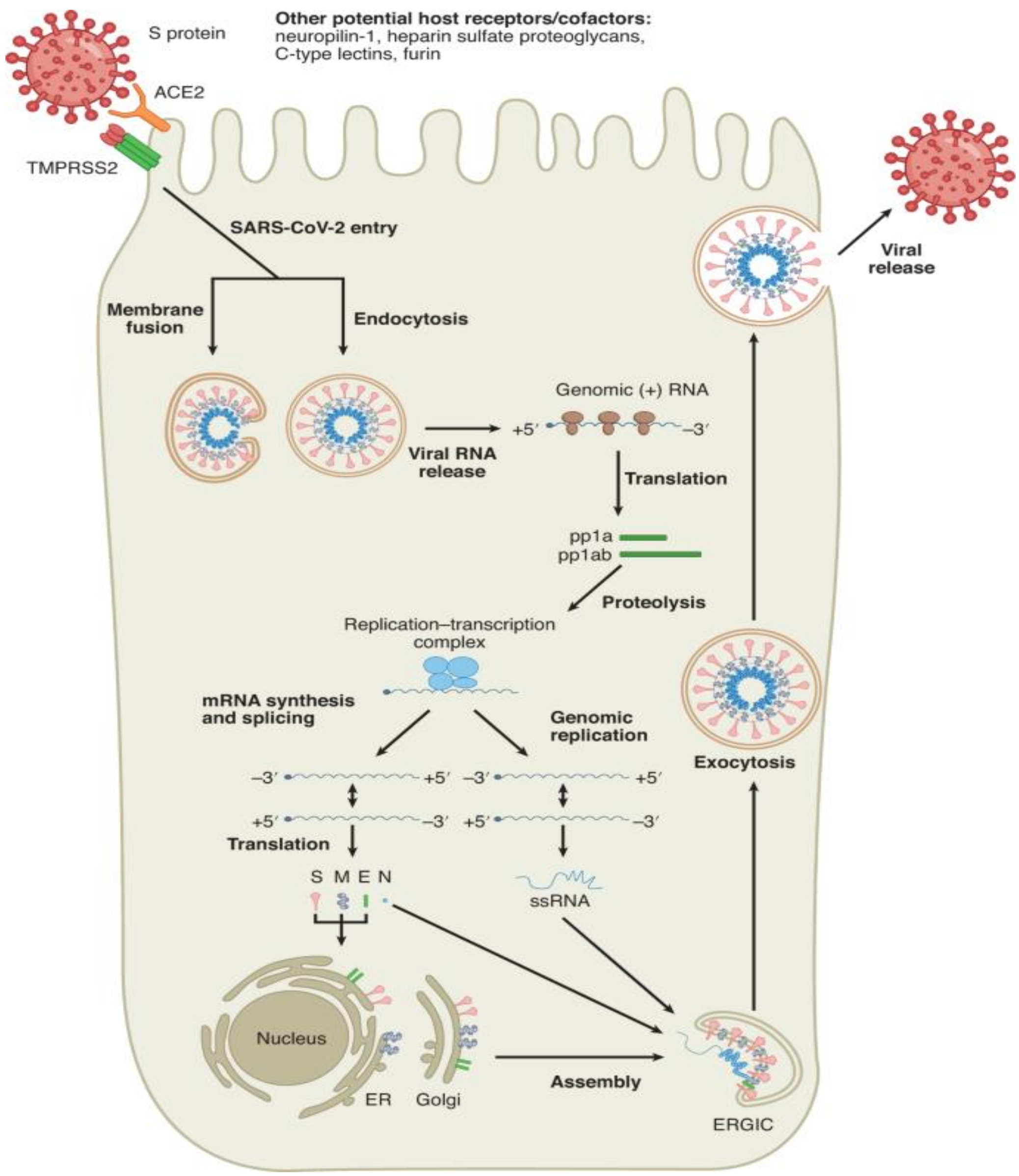


Figure2: SARS-COV-2 virus entering the host cell and its replication [2]

COVID-19 virus is a crown shaped RNA virus. One of its sides is concave which has ridges on it. The SARS-COV-2 virus easily transmits through droplets as aerosolized pathogens into the air through sneezing and coughs. Once the droplets are inhaled the virus starts to replicate. ACE-2 (Angiotensin-converting enzyme 2) receptors are found on the cells of the lower respiratory tract and the epithelial cells of the mouth and tongue. The spike protein (s-protein) in the virus enters the host cell by binding to the ACE-2 receptors. Furin is found to be assisting the SARS-COV-2 virus.

The innate immune response forms the first line of defense against the virus. In rapid response to the threats from the virus, innate immunity has barriers and a variety of defensive cells to defend (Figure 2). The innate response limits the entry of the virus and hence preventing their translation and replication and helps identifying and removing infected cells leading to coordinate with adaptive immunity (Figure 3).

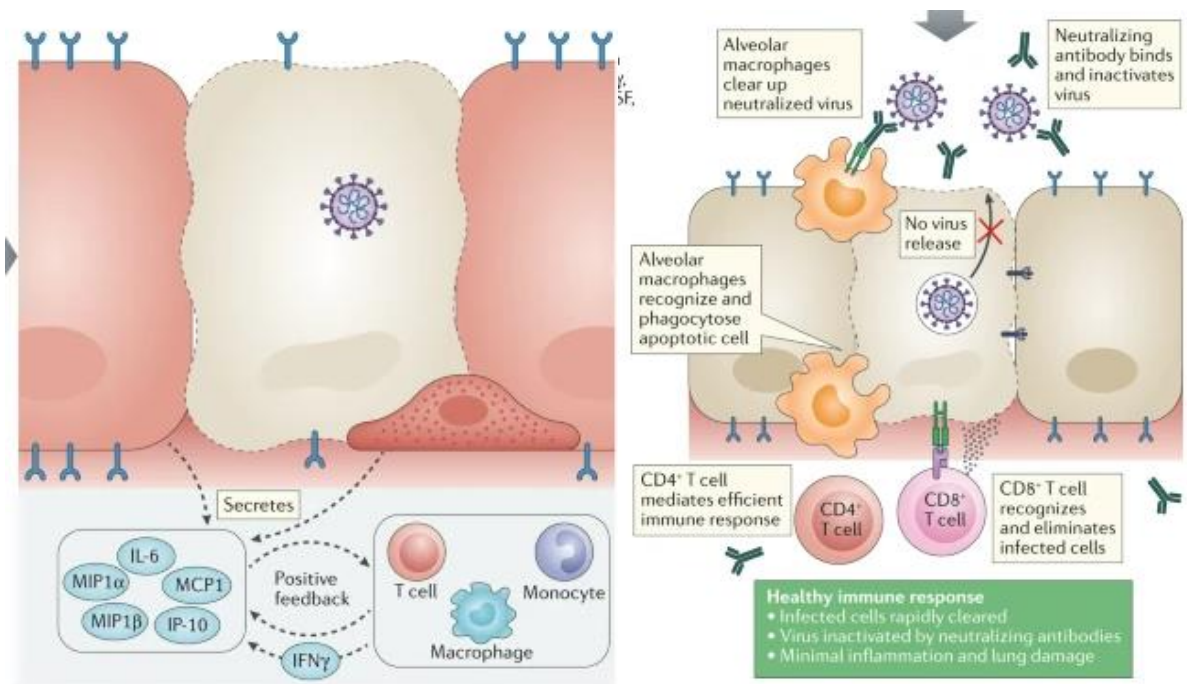


Figure 3: (left) release of antibodies in positive feedback response (right) the healthy immune response [18]

Inflammation occurs because of immune response which can also damage our tissues and affect multiple organs too. The severity of the disease in patients is not just due to the viral infection but also because of the response from the host.

The COVID-19 infected patients show high levels of pro-inflammatory cytokines including IFN-g, IL-1B, IL-6 and IL-2, and chemokines. Cytokine storms occur in response to normal inflammation producing various inflammatory cytokines at a higher rate. The cytokine storm causes the more immune cells to be released to the site of injury that could lead to organ damage.

Regardless of the inflammation site, the increased flow of blood will release plasma proteins and leukocytes to the injury site. The adaptive immune response involves specialized immune cells and antibodies that overcome the foreign macrophages and prevents the relapse of the disease. The fundamental components of this immune response are B-cells, CD4+ T cells, CD8+ T cells. The B and T cells produce antibodies to the viral antigen. The antibody blocks the virus entry and prevents the infection from relapsing. A cellular immunity response can then be observed inside the infected cells, which is brought about by T- lymphocytes. The overall adaptive immune response is led by helper T cells, and cytotoxic T cells play a role in eradicating the viral-infected cells.

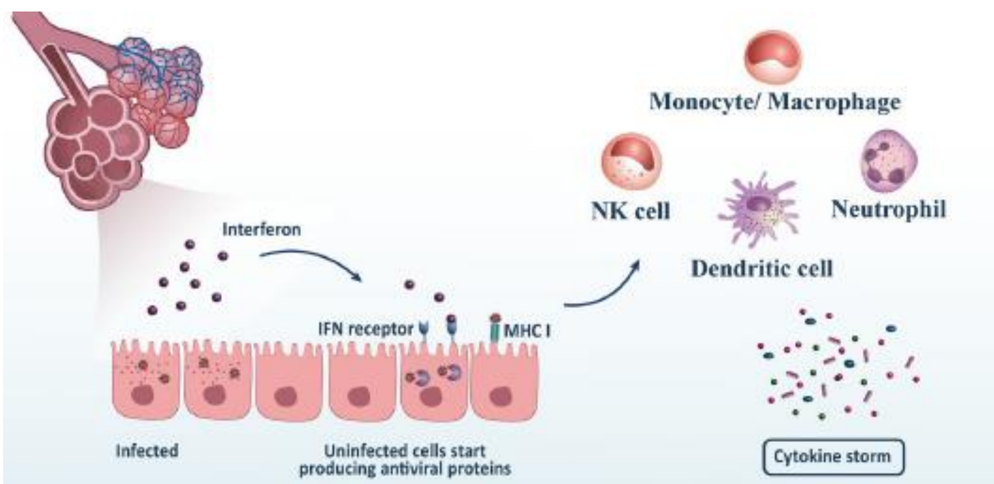


Figure 4: the cytokine storm causing inflammation and release of plasma proteins in immune response [14]

1.3 The risk factors of COVID-19

The common risks have also been vastly studied. The most prevailing of them include old age, more likely to be female, clinically severe at acute phase of the infection, greater number of underlying comorbidities, acquired hospital assessment and admission and need for oxygen at the acute phase. [10]

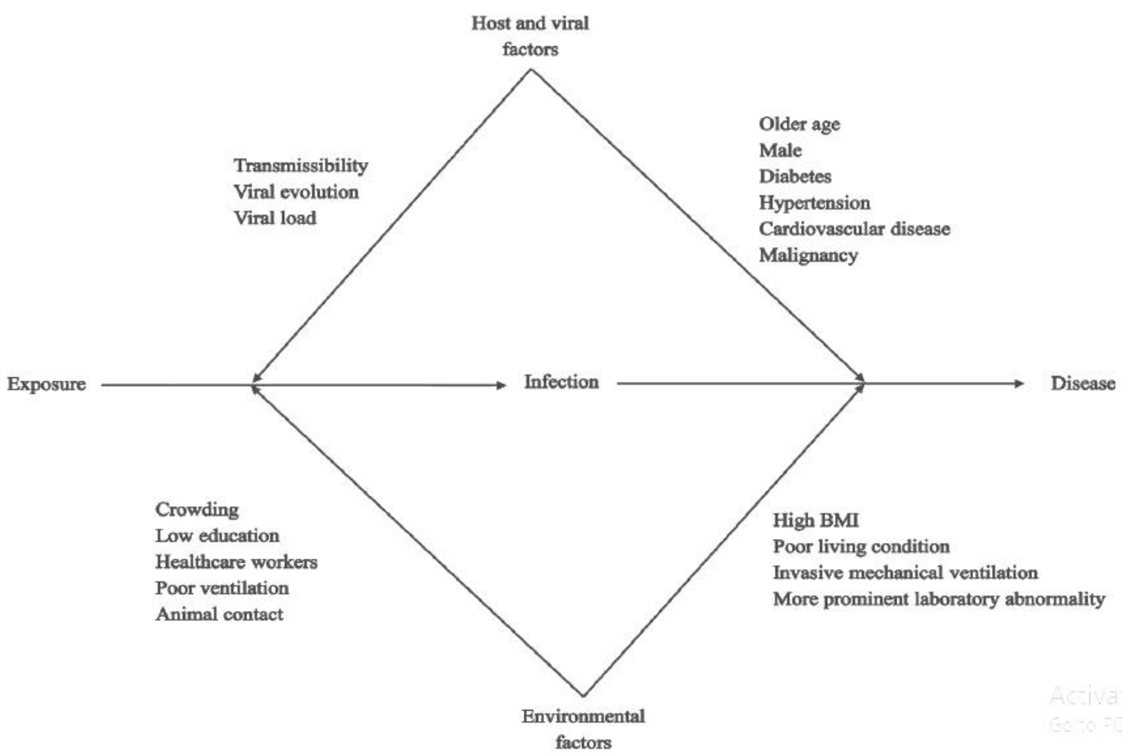


Figure 5: Risk Factors of COVID-19 [19]

The risk factors are distinguished as follows in a review by J. Rashedi. (Figure 5)

- Host risk factors
- Environmental risk factors
- Viral risk factors

The presence of comorbidities increases the susceptibility to COVID-19 infection, resulting in poorer outcomes and increased mortality led by severe lung injury. [20] The lungs tend to be affected by the severity of the infection (Figure 6). ACE-2 polymorphisms influence the blood pressure which increases the damage to the lungs and heart by an oxidative stress stimulated by angiotensin II. [21] Patients admitted in the ICU showed majority (72.2%) of comorbidities compared to those who did not require hospital/ICU admission. This suggests the poor outcomes are the risk of comorbidities. [22]

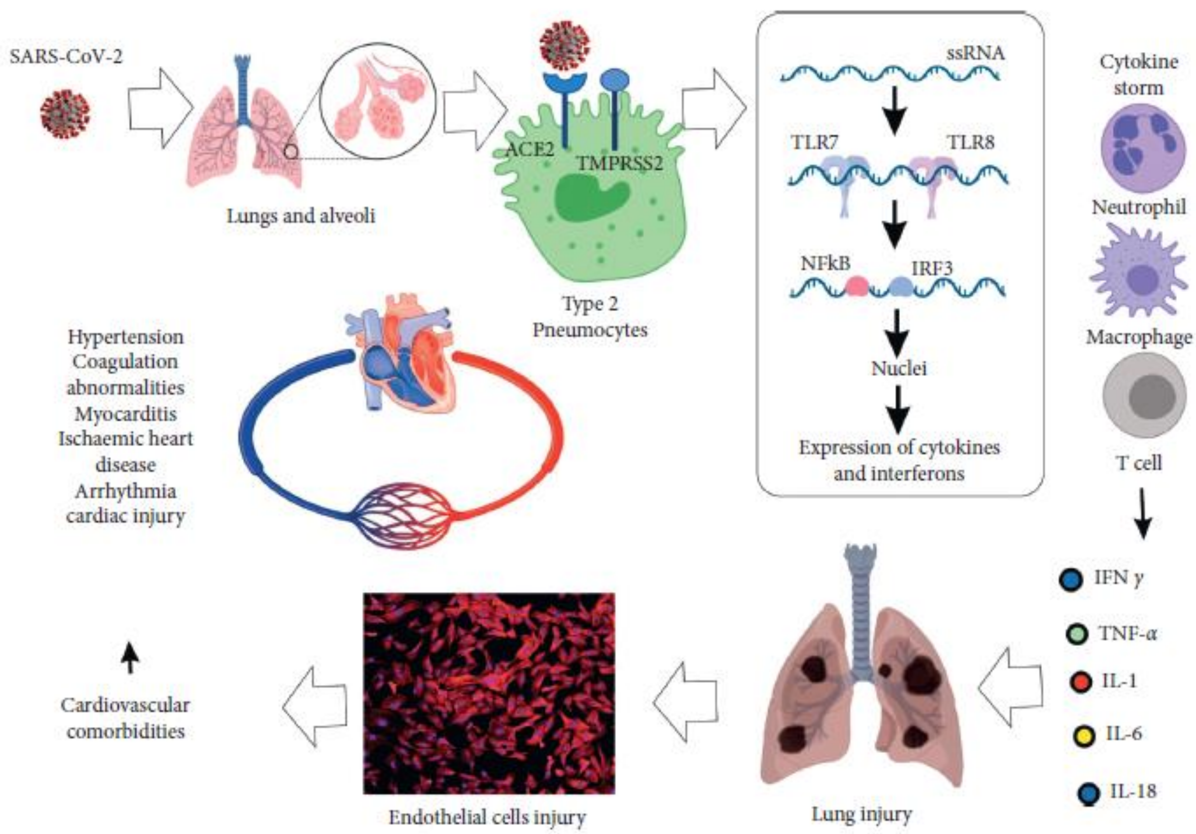


Figure 6: SARS-COV- infection progression and development of cardiovascular comorbidities

The risk factors by experienced by the host include:

Old age

COVID -19 can infect all the ages, but elderly people are more susceptible to the illness and have more chances of getting ICU admission, which also leads to high mortality rate. [23] Aging itself affects the lungs' function and when needed there is delay in adapting the acquired immune response.[24] A retrospective study included middle age and elderly patients infected with COVID showed that the elderly people had physiological changes due to the anatomical changes in lungs, muscle atrophy and reduced lung reserve which leads to compromised airways clearance the minimal function of defense barrier in return. [25] Hence, the virus keeps replicating, increasing the inflammation and therefore increased risk of death.

Gender

Men have higher ACE-2 expressions in the lungs which makes them more at risk than women to catch the COVID-19 infection. [26] When the protein, A disintegrin and metalloprotease (ADAM17) is expressed by the lungs and liver at higher levels sheds away the surface protein ACE-2 which is involved in stopping the COVID virus to enter. Whereas, in women, estradoil is present in high concentration which increases the activity of ADAM17 thus increasing the ACE-2 levels reducing the chances of COVID infection in women than in men. [27]

Diabetes

Mendelian randomization analysis helped relate diabetes to an increased level of ACE-2 receptors. This becomes an issue and risk for people with diabetes to COVID-19 infection.[28] In diabetic patients, a membrane bound protease called the furin is expressed in high levels. [29] The activated process of the virus entering the host cell decreases the COVID-19 dependency on human proteases. The virus attaches to ACE-2 receptors which are activated by high furin levels. The protein activation with viral entry into the cell has now escaped from the immune system.[30] Hence, higher furin levels and ACE-2 receptors lead to higher rate of lung inflammation and lower levels of insulin. And so, the easy entry of virus leads to a critical condition for patients with diabetes. Impaired function of T-cells and raises levels of interleukin-6 develops COVID disease in diabetics. [31]

SARS-COV- infects the lung tissues with the help of ACE-2 receptors which lets the virus enter. Those who are diabetic have higher ACE-2 levels. Another cause of prevalence of COVID-19 is the higher levels of glucose which facilitates SARS-COV-2 replication. Diabetic individuals will have pro-inflammation cytokine storms which eventually causes damage to the lungs. This may result in multiple systematic coagulation (Figure 7).

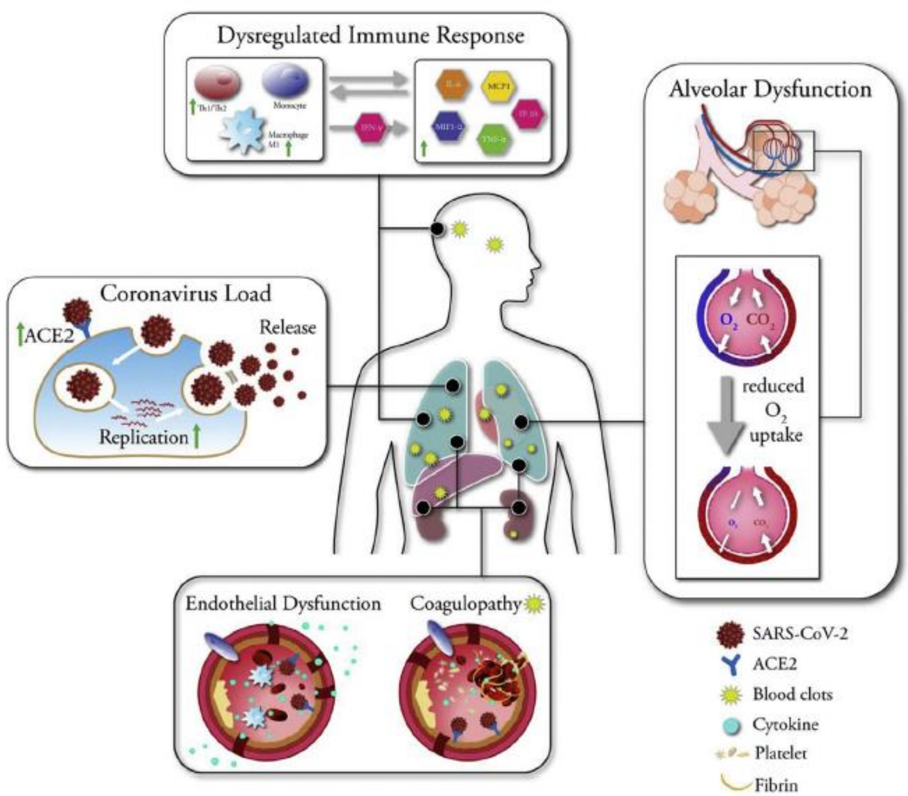


Figure 7: Increased COVID-19 severity with diabetes

Diabetes can also cause alveolar dysfunction with impaired respiratory function leading to pulmonary complications which may require mechanical aid to ventilation. Blood clots can be commonly found in multiple organs since patients with diabetes create a favorable environment for thromboembolic events. SARS-COV-2 invades the endothelial cells via the ACE-2 receptors present causing vasoconstriction leading to organ ischemia and tissue edema, figure 7. [32]

Hypertension

The common causes of hypertension are lifestyle, stress, and diet. Due to a disorder in blood vessels and with age, the elevated blood pressure has a high mortality rate with COVID-19. [19] In patients with hypertension, angiotensin receptor blockers (ARBs) and ACE-2 inhibitors are used for its treatment. With the increased use of these inhibitors, ACE-2 receptors expressions tend to rise too leaving the hypertension patients to be more prone to COVID-19 infection. The more ACE-2 receptors released, the higher the chances of the lungs getting infected leading to respiratory failure. [33]

Arterial hypertension is found to be the most common of the cardiovascular comorbidities in patients with COVID-19 infection. The condition can worsen the outcomes and hence the increased chances of getting admitted in the ICU. [34]

Cardiovascular diseases as an already existing issue increases the susceptibility to COVID-19 just like any other comorbidity. COVID-19 can also result in more cardiac complications. [35]

Cardiovascular disease

Cardiovascular disease (CVD) was commonly known at the time of SARS and MERS. [36], [37] The association of COVID-19 and CVD is not precise but compromised immune system at COVID, is commonly seen in those with CVD. [38]The presence of ACE- receptors on cardiac muscle cells involves the cardiovascular system in the COVID-19 infection. Individuals with CVD have higher chances of experiencing acute coronary syndrome in acute infections. This could lead to myocardial infarction or injury. Also, the cytokine storm causes atherosclerosis, procoagulant activation, and hemodynamic instability which leads to thrombosis and ischemia (Figure 8). [34]

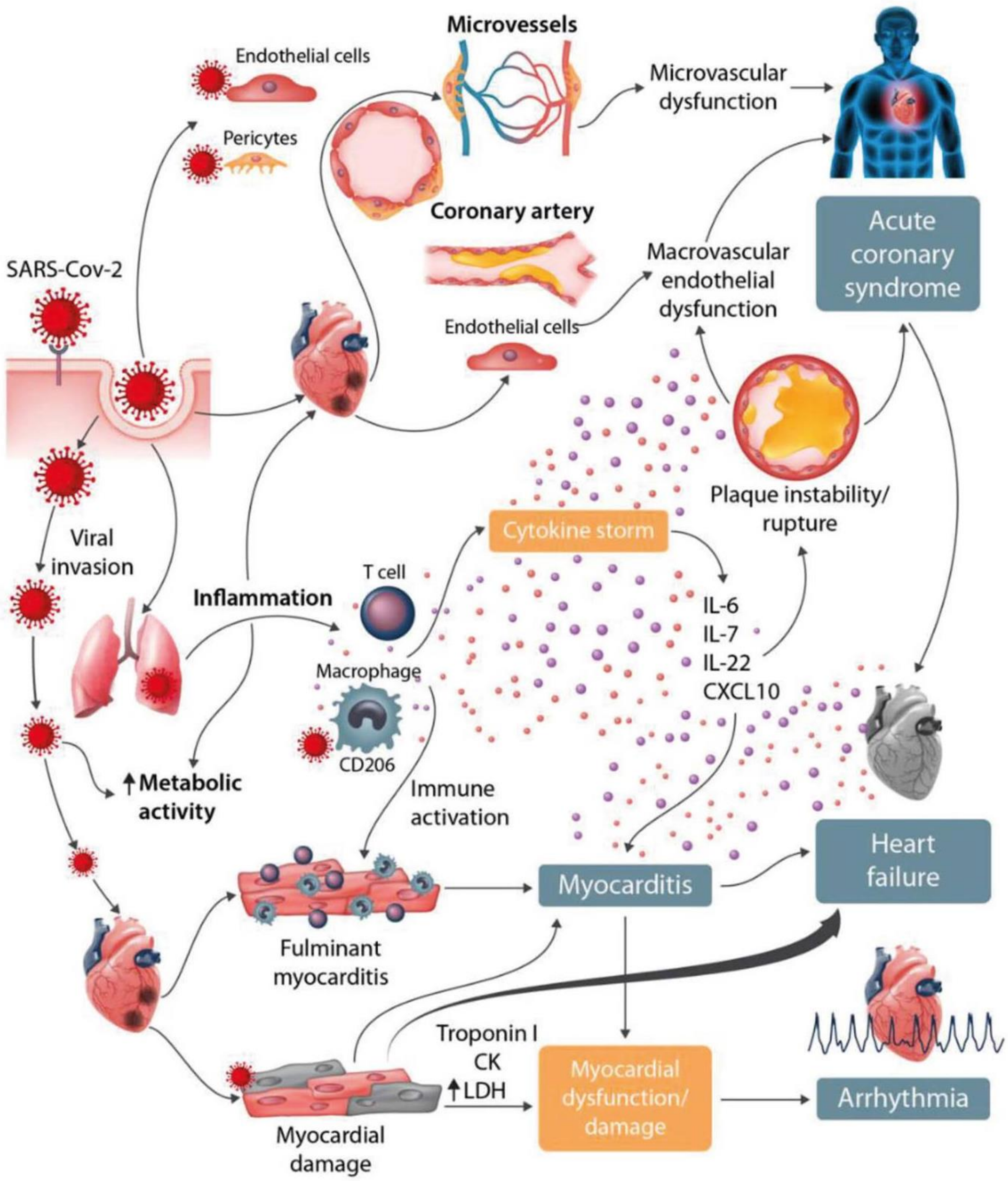


Figure 8: Cardiovascular involvement in COVID-19

Liver diseases

Earlier at the times of SARS and MERS, liver injuries and abnormal liver biochemistry were found. This is now similar in COVID-19 patients too. The coronavirus infection stimulates the release of abnormal liver enzyme. The SARS-COV-2 infection enters via the ACE-2 receptors on the liver cells. Among the infected ones with COVID-19, there was abnormal secretion of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactic dehydrogenase (LDH). Other than abnormal liver function tests, there are elevated levels of enzymes from cardiac and muscle body, during COVID infection (Figure 9). The temporary rise in ALT and AST causes damage to liver. [39], [40]

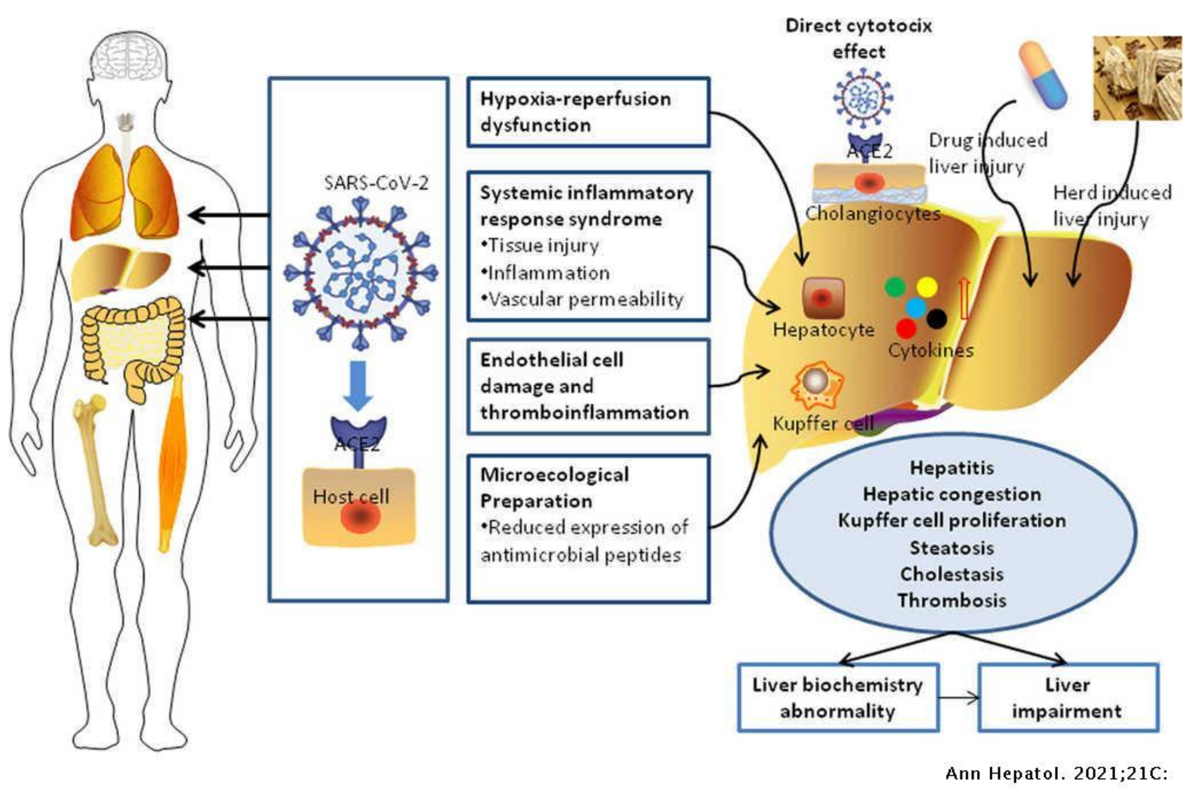


Figure 9: COVID-19 and liver diseases [41]

Malignancy

The abnormal growth of cells, in cancer, where SARS-COV-2 gets the perfect environment to replicate in the individuals with cancer. Cancer patients are at more risk to COVID-19 infection due to their weak immune response. The patients are either suffering with lung carcinoma or any other cancer, and those taking immunotherapy, chemotherapy and radiotherapy have their immune responses lowered. [34]

The environmental risk factors include:

Crowding*:* If social distancing is not maintained, then there is a risk of getting infected amongst people in gatherings without any protection.

Lower education*:* People with lack of awareness or proper training will transmit the virus unconsciously.

Occupational risk*:* The most sensitive of people to COVID infection at their workplace are the health care workers as the virus has the ability to spread rapidly and patients infected end up at the medical centers. Other jobs like cleaners and sweepers who could get contaminated when disposing of infected waste. [42]

Poor ventilation: Places where there is poor air conditioning can infect people gathered in the environment. It is necessary for proper airflow in an enclosed area like offices, hospitals, clinics, banks etc.

The viral risk factors include the transmission of the virus, the virus evolution, and the viral load. The virus is easily transmitted from those infected and showing symptoms as well as in the case of asymptomatic the virus very conveniently gets transferred when in close contact. The SARS-COV-2 can also be transmitted during incubation periods. And since the virus also stays active on surfaces like Teflon, glass, surgical gloves, and steel. [43], [44] Mutations of the virus are seen differently in every region around the world. The evolution of the virus includes changes in its replication, their immune response, their ability to transfer, drug resistance. [45]

The SARS-COV-2 virus sheds for around 37 days. The viral load on asymptomatic patients is higher than in patients showing symptoms, therefore they can infect more people. The entry of the virus via the ACE-2 receptors in the cells of lower respiratory tract and the epithelial cells of the mouth and tongue, causes inflammation and cytokine storm which makes the situation even worse once infected. [46]–[49]

Pregnancy

Pregnancy is not a comorbidity, but it has been proven to be a risk for getting infected with COVID-19. Healthy pregnant women are susceptible to having COVID due to the altered immune response. The conditions during pregnancy and COVID-19 show lowered lymphocytes, and increased ACE-2 receptors (table 2) which eases the virus to enter the lungs. Therefore, pregnancy is a risk factor for developing COVID-19.

PREGNANCY	COVID-19
↓ Natural Killer cells	↓ Natural Killer cells
↑ NKG2A receptors	↑ NKG2A receptors
↓ Lymphocytes	↓ Lymphocytes
↑ Pro-inflammatory Factors	↑ Pro-inflammatory factors
↑ ACE2 receptors	↑ ACE2 receptors

Table 2: Immune response in normal pregnancy and pregnancy in COVID-19

1.4 Aims and Objectives

Diagnosis of long-COVID is challenging without any preceding evidence during the infection. Since COVID-19 is a newly emerging topic, there have been just a few studies made on the virus and its later effects. To ensure the condition after viral infection, are not left untreated, can avoid the worsening of symptoms. This research can help to get a better understanding of underlying risk factors and mechanisms and help develop appropriate prevention and management strategies. The core objectives are:

- to diagnose or detect the common symptoms in long-COVID
- to treat and manage the prolonged symptoms from getting worse
- Who is at risk to get long-COVID
- To find any association between the post-covid symptoms with the previous comorbidities

1.5 Areas of application

Patients treated for COVID on an outpatient basis as well as those discharged from the hospitals.

1.6 Relevance to national needs

To identify the support and treatment needed by the post COVID patients should be a part of the overall COVD-19 response globally. This review will help in educating the medical staff and those who recovered, to be able to assess the symptoms and manage them on time without getting into serious issues.

1.7 Advantages of the study

The patients may be able to get back to their daily routines and be safe from mental health issues like anxiety, depression, and post-traumatic stress disorder

2.3 Long-COVID (Post-COVID-19)

The continuous symptoms or conditions experienced after recovering from the acute COVID-19 infection is termed as 'long-COVID'. These symptoms can span from weeks to months in those after negative swab test result, recovering from COVID-19 [50]

The consistent occurrence of symptoms (continuous or relapsing and remitting)[51], during or after the infection, normally continues for 4 weeks or longer [52]. The definitions of long-COVID vary in their severities and durations[53] (Figure 10.). Long COVID symptoms extending from 4-12 weeks is termed as 'post-acute COVID'. Whereas the symptoms extending 12 weeks or longer is called the 'post-COVID syndrome'. Post-COVID syndrome denoted as the time lag between the microbiological recovery and clinical recovery[50]. As it is a relatively newly emerging issue, there is lack of awareness on the syndrome and its treatment.

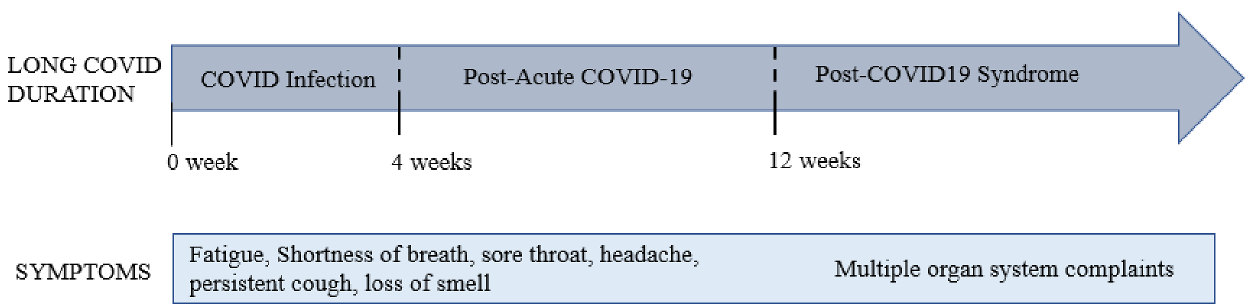


Figure 10. Division of Long-COVID; with severity and duration

It was reported from Italy that 87% of those recovered from COVID, had at least one symptom showing up at 60 days[54] . In a study in UK found out the discharged patients experienced breathlessness and excessive fatigue at 3 months [55]. The occurrence of long-covid patterns comprises of fatigue, shortness of breath, sore throat, headache, persistent cough, and loss of smell, as well as multiple organ-systems complaints associated with fever. Other less common symptoms include hair loss, insomnia, and wheezing. There is also link of symptoms with the other factors like age, weight, and disease severity[52] .

Young adults and those with moderate COVID-19 infection, get affected by long-COVID. Survivors discharged from the hospital as well as those in self-care, develop long-COVID. It is still not sure as to who is at greater risk of experiencing long-COVID, but there are certain studies which tells an association between the comorbidities and the chances and severity of the long-COVID symptoms[56], [57] . Those in the age group of 65-70 years are more prone to be having some illnesses like cardiovascular condition and type 2 diabetes and hence they become more at risk to develop the post-COVID symptoms[58]. Those suffering with acute COVID infection, are less likely to experience prolonged post-COVID symptoms[59].

As mentioned earlier, the elderly is more likely to develop symptoms after the infection. The severity is also affected depending on the duration one has been having the COVID-infection[60], [61]. The idea that the symptoms experienced at long-COVID are very much like the SARS attack in 2003[62]. There has also been multiple resemblance to the ME/CFS, where Sonia Poeneru et al., reviews the similarities and differences of ME/CFS with the post-acute COVID symptoms and understand the mechanisms and their management strategies[63].
The core symptoms of ME/CFS, as per the Institute of Medicine, include fatigue, post-exertional malaise, sleep disturbances and unrefreshing sleep[64].

Condition	Description
Long COVID-19 or post COVID syndrome	• Condition lasts for more than 3 months after COVID-19 onset. • Fatigue and dyspnoea with neurological, cardiac, or gastrointestinal complications.

ME/CFS	• Condition lasts for 6 months after possible triggers such as stress or viral infection. • Fatigue with headache, myalgia, joint pain, sore throat, unrefreshing sleep.
SARS (2003)	• Fatigue, myalgia, depression, and weakness.

Table 3. Descriptions of conditions like Long-COVID [1]**.**

2.2 Fatigue

There have been functional limitations to those recovering from the acute symptoms of COVID-19 viral infection. With ongoing research, it is observed that fatigue is the most persistent symptom seen in the patients. Since the cause of fatigue cannot be well deduced, the definition remains poorly understood[65]. In a study by Rudroff et al, described fatigue to be resulting from changes in psychological, and peripheral factors[66]. Any reduced physical activity or mental performance is said to be fatigue.

Fatigue is proven to be the most prominently experienced symptom which can turn to chronicity if left untreated [67] . Upper respiratory tract infections often lead to short-live fatigue, revealing the importance of knowing the durations of having the acute symptoms. Fatigue is a multifaceted health issue, associated commonly with breathlessness, psychological distress, and cognitive behavioral changes. An article discusses the post-viral fatigue and its risks, the diagnosis, and its management with its chronic variant, myalgia encephalomyelitis/chronic fatigue syndrome *(hereafter 'ME/CFS')*, highlighting, that further research is urgently needed to guide clinical practice[67].

Clearer definitions and diagnostic methods of ME/CFS have evolved over time which has become easier to associate them with COVID-19 post-viral conditions. These symptoms are similar to those that are seen in post-infectious ME/CFS such as the persistent fatigue, followed by Post Exertional Malaise *(hereafter, -PEM),* difference in cognitive responses, widespread pain, and unrefreshing sleep[68]. The significant symptom of ME/CFS is the post-exertional malaise, that is the worsening of symptoms with compromised functional activities that never occurred before the illness. [69] PEM can be triggered by physical activity, sensory overload, and cognitive overexertion. The statistics show that out of 233 SARS survivors, 27.1% met the criteria for ME/CFS at 41 months after infection[70], [71]. On 28 post-COVID symptoms, a systematic review carried out found the most frequently occurring symptoms (fatigue, dyspnea, anosmia) lasting more than 3 weeks[72]. A longitudinal study of 1733 patients with COVID-19, admitted to hospital found that 63% of those still experiencing fatigue/myalgia even after discharge at 6 months[63]. However, this is still insufficient to diagnose ME/CFS alone in the presence of chronic fatigue. Further advances are expected to result in establishing, if COVID-19 infection triggers the ME/CFS. For this, follow-up for longer durations and a well-defined criterion for diagnosis will be needed.

The symptoms like fatigue, breathlessness, and psychological distress are more prevalent in those who recovered ICU care than those in wards and self-care. Research was conducted with the risks that could lead to fatigue chronicity and an association was found with the biological, social, behavioral cognitive and social factors which may lead to the chronic stage of post-viral fatigue. It also depends on how severe and how long the acute infection phase is [73].

It is quite evident that the stress corresponding to COVID-19 (than any other infection) has more impact on the likelihood of chronic fatigue. This is due to the prevalence of trauma, due to the deathly consequences of the disease, the stress due to lockdown, social distancing, isolation when ill, pressure of job security and anxiety from overall economic condition[67].

Patients recovering from COVID-19, experiencing cognitive and behavioral responses affect long term health conditions. Anxiety of health issues, fear of the disease is a result of dysfunctional cognitive response. Maladaptive behaviors such as overdoing activities or excessive bed rest can give rise to another state that ends up even worse i.e., the post-exertional malaise *(hereafter, PEM)*. PEM is common in cases which is the result of one pushing themselves hard to feel good and active, and resulting in 'crashing'. Thus, it must be well understood that in overcoming fatigue, as something that one must not overdo[74].

2.4 Prevention and therapy management

2.4.1 Prevention and challenges

With no effective SARS-COV-2 antiviral medications, treating the COVID-19 infected patient had been a challenge. Although with time, the availability of vaccinations has made it easy to tackle the virus. The lungs, heart, kidneys, and liver are caused harm when an individual with comorbidities is infected with COVID-19. The complications end up in high rates of poor outcomes, multiple organ failure and ultimately, death. WHO and National Institute of Health (NIH) recommend management protocols, relevant to the symptoms of every individual affected with COVID. Patients must be appropriately assessed at hospital admission by separating those with the comorbidities and those without any previous illnesses. This way it would be easy to give special consideration to those in need with previous CVD, diabetes, hypertension etc. [75], [76]

Respiratory manifestations and fatigue are found to be most frequently occurring attributed to long-COVID-19, which can lead us to appropriate rehabilitation services reconstruction and prepare with their needs respectively. [77] To avoid the higher risk of developing organ failure (lung), blood pressure should be consistently monitored and managed to help avoid broad blood pressure fluctuations. [22]

A model design to separate short and long COVID, was generalized to the population with reported antibody testing. This information could be used in targeted education material for both the affected individual and healthcare providers. This method could help determine those at risk of getting COVID-19 and hence experiencing long-COVID so that early trials and clinical services could support rehabilitation in primary and specialist care. [77]

2.3.2 Rehabilitation

During the earlier phase of COVID-19 pandemic, many patients stayed away from health services manage those seriously affected with COVID-19, and not much focus was implied to those in need for post-COVID support and treatment[67]. There has been further research carried out in this regard that is the need for therapy and rehabilitation for the survivors of post-COVID patients. In the UK, multidisciplinary clinics have been sorted, involving medical specialists, psychologists, physiotherapists, and occupational health practitioners. Matters to resolve included social, psychological, and biological factors[78].

The main goal of the physiotherapists must be to avoid deconditioning by keeping the right balance and rest in activities to avoid PEM. This way, the relapsing and crashing can be prevented. The therapists adapt 'pacing', which is the gradual progress with the levels of activity, and limit them accordingly when over-exertion is felt, to avoid PEM[79].

Cognitive Behavioral Therapy (*hereafter, CBT*) is a psychological treatment improving the functioning and quality of life and being effective for depression, anxiety, and severe mental illnesses. A trial found that CBT and Graded exercise therapy (hereafter, GET) led to a greater satisfaction to the participants (82%) while only 50% had improved outcomes with specialist medical care [78]. GET are effective in managing any functional impairment like fatigue, as well as anxiety and depression (table 4). Clinicians looking after the long haulers, told the BMJ that the post-viral syndromes are a serious/very real condition and that the long COVID situation must be taken as an opportunity to understand more about the syndromes[78].

A study in the UK recommends the management of the post-COVID symptoms and hence improve the functional barriers and inabilities in patients. It therefore becomes imperative to form rehabilitation services and long-term planning to be able to combat post-viral symptoms, such as fatigue. Since, fatigue is said to be a multidimensional health problem, so the rehabilitation will have to be a multifaceted program which is customized to deal with the other overlapping problems like breathlessness, cognitive dysfunction, and psychological distress[80].

To be able to return to normal after getting infected, it was essential to understand the physical and emotional needs for the appropriate rehabilitation plans. A comprehensive rehabilitation program was identified by the European Respiratory Society for the survivors at hospital discharges[81].

A unidimensional program may not help fulfil the need of COVID-19 survivors therefore, to meet the complex needs of the survivors, the model of Pulmonary Rehabilitation population can also be adapted to develop the rehabilitation for COVID patients, since there is some affinity of their symptoms with the post-covid needs too. The common complexities were found, as mentioned earlier, low energy, breathlessness and so on. This program made sure to provide comprehensive and efficient exercise therapy to avoid worsening fatigue and other symptoms. Along with this, it also becomes necessary to provide educational awareness to prioritize the rehabilitation and psychological support[82], [83].

Therapies	**Description**
CBT	A psychological treatment to overcome depression and anxiety. Has been considered effective for ME/CFS too[84].
GET	Physical activities to overcome chronic fatigue by preventing deconditioning.

Pacing	Activity management strategy to minimize/prevent relapsing while remaining as active as possible[85].
Pulmonary Rehabilitation	6- minute walk distance and assessing fatigue on Borg's scale. [86]

Table 4. Managing long-COVID using therapies.

Although further research is still needed as to which management strategy best suits to overcome the post-acute COVID symptoms. Since, some more recent research claims graded exercise therapy to be causing worsening of post-exertional malaise. Therefore, the therapists must guide to maintain sufficient activity to avoid any daily activities disruptions. The survivors in their recovery phase must also be referred by the specialists to manage comorbidities along with the multifaceted approach to socio-economic support too[87].

The idea of our study is to assess the post-COVID conditions i.e., the commonly experienced symptoms by the Pakistani population. Also, to determine the correlations with gender, age, previous illnesses (comorbidities) and severity and duration of long-COVID symptoms. The aim of this article is to associate gradual increase in daily activities to revive the normal functionality after recovering from COVID-19 infection.

Chapter 3: Methodology

3.1 Study design and participants

This study was carried out on 83 Pakistani participants, who have recovered from the COVID-19 viral infection, with a negative swab test. The survey was carried out from March'2022 till May'2022. A questionnaire design resembled the DePaul Symptom Questionnaire (DSQ-1) [88], which is used to measure ME/CFS symptomology. As there are no biomarkers for the ME/CFS diagnosis, it can be diagnosed using self-reporting items. The DSQ-1 has shown reliability and validity to the results. DSQ-1 responses make it easy to discriminate between the symptoms of fatigue experienced in ME/CFS and any other chronic illnesses. Our questionnaire was designed to compare the current health status to the persistent symptoms experienced during and at COVID-19 recovery. The questionnaire was filled in by every individual on their own for a more reliable response. The DSQ-PEM measures post-exertional malaise.

All survivors of COVID-19 infection were asked feedback on their experience at recovery from the virus. Those survivors who met the WHO criteria for discontinued isolation, were followed up. Our data did not include those who did not experience symptoms of post- COVID-19. Only between the age 16-40 years were included, which was considered more relevant for our survey. It was also made sure that the respondents had been COVID-19 positive followed by an evident negative PCR at recovery. It was made sure that the participants confirmed infection, having had close contact with an infected case.

The scope of the survey was to understand the assessment and management of the long-COVID manifestations. The study performed research on 83 Pakistani participants who were affected by COVID-19 infection. A consent was taken at the beginning of the survey. A questionnaire survey was designed with both open-ended and closed-ended questions. Responses were received on Google Forms while all the literature was extracted from Google Scholars.

3.2 Content of survey

The survey was a crosse-sectional study. The information included in the questionnaire were age, sex, previous illnesses (comorbid diseases), duration of COVID-19 infection, time of onset of symptoms, symptoms experienced at COVID-19 recovery and vaccination status. A questionnaire design was inspired by the DePaul Symptom Questionnaire [17] to assess the fatigue status in those recovering. The survey was shared online with all the participants. It was non-experimental research where data on the experience of symptoms, their duration and severity were asked. The participants' demographic data, comorbidities, and daily activity status were included in the questionnaire. Along with the fatigue experience, any preventive protocols or need for exercising were asked too. While the frequency and severity of fatigue symptoms were assessed on the score scale of 0-4, for frequency (0= none of the time, = a little of the time, 2= about half of the time, 3= most of the time, 4= all the time) and for severity, (0= symptom not present, 1= mild, 2= moderate, 3= severe, 4= very severe) (table 5).

Overall improvement in symptoms

No Improvement Complete Recovery

0	1	2	3	4

Table 5. Post-COVID status assessment scale.

3.3 Statistical analysis

Data was analyzed by using SPSS version 26. Frequency and percentages were reported for the categorical variables. Chi-square/Fisher exact test was applied to see the association of year COVID-19 infection, gender, comorbidities, age group, and vaccination status with frequently occurring of fatigue symptoms and severity of fatigue symptoms. P-value <0.05 was considered statistically significant. We had 16 questions about frequently occuring fatigue symptoms and similarly for severity of fatigue symptoms. To generalize the data one variable was created for frequently occurring fatigue symptoms and severity of fatigue symptoms by calculating average of 16 questions asked.

Chapter 4: Results

Out of 83 of the participants, more than half of them 46(55.4%) were female. Majority of the participants 38 (45.8%) belonged to age group less than <30 years, Table-6. Almost all the participants were from Pakistan. Results showed 30 (36.1%) of the participants got COVID-19 infection in the year 2020 i.e., during the initial wave of coronavirus, figure 10.

Table 6- Demographic Data -Descriptive	
Gender	**N (%)**
Female	46 (55.4)
Male	37(44.6)
Age group	
<30 years	38 (45.8)
30-39 years	26 (31.3)
>=40 years	19 (22.9)
Year of 1st COVID-19 Infection	
2020	30 (36.1)
2021	24 (28.9)
2022	29 (34.9)

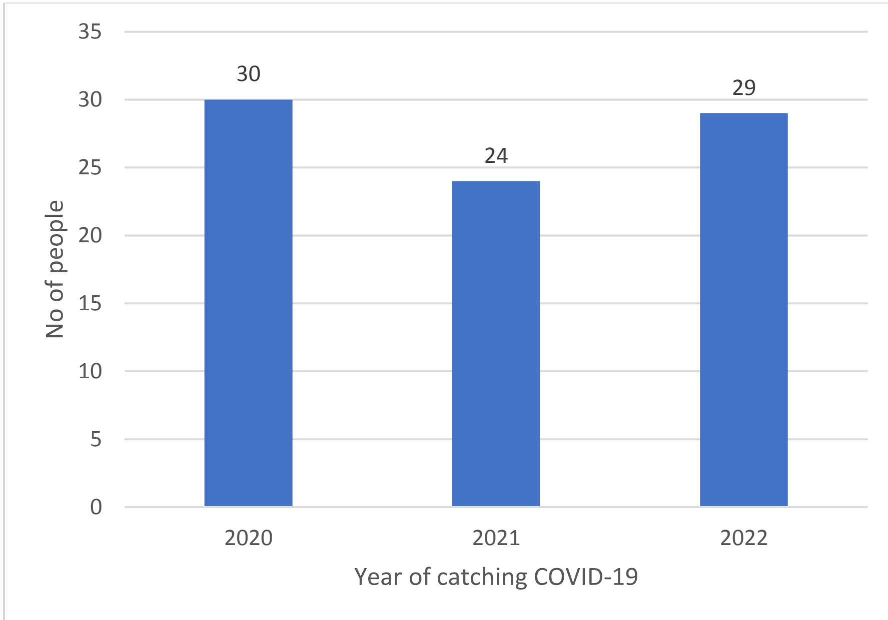


Figure 10. Year of First COVID-19 infection

Seventy-two (86.7%) of the participants experienced relapsing symptoms at recovery. About 59 (71.1%) of the survivors were able to detect their post-COVID symptoms at 3 weeks or less than that, from the time of the onset of the infection figure 11.

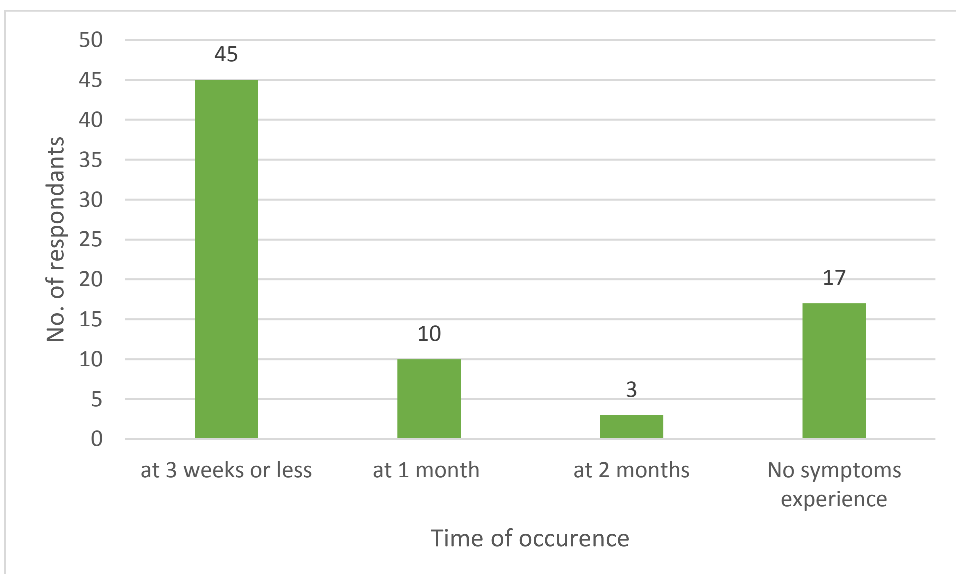


Figure 11. Experiencing long-COVID symptoms after the onset of COVID-19 infection

There were only 10 (12%) and 3(3.6%) respondents who experienced problems at recovery, after a month and two months later, respectively.

Out of all the symptoms' prolonged fatigue was found to be more prevalent followed by muscle pain, unrefreshing sleep and so on, figure 12. The commonly found duration of fatigue was 3-4 weeks by 37(44.6%) survivors, figure 13. We asked 16 different questions about fatigue. Overall results showed the majority 34.9% of the participants had frequency and severity of fatigue related symptoms 'a little of the time' to 'half of the time'.

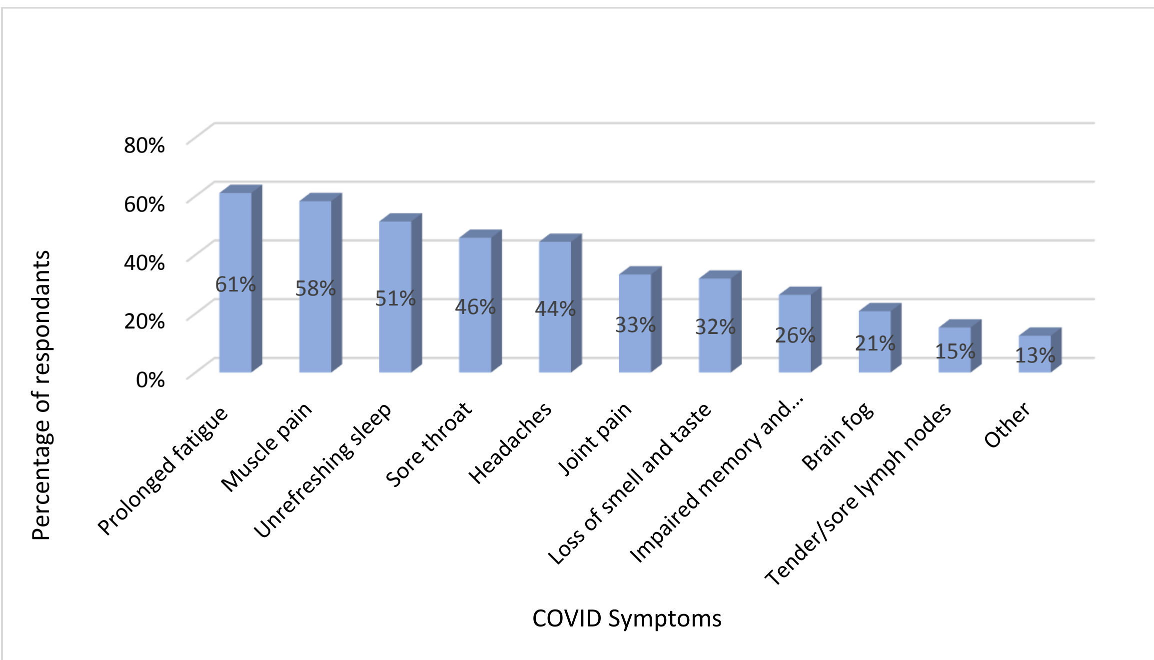


Figure 12. Common symptoms at post-COVID.

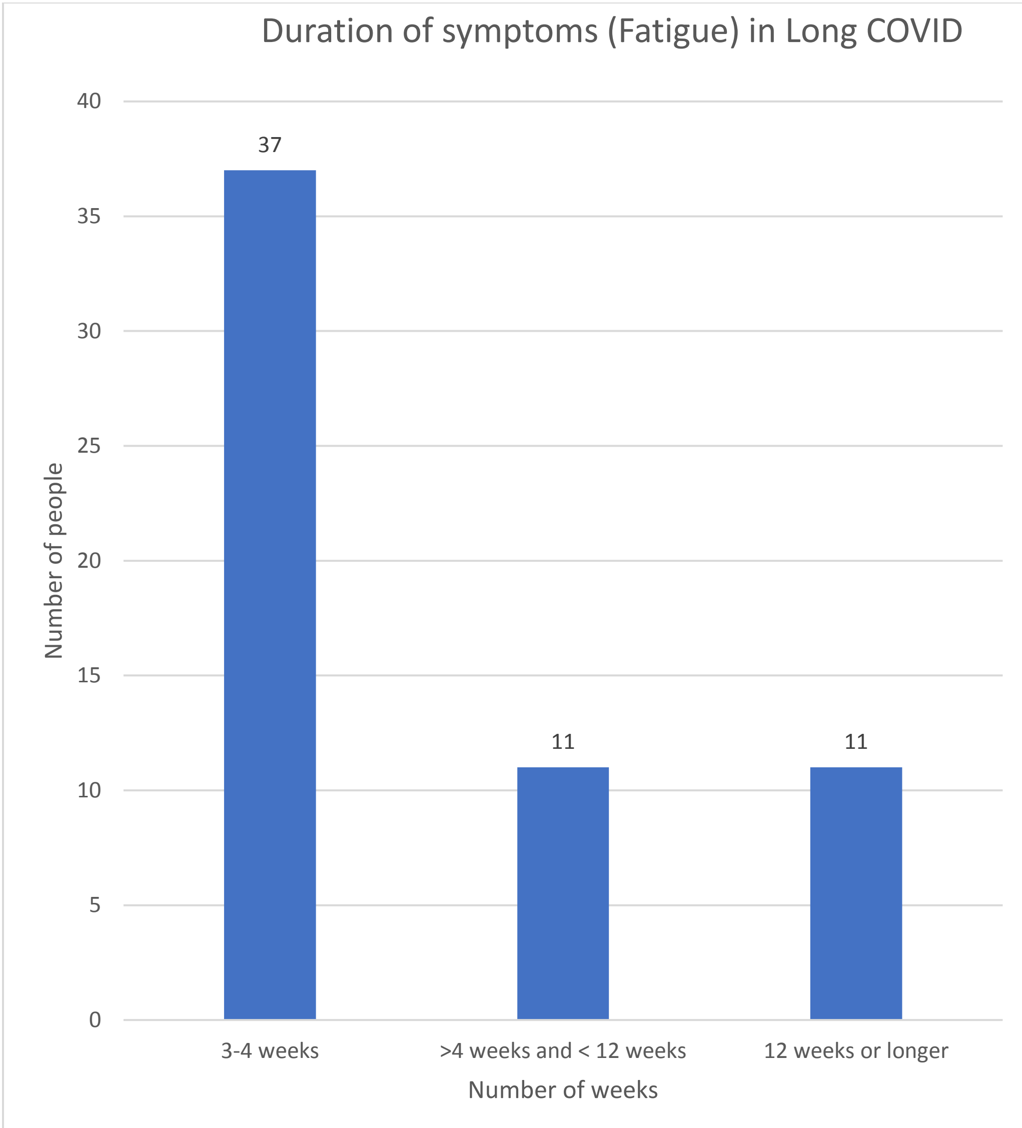


Figure 13. Duration of Symptoms (fatigue) in long-COVID

It was also observed that majority of the females had fatigue symptoms after COVID in 'a little of the time' followed by 'half of the time'. While in male majority of the patients reported that they had fatigue symptoms about 'none of the time' followed by 'a little of the time'. P-value was statistically significant (p=0.014), table7.

Table-7: Association of FREQUENCY of fatigue symptoms with Gender and Age group.

Gender							
	None of the time N(%)	A little of the time N(%)	About half of the time N(%)	Most of the time N(%)	All the time N(%)	Total	p- value
Female	7(15.2)	17(37)	13(28.3)	8(17.4)	1(2.2)	46(100)	0.014*⍰
Male	14(37.8)	12(32.4)	10(27)	-	1(2.7)	37(100)	
Total	21(25.3)	29(34.9)	23(27.7)	8(9.6)	2(2.4)	83(100)	
Age group							
<30 years	12(31.6)	9(23.7)	11(28.9)	6(15.8)	-	38(100)	0.209ƚ
30-39 years	5(19.2)	11(42.3)	6(23.1)	2(7.7)	2(7.7)	26(100)	
>=40 years	4(21.1)	9(47.4)	6(31.6)	-	-	19(100)	
Total	21(25.3)	29(34.9)	23(27.7)	8(9.6)	2(2.4)	83(100)	
* p <0.05, ƚ Chi square test, ⍰ Fischer exact test							

Table-8: Association of SEVERITY of fatigue symptoms with Gender and Age group

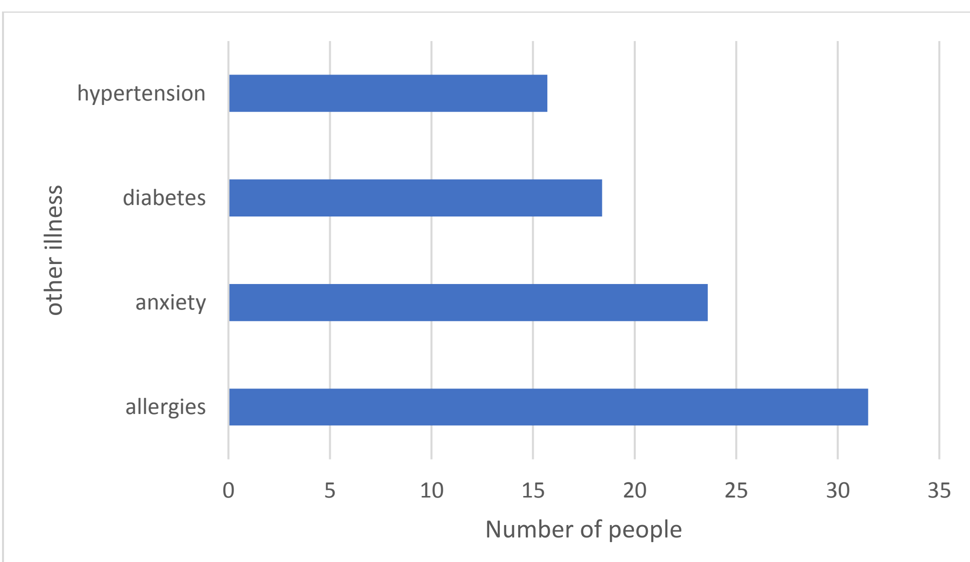
Gender							
	Symptom not present N(%)	Mild N(%)	Moderate N(%)	Severe N(%)	Very Severe N(%)	Total	p- value
Female	9(19.6)	15(32.6)	10(21.7)	9(19.6)	3(6.5)	46(100)	0.032*⍰
Male	13(35.1)	14(37.8)	8(21.6)	-	2(5.4)	37(100)	
Total	22(26.5)	29(34.9)	18(21.7)	9(10.8)	5(6)	83(100)	
Age group							

	Symptom not present N (%)	Mild N(%)	Moderate N(%)	Severe N(%)	Very Severe N(%)	total	p-value
<30 years	12(31.6)	10(26.3)	10(26.3)	4(10.5)	2(5.3)	38(100)	0.671ǂ
30-39 years	5(19.2)	11(42.3)	5(19.2)	2(7.7)	3(11.5)	26(100)	
>=40 years	5(26.3)	8(42.1)	3(15.8)	3(15.8)	-	19(100)	
Total	22(26.5)	29(34.9)	18(21.7)	9(10.8)	5(6)	83(100)	

* p <0.05, ǂ Chi square test, □ Fischer exact test

Almost the same trend was observed with severity of fatigue in gender (p=0.032), table 8. 32.6% of the females had mild symptoms followed by 21.7% to have experienced moderate. There was no association found between the age group and the frequency and severity of the symptoms experienced. The Chi-square test was also applied to find an association between the comorbidities/other illnesses and the severity and the frequency of symptoms which gave a significant result with p-value as 0.002, table 9. The common comorbidities and other illnesses included diabetes (18.4%) and hypertension (15.7%) allergies (31.5%) and anxiety (23.6%) respectively, figure14.

Figure 14. Other illnesses experienced by number of people



1. Severity of symptoms

	Symptom not present	Mild	Moderate	Severe	Very severe	Total	p-value
Yes	7(31.8)	13(4.8)	13(72.2)	6(66.7)	3(60)	42(50.6)	0.088�
No	15(68.2)	16(55.2)	5(27.8)	3(33.3)	2(40)	41(49.4)	

2. Frequency of symptoms

	None of the time	A little of the time	About half of the time	Most of the time	All the time	Total	p-value
Yes	6(28.6)	14(48.3)	14(60.9)	6(75)	2(100)	42(50.6)	0.002�
No	15(71.4)	15(51.7)	9(39.1)	2(25)	0(0.0)	41(49.4)	

* p <0.05, ɫ Chi square test, � Fischer exact test

Table 9. Association of frequency and severity of symptoms with comorbidities.

1. **Severity of symptoms**
2. **Frequency of symptoms**

A few questions were asked to analyze the importance of rest and/or activities for overcoming fatigue like symptoms. The majority experienced worsening of symptoms with physical exercise which was overcome by rest (45.8%) and reduced activity (48.2%), table 11. While no association was found between the need to exercise and severity and frequency of symptoms like fatigue, table 9.

Involved in exercise							
	None of the time N (%)	**A little of the time N (%)**	**About half of the time N (%)**	**Most of the time N (%)**	**All the time N (%)**	**Total**	**P-value**
Yes	5(31.3)	6(37.5)	5(31.3)	-	-	16(100)	0.716□
No	16(23.9)	23(34.3)	18(26.9)	8(11.9)	2(3)	67(100)	
Total	21(25.3)	29(34.9)	23(27.7)	8(9.6)	2(2.4)	83(100)	
* p <0.05, ɫ Chi square test, □ Fischer exact test							

Involved in exercise							
	Symptom not present N (%)	**Mild N (%)**	**Moderate N (%)**	**Severe N (%)**	**Very Severe N (%)**	**Total**	**p-value**
Yes	5(31.3)	5(31.3)	5(31.3)	1(6.3)	-	16(100)	
No	17(25.4)	24(35.8)	13(19.4)	8(11.9)	5(7.5)	67(100)	0.716□
Total	22(26.5)	29(34.9)	18(21.7)	9(10.8)	5(6)	83(100)	

* p <0.05, ɫ Chi square test, □ Fischer exact test

Table 10. association of exercising with occurrence of symptoms and severity, respectively.

Fatigue goes after rest?	
Yes	38 (45.8)
Faced to reduce activity level to avoid experiencing problem?	
Yes	40 (48.2)
Experience worsening of fatigue/energy related illness after engaging physical effort	

Yes	35 (42.2)
Have you been engaged in any kind of exercise	
Yes	16 (19.3)

Table 11. Activities and rest, effect on fatigue.

Chapter 5: Discussion

With the rise of the COVID-19 infection since 2020, until today, the infection itself has not been much a problem. The time after the negative PCR, there is occurrence of persistent symptoms that could be relapsing or remitting. This phase is now known as the 'Long COVID-19' or the 'Long haulers. Although many have been recovering well from the infection, there is still lack of awareness regarding the post-COVID situation. And if left ignored, the symptoms could get severe and lead to chronicity, forming the post-COVID 'syndrome'[52].

The focus of this study was to analyze the symptoms faced by the Pakistani population, after the COVID-19 infection and how to manage them before it gets serious. The association was significant between the gender, with the frequency and severity of the symptoms, with females are in majority in our study. This shows consistency with the findings from a previous study, that women are more at risk to experience long COVID-19 than men[89]. Regarding the previous CFS findings too, females are at a higher ratio to experience fatigue.

As mentioned earlier to compare the long-COVID fatigue to the ME/CFS criteria [90], our study has inclined towards proving the symptoms to appear as mild. Had it been severe, we could have followed the protocol of that of ME/CFS for the diagnosis, management, and treatment of the post-viral conditions.

Our data contributes to the clearer understanding of the acute COVID-19 infection, with relapsing symptoms occurring at 3 weeks or less from the onset of the COVID-19 infection. The most common symptoms experienced were prolonged fatigue being the most prevalent, followed by muscle pain, unrefreshing sleep, sore throat, headaches, joint pain etc. (Fig. 1) These symptoms continued for 3-4 weeks, hence proving the occurrence of post-acute COVID-19 in Pakistan population. Severity varies with the time duration of the symptoms experienced. However, based on the findings of similar studies, that there may be an association of mild COVID-19 with long term symptoms, a more plausible explanation is that these relapsing and remitting symptoms do not need to be investigated if the patient is otherwise well[91].

A statistically insignificant association was found between the exercising and the severity and frequency of symptoms like fatigue occurring. While previous research has focused on avoiding maladaptive behavior, which could lead to PEM, our results demonstrate that pacing, the right balance of activity and rest, can help overcome fatigue and prevent worsening symptoms. Our analysis also contradicts the claim that the symptoms might have a link with age. Although there were majority (45.8%) of the participants under the age of 30 years, the results affirm the risk of getting the post-COVID-19 symptoms by all.

The severity of the disease is also related to the comorbidities infected subjects (p-value 0.012) in our findings. The elderly is severely affected by the need for ICU. Common previous illnesses included anxiety, allergies, diabetes, and hypertension. According to many studies, hypertension is one of the most common comorbidities in cardiovascular patients. [31] Followed by another research, 98% of the adults suffering with type 2 diabetes showed an increased risk of getting severe COVID-19 infection. [92] Not much was proven for allergies to have any chances of getting COVID-infection. In fact, those who had asthma were safer to cope with COVID-19 infection. [93]

Irrespective of the vaccination doses, even today with different variants of COVID-19 virus, patients having had the infection will have to experience the post-COVID symptoms, especially fatigue. Our findings show that there is no association of the symptoms' frequency and severity with the vaccination status, although almost half of the responders had caught the infection before the first vaccination dose (49.4%) when COVID-19 infection was fatal. Mostly half the time, the sufferers had to experience the continuous, relapsing long-COVID symptoms with no severity as such.

Further research may be needed to know any association with the vaccination status and the severity of the symptoms. Our study had several limitations. Since COVID-19 virus is a relatively new subject with evolving dimensions, there is lack of awareness and knowledge regarding the viral itself, as well as the post-viral care. There is still research going on in this matter with not much on the past papers to compare in a longitudinal manner since our participants are assessed at a single timepoint. Another limitation of our study was whether the responders were able to record their persistent symptoms with certainty. Further studies for analysis and management awareness will be required in large cohorts.

Chapter 6: CONCLUSION

In this study, most of the patients had undergone acute COVID-19 viral infection. The occurrence of the post-COVID, persistent symptoms were detected which were mild. The commonly experienced manifestations were fatigue, muscle pain, joint pain, and headaches. Since the severity of fatigue was found the most in women, it gets necessary to recommend appropriate medications to revive their strengths back. While a balanced adaptation of lifestyle apprehended i.e., pacing, can help prevent chronic symptoms in long COVID-19. It is required to know how to assess and manage COVID-19 and its post-viral care without getting into clinical rehabilitation and therapies.

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